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Oral drug absorption in paediatrics: What we know and where we are going?

Dr Hannah Batchelor

University of Birmingham

Children are not just small adults

- But they do represent a small commercial market!

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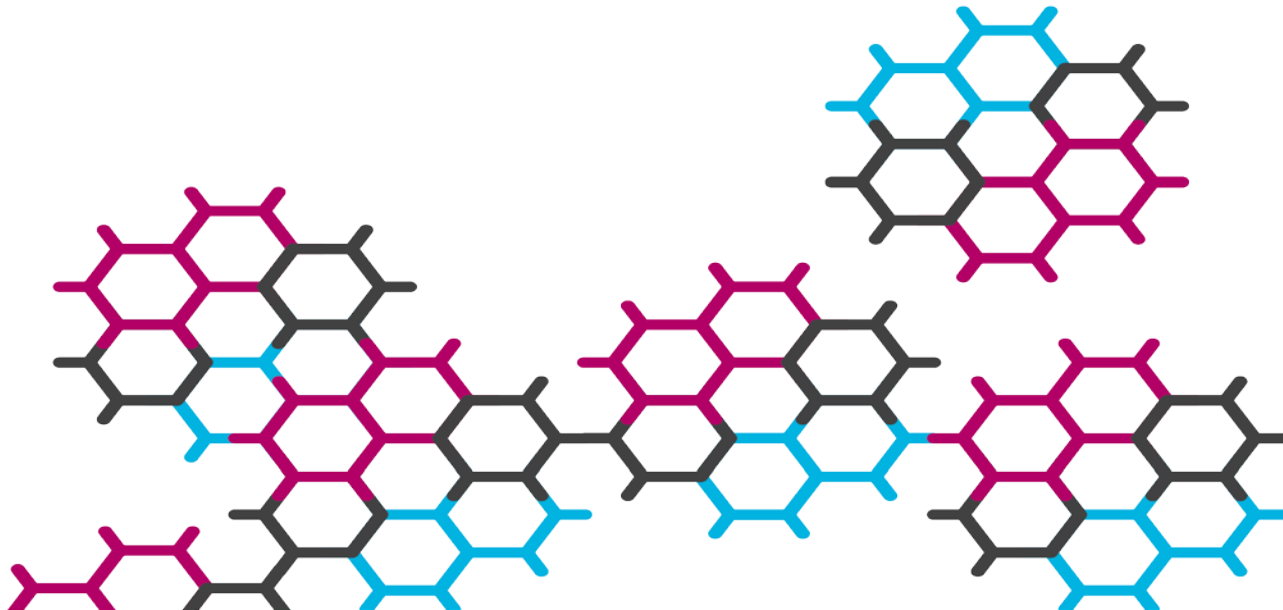
Risks associated with absorption in children…

- Clinical testing is conducted in adults
- It is assumed that extrapolation to children is risk free….
  - Generic medicines
  - Alternative formulations
  - Manipulation of medicines



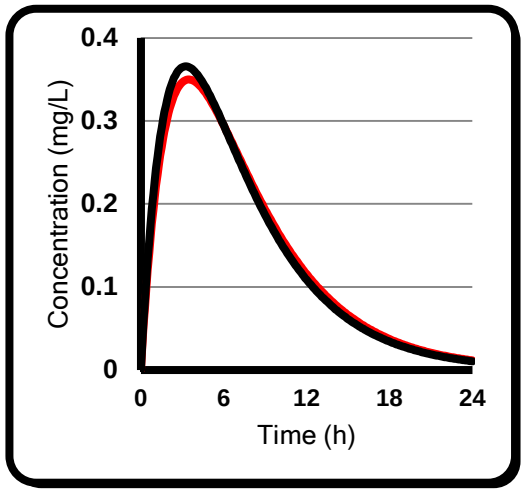
Guidance recommendations

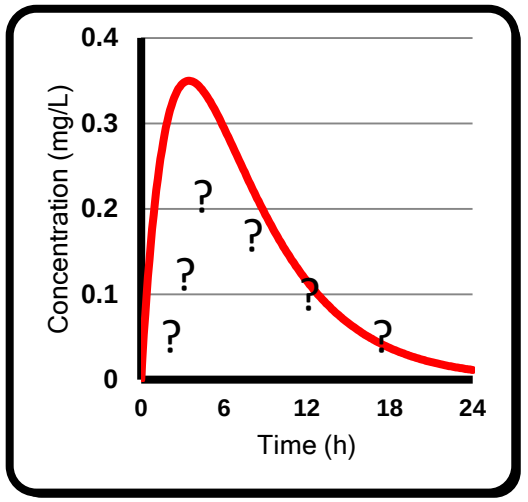
Relative bioavailability studies
(bridge adult to pediatric formulation)

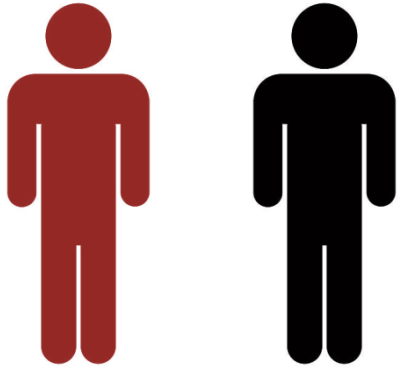
- **ICH E11** Relative bioavailability comparisons of pediatric formulations with the adult oral formulation **typically should be done in adults**.
- **FDA** The bioavailability of any formulation used in pediatric studies should be characterized in relation to the adult formulation. If needed, a relative bioavailability study comparing the age-appropriate formulation to the approved drug should be **conducted in adults**.
- **EMA** Bioequivalence studies for bridging paediatric clinical documentation between two formulations should **preferably be performed in adults**, **but the applicant should justify that the study results can be extrapolated to the paediatric population**.

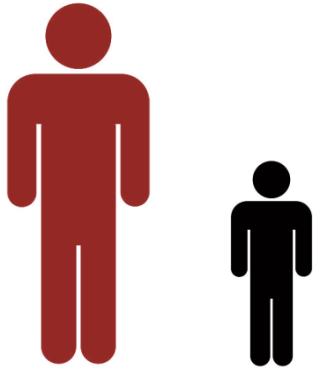
Innovator

Generic

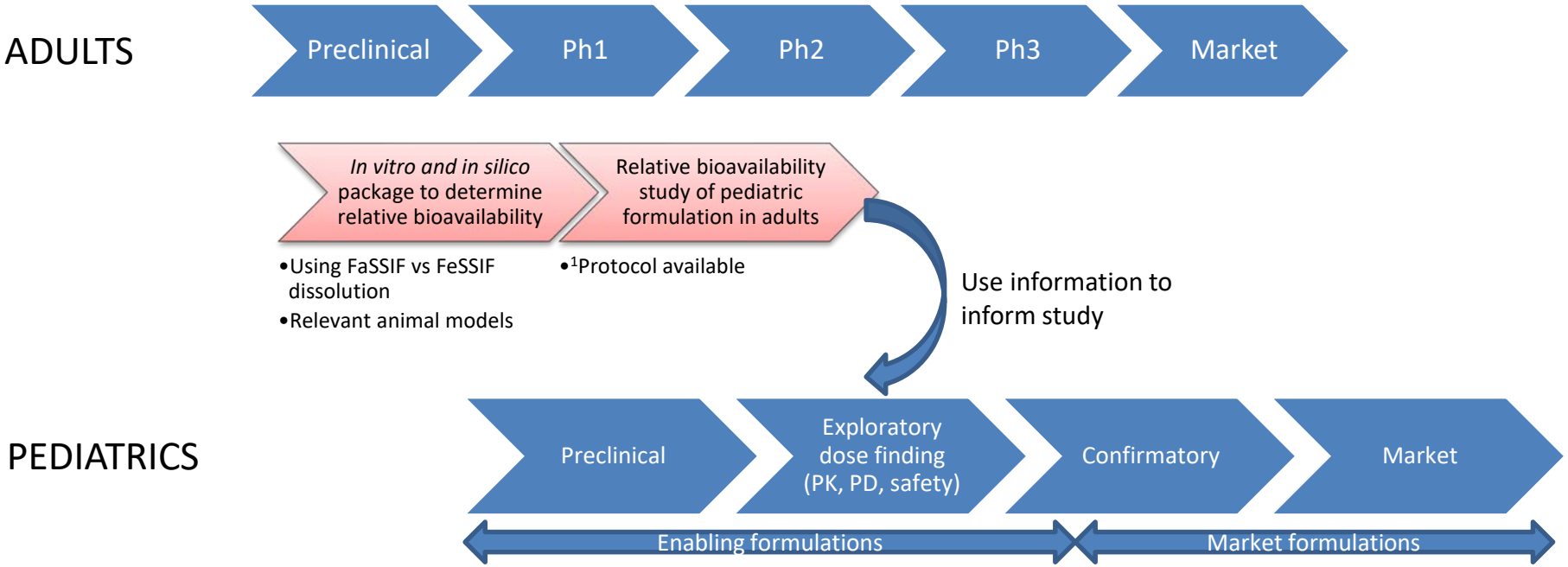








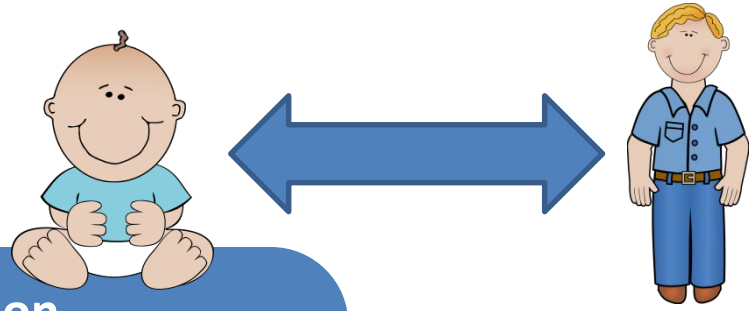
Typical bridging from adult to pediatric formulation



No guidance to support *in vitro* or *in silico* risk assessment to understand relative bioavailability

No clear protocol to undertake study

Key risks: patient



Absorption

Slow and irregular gastric emptying

Intestinal surface area

Intestinal transit time

Impact of food

Blood flow changes

Distribution

Increased total body water

Decreased total body fat

Altered blood flow

ADME

Metabolism

Ontogeny of intestinal transporters

Ontogeny of hepatic transporters

Elimination

Renal function

Hepatic function

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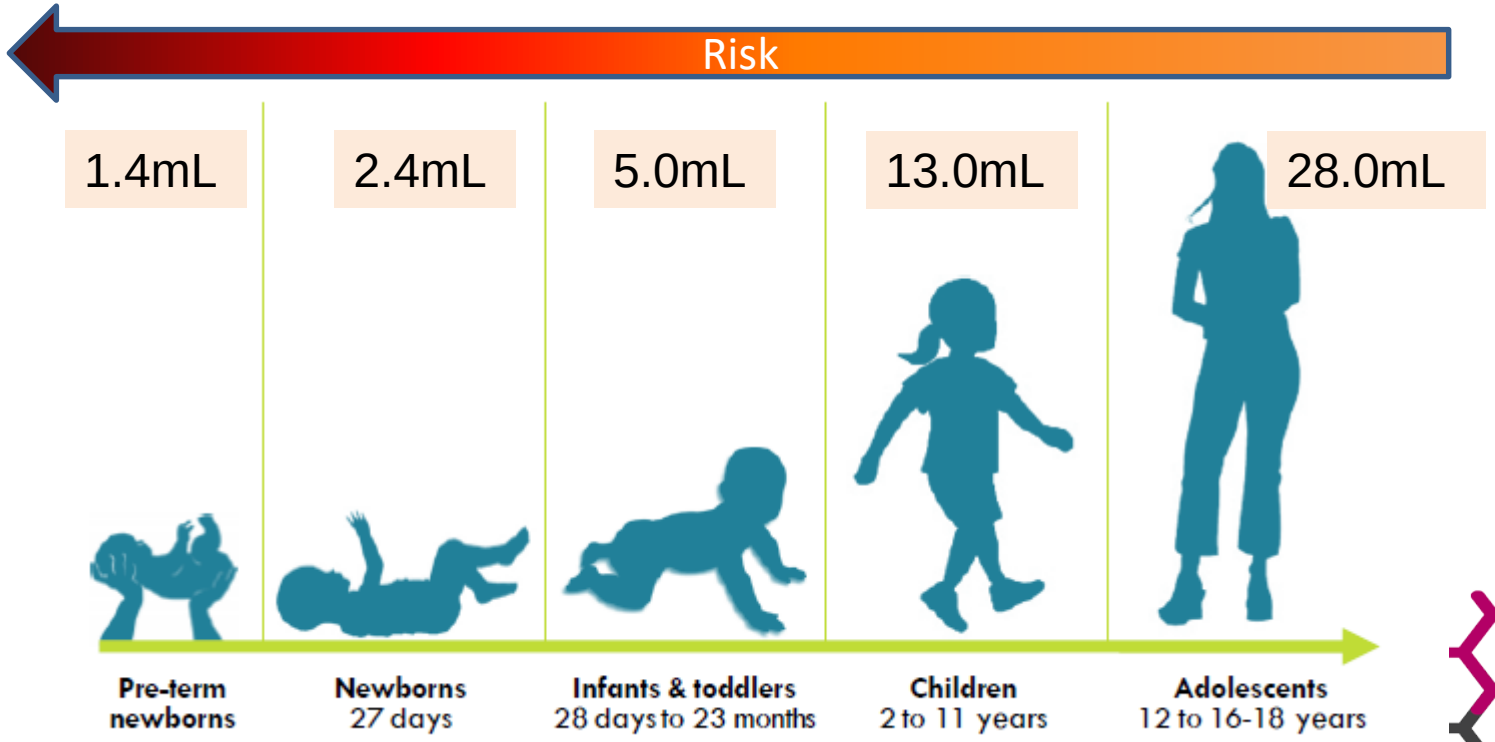
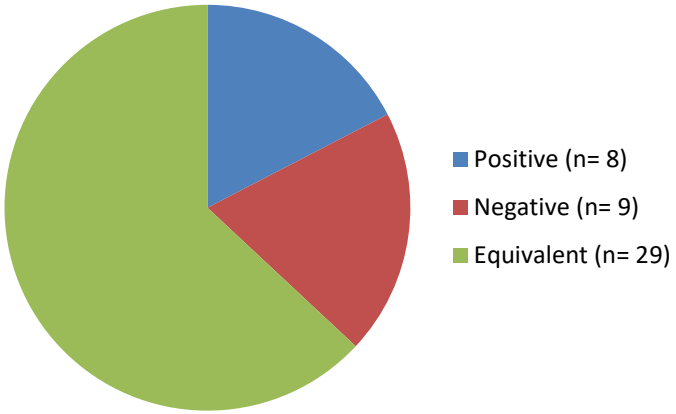
Key risks: Age

- *Example:* Solubility and dissolution media - volume
  - The volume of gastric fluids in children is not widely reported although a value of approximately 0.56mL/kg has been reported in fasted children
  - Equates to a volume of 37.1mL in adults



Studies where bioinequivalence has been seen in children are hard to find…

- 46 literature studies were identified that compared the relative bioavailability of paediatric medicines



Positive effect means that the relative bioavailability of the pediatric formulation was higher than the reference

In total 63% of pediatric formulations showed comparable PK profiles

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The lamivudine case

- The ARROW trial provided an opportunity to collect (post-approval) PK data in children switching from solution to tablet
- In children, the bioavailability after the solution was ~40% lower compared to the tablet formulation
- In adults, the two formulations were bioequivalent

Pharmacokinetics of Antiretroviral Drug Varies With Formulation in the Target Population of Children With HIV-1

P Kasirye[1], L Kendall[2], KK Adkison[3], C Tumusiime[4], M Ssenyonga[4], S Bakeera-Kitaka[1], P Nahirya-Ntege[5], T Mhute[6], A Kekitiinwa[1], W Snowden[7], DM Burger[8], DM Gibb[2] and AS Walker[2]; on behalf of the ARROW Trial Team

The bioequivalence of formulations is usually evaluated in healthy adult volunteers. In our study in 19 HIV-1-infected Ugandan children (1.8–4 years of age, weight 12 to <15 kg) receiving zidovudine, lamivudine, and abacavir solutions twice a day for ≥24 weeks, the use of scored tablets allowed comparison of plasma pharmacokinetics of oral solutions vs. tablets. Samples were collected 0, 1, 2, 4, 6, 8, and 12 h after each child's last morning dose of oral solution before changing to scored tablets of Combivir (coformulated zidovudine + lamivudine) and abacavir; this was repeated 4 weeks later. Dose-normalized area under curve $(AUC)_{0-12}$ and peak concentration (C_{max}) for the tablet formulation were bioequivalent with those of the oral solution with respect to zidovudine and abacavir (e.g., dose-normalized geometric mean ratio (dnGMR) (tablet:solution) for zidovudine and abacavir AUC_{0-12} were 1.01 (90% confidence interval (CI) 0.87–1.18) and 0.96 (0.83–1.12), respectively). However, lamivudine exposure was ~55% higher with the tablet formulation (AUC_{0-12} dnGMR = 1.58 (1.37–1.81), C_{max} dnGMR = 1.55 (1.33–1.81)). Although the clinical relevance of this finding is unclear, it highlights the impact of the formulation and the importance of conducting bioequivalence studies in target pediatric populations.

Epivir, label 12.3

The relative bioavailability of EPIVIR oral solution is approximately 40% lower than tablets containing lamivudine in pediatric subjects despite no difference in adults. The mechanisms for the diminished absolute bioavailability of lamivudine and relative bioavailability of lamivudine solution are unknown.

Key risks: drug solubility

- 88% of studies (15/17) showed equivalence in paediatric to adult product where drug was high solubility
  - BCS 1 or 3

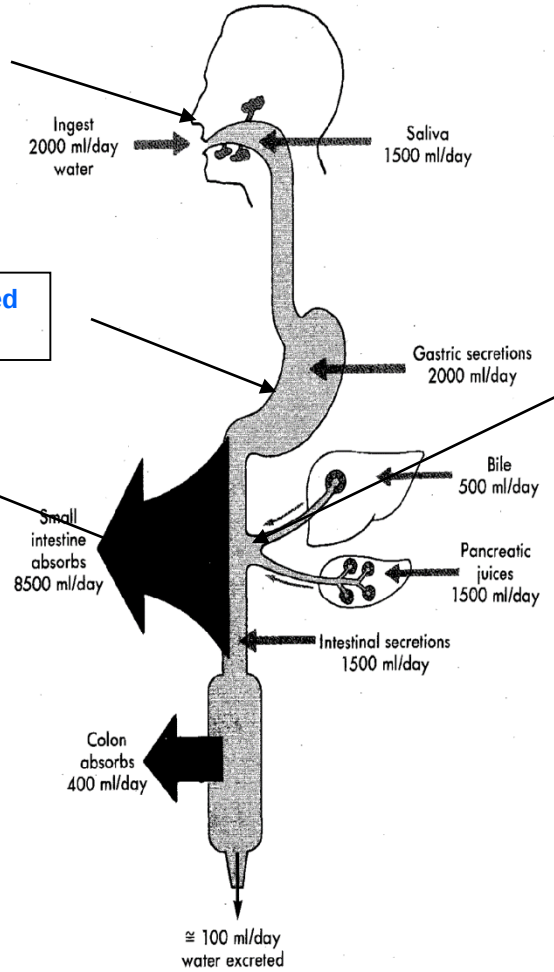
- 48% of studies (14/29) showed equivalence in paediatric to adult product where drug was low solubility
  - BCS 2 or 4

Why is GI anatomy and physiology important anyway?

100 - 250 mL with drug

pH 1.3 in fasted
pH 4.9 in fed

pH 6.5-7.4 in fasted
pH 5.4-7.5 in fed



Bile salt conc:
~ 5 mM in fasted
~15 mM in fed (30-60 min)

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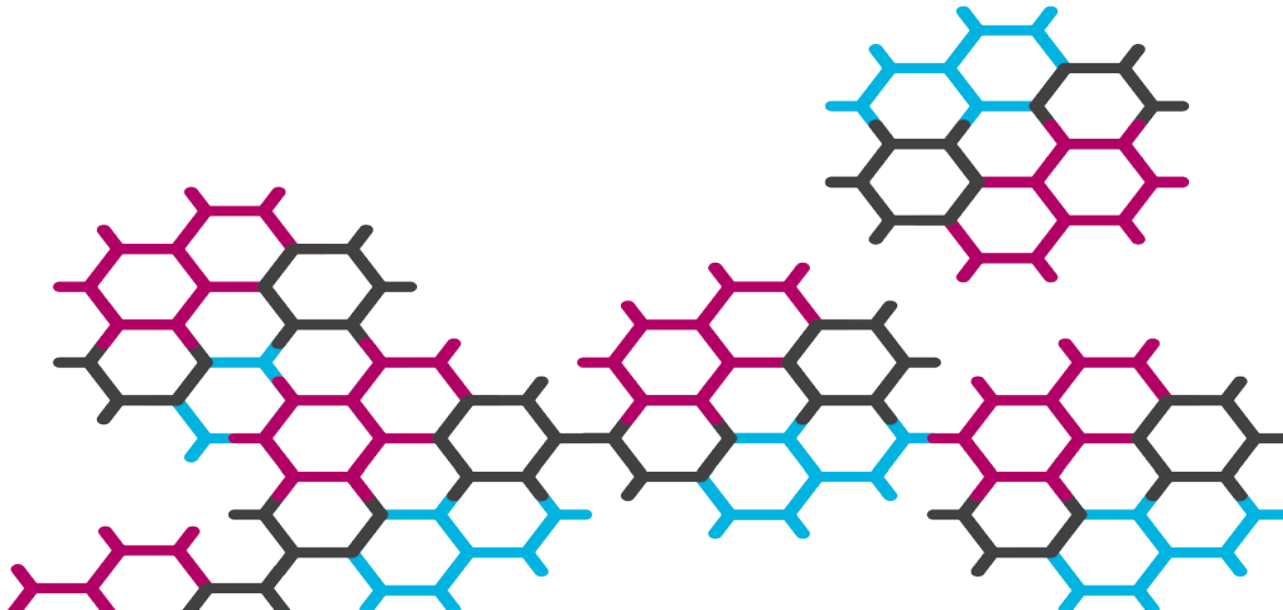
History of dissolution and biorelevant media

- Adult FaSSIF introduced in 1998
- Adult FeSSIF introduced in 2008

- Details about paediatric FaSSIF/FeSSIF first muted in 2014…



Current paediatric simulated intestinal fluids….

Table 4.4 Pediatric Fasted-State Simulated Gastric Fluids (P-FaSSGF)

Component	Pn-FaSSGF[a]	Pi-FaSSGF[b]
Sodium Taurocholate (uM)	20	60
Lecithin (uM)	5	15
Pepsin (mg/mL)	0.015	0.025
Sodium Chloride (mM)	34.2	34.2
HCl qs	pH 1.6	pH 1.6
pH	1.6	1.6
Osmolarity (mOsm/kg)	120.7	120.7
Buffering Capacity (mEq/L/ ΔpH)	-	-

a - Pn-FaSSGF – pediatric fasted-state gastric media representative of neonates (0-28 days)

b - Pi-FaSSGF – pediatric fasted-state gastric media representative of infants (1-12 months)

Table 4.6 Pediatric Fed-State Simulated Gastric Fluids (P-FeSSGF)

Component	Pnc-FeSSGF[a]	Pns-FeSSGF[b]
Sodium Chloride (mM)	100.35	94.79
Acetic Acid (mM)	7.25	7.25
Sodium Acetate (mM)	64.65	64.65
Milk:buffer	1:1	1:1
HCl/NaOH qs	pH 5.7	pH 5.7
pH	5.7	5.7
Osmolarity (mOsm/kg)	340	240
Buffering Capacity (mEq/L/ ΔpH)	15	15

a - Pnc-FeSSGF – pediatric fed-state gastric media representative of neonates (0-28 days) fed cow's milk-based formula

b - Pns-FeSSGF – pediatric fed-state gastric media representative of neonates (0-28 days) fed soy-based formula

Parameterization of In Silico Oral Disposition Models: Focus on Pediatrics by Anil Maharaj Pharmacy Waterloo, Ontario, Canada, 2017

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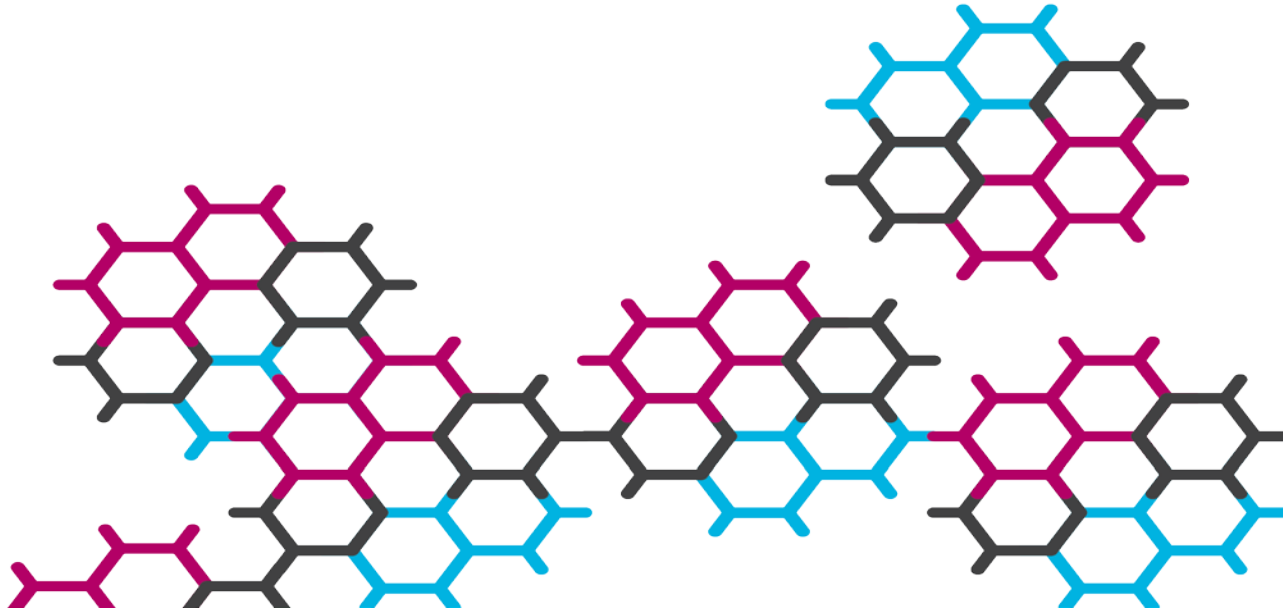
What fluid is present in a child's intestines?

- Volume that children drink with medicines?

- Internal studies (University of Birmingham) show <50mL water is consumed with multiparticulate or tablet formulations in children aged 4-12 years.



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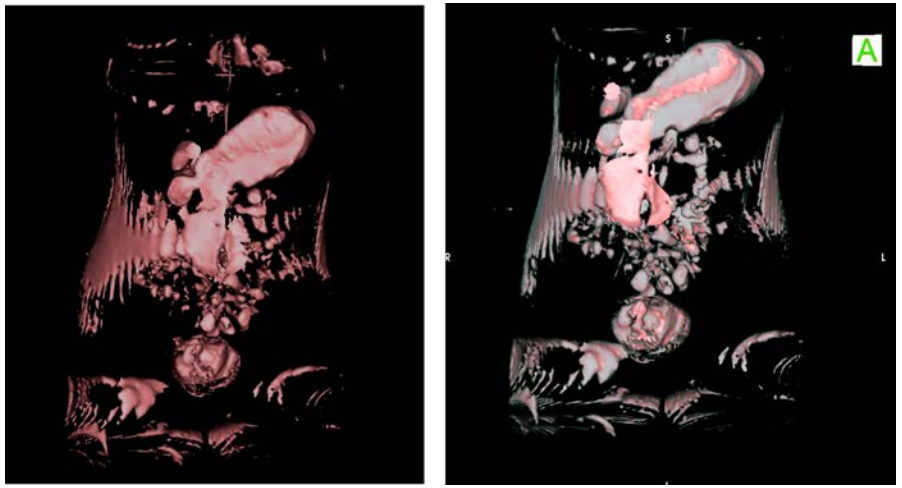
Paediatric intestinal volumes



molecular pharmaceutics

Article

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pubs.acs.org/molecularpharmaceutics

Magnetic Resonance Imaging Quantification of Gastrointestinal Liquid Volumes and Distribution in the Gastrointestinal Tract of Children

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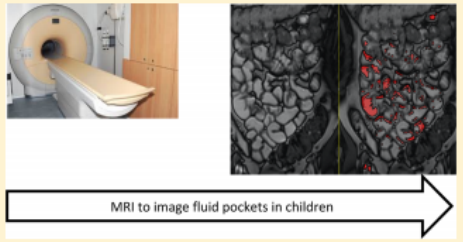
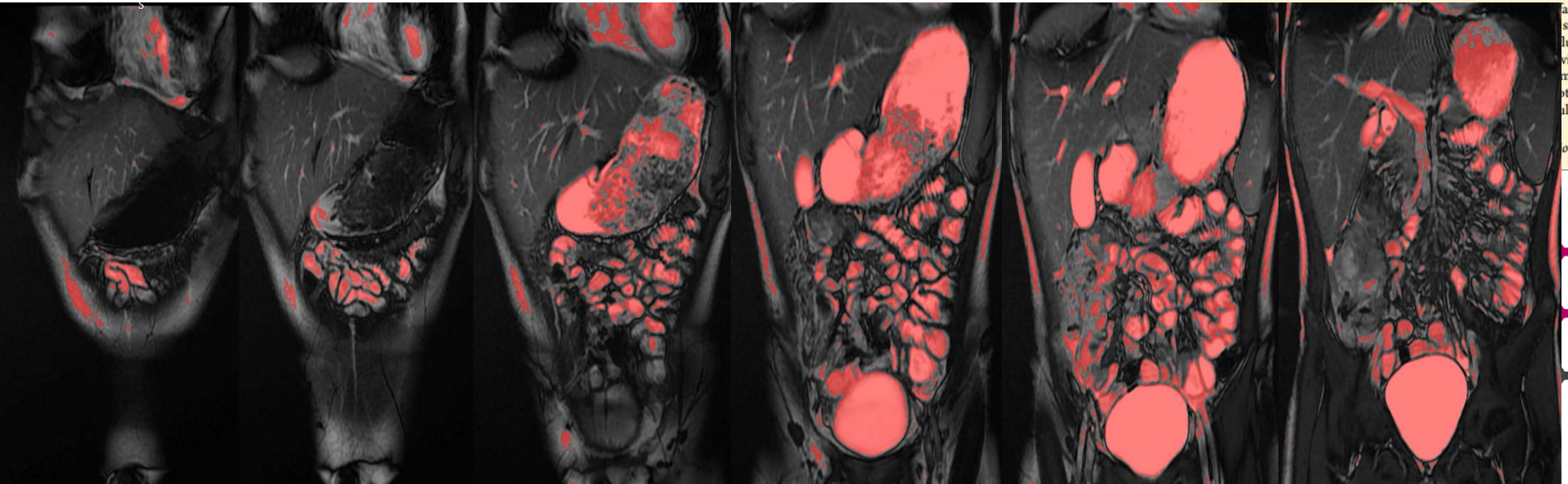
Supporting Information

ABSTRACT: The volume and localization of fluid in the paediatric gastrointestinal tract is crucial to the design of in vitro and in silico models that predict the absorption of oral drugs administered to children. Previous studies have used magnetic resonance imaging (MRI) to quantify fluid volumes and localization in the intestines of adults; this study is the first to undertake similar analysis of pediatric participants. This study quantified the amount and distribution of fluid in fasted and fluid-fed children using MRI data captured during the routine clinical assessment. Data from 32 fasted children (aged 0−16 years) and 23 fluid-fed children (aged 8−16 years) were evaluated. The gastric volume ranged from 0 to 9 mL in the fasted and 19−423 mL in the fluid-fed state. The

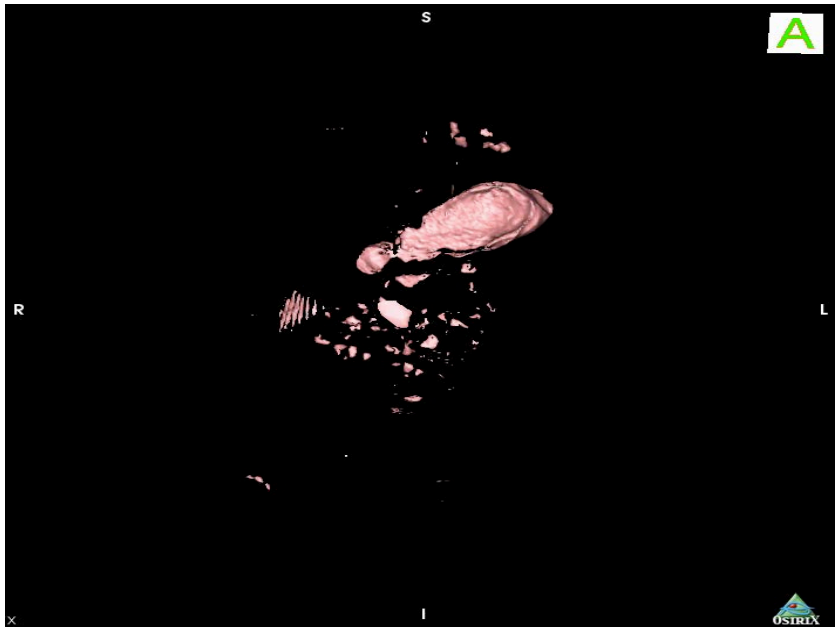


asted and 6−91 mL in the fluid-fed state with an average number of significant differences in gastric volumes and the number of fluid luid-fed children ($p < 0.05$). Both the number and the volume of viously reported in adults. This study is the first to report intestinal mation to achieve the design of biorelevant in vitro models and real th fluid-fed and fasted children show the extremes of fluid volumes l to understand the variability associated with drug absorption in

orelevant dissolution



Video of fluid location



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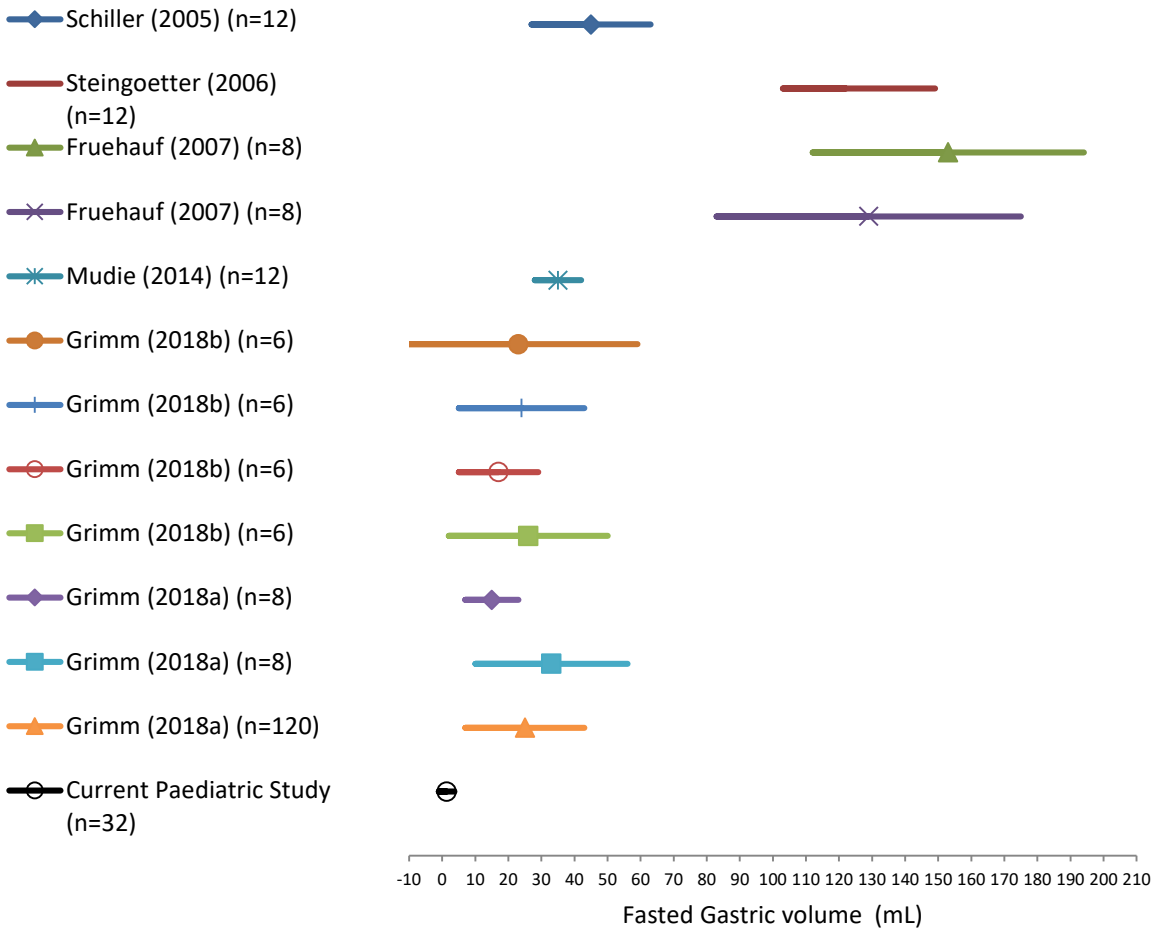
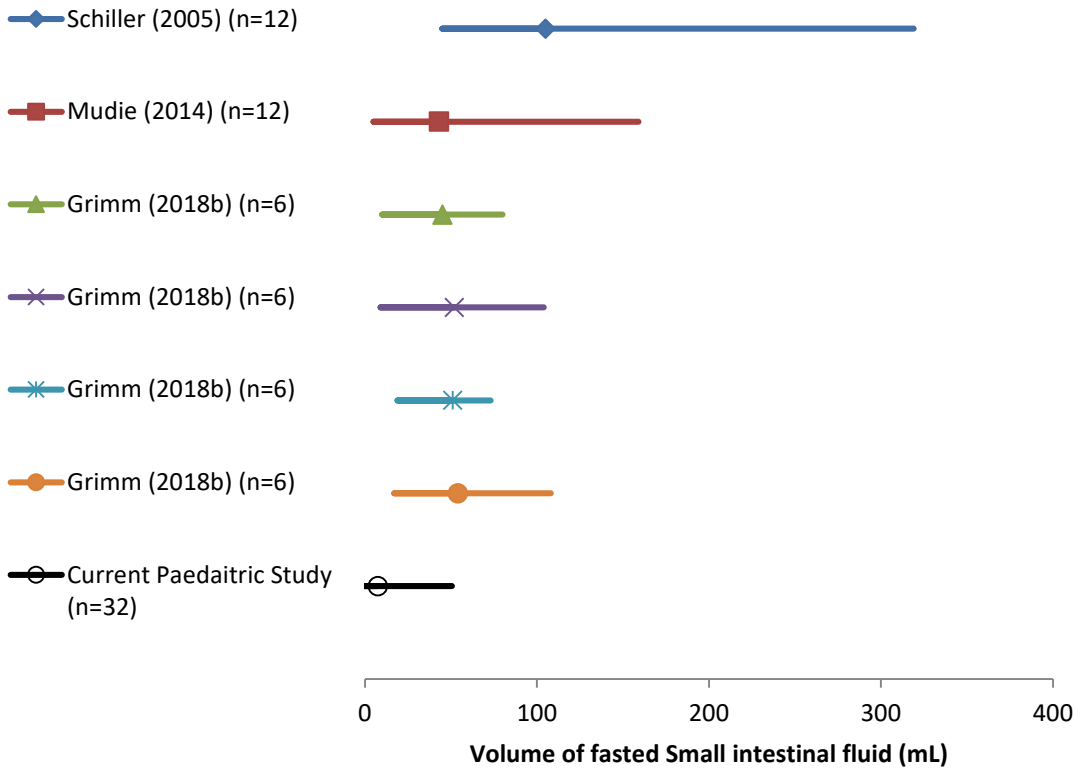
Volumes present





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Simple modelling on impact of fluid present

- **The impact of using relevant luminal fluid volumes on a PBPK model of Ritonavir absorption in children**

	Duodenum	Jejunum I	Jejujum II	Ileum I	Ileum II	Ileum III	Ileum IV
Default **FASTED**	34.4	21.2	21.1	12.6	12.6	12.6	12.6
Default **FED**	34.4	21.2	21.1	12.6	12.6	12.6	12.6
New Data **FASTED**	34.4	43	43	3.5	3.5	3.5	3.5
New Data **FED**	34.4	46.5	46.5	1.7	1.7	1.7	1.7

Table 1: Parameters used for the default Simcyp paediatric model and for our study using relevant intestinal volumes.

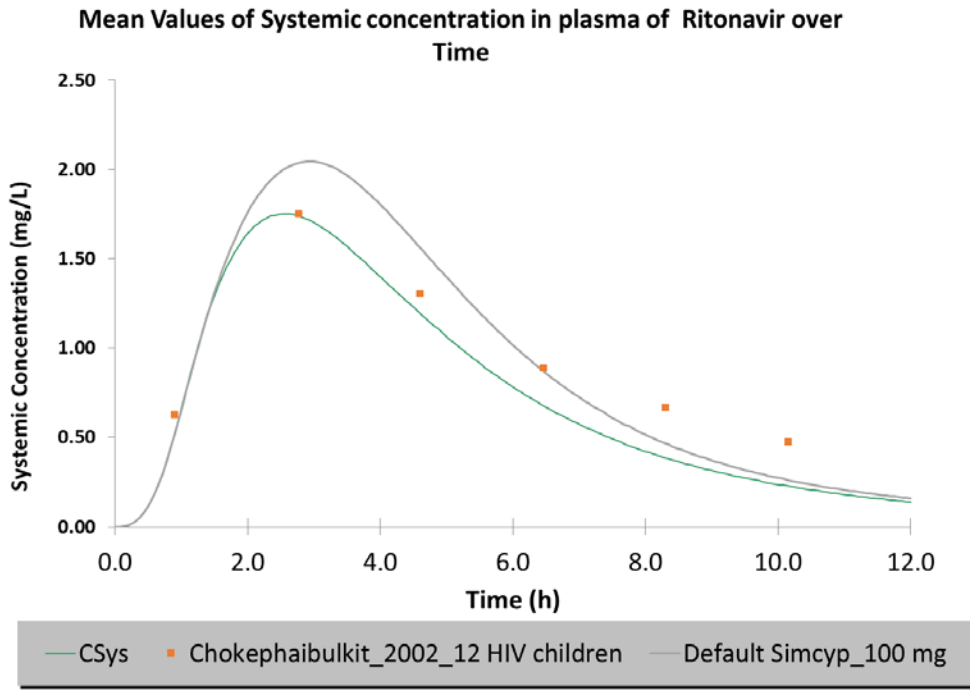

Figure 2: Model Verification using data from HIV infected children. Dose 100 mg soft gel capsules twice a day. The data points show the observed data and the green line the predicted concentration using the new GI volumes [CSys: Systemic Concentration].

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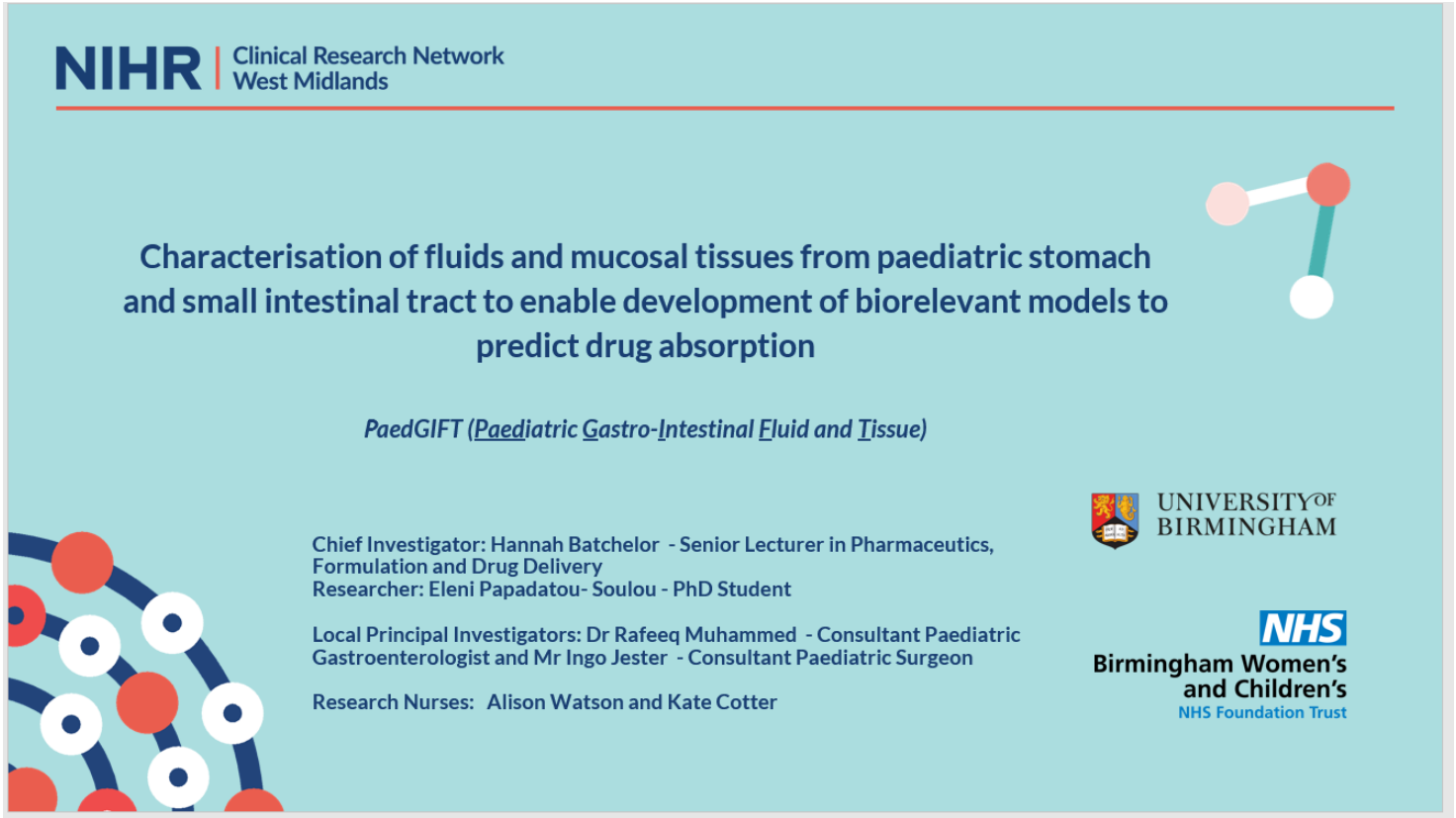
Fluid composition

- We have an existing project that seeks to characterise the paediatric intestine
- We can use this data to better understand key inputs for accurate modelling and simulation.



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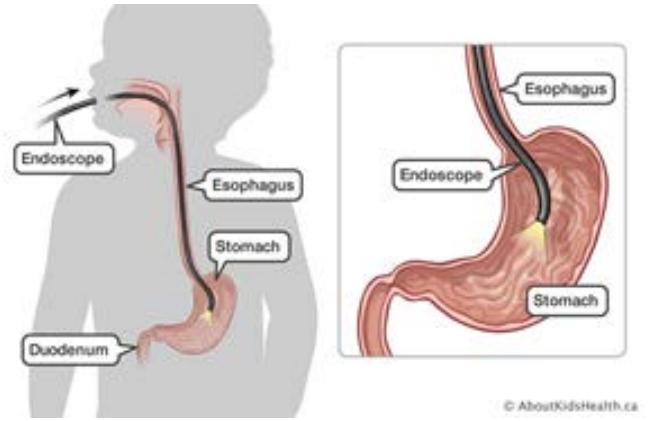
How do we get fluids from stomachs and small intestines from children??

When children have an endoscopy we asked to collect the spare fluid

We can then analyse this in the laboratory

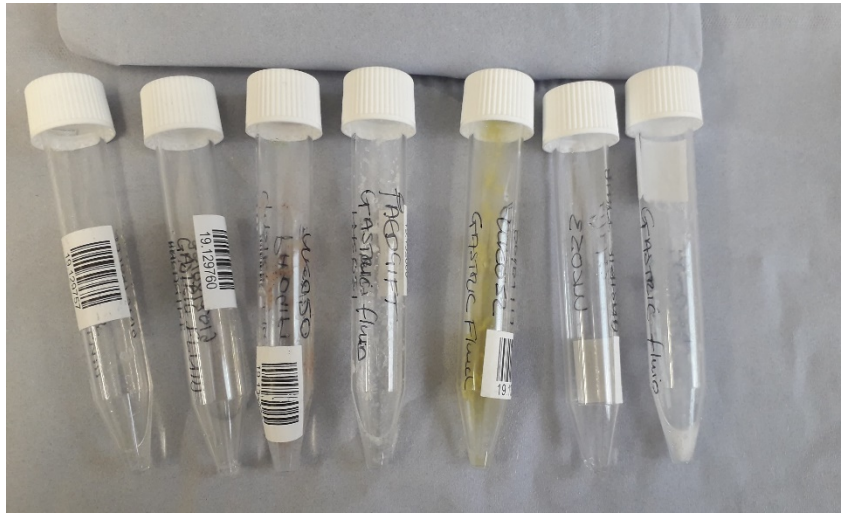


Also requesting enterostomy tissues – larger tissue samples

Paediatric GI samples collected to date (since April 2019)

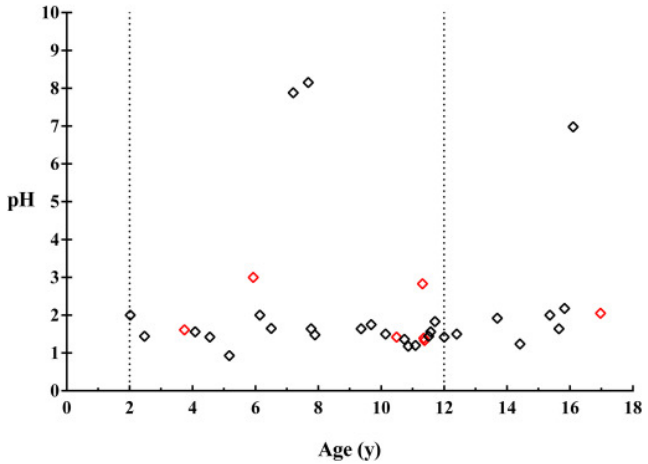
Age groups				Recruitment per Group		
Neonate: 0 -31 days					0	
Infant: >31 days - day before 2nd birthday					2	
Young child: 2 - day before 6th birthday					7	
Child: 6 - day before 12th birthday					19	
Adolescent: 12 - day before 16th birthday					21	

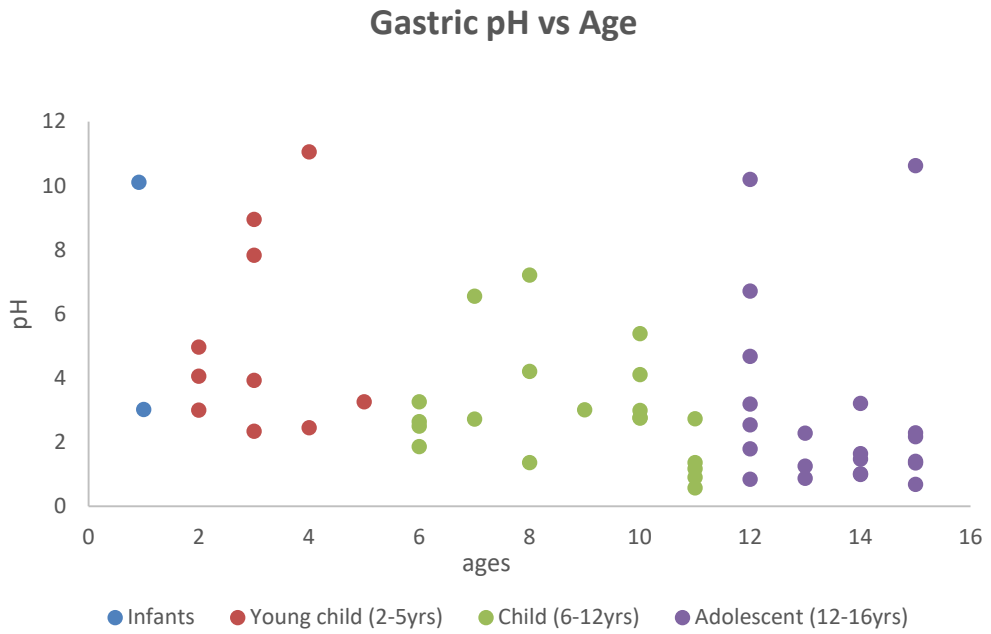
- Gastric Fluid: 50
- Duodenal Fluid: 39
- Duodenal Biopsy: 34

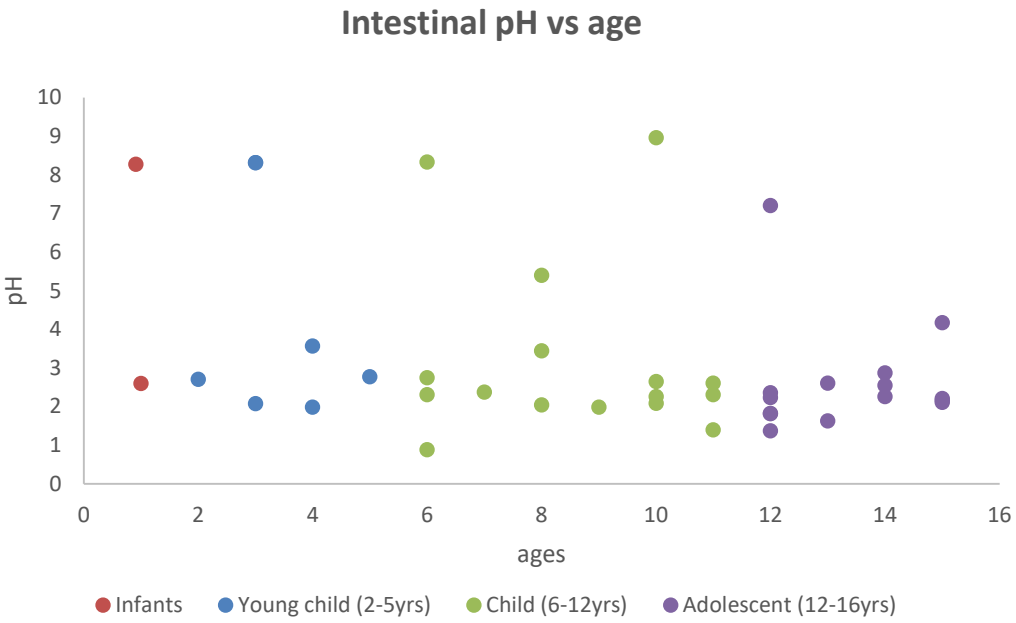


Preliminary data: pH

	Gastric ph	Instestinal ph
max	10.6	8,97
mean	3,23	3,13
min	0,57	1,38



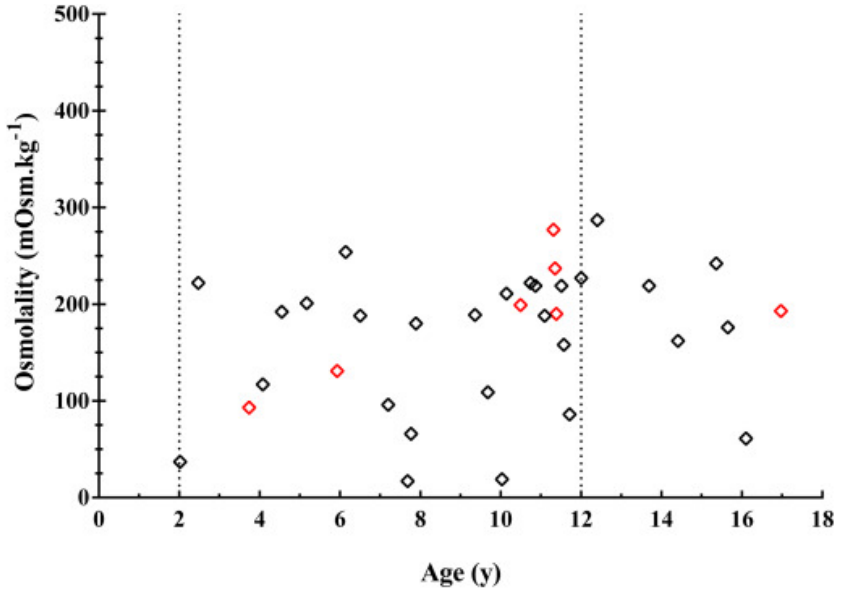


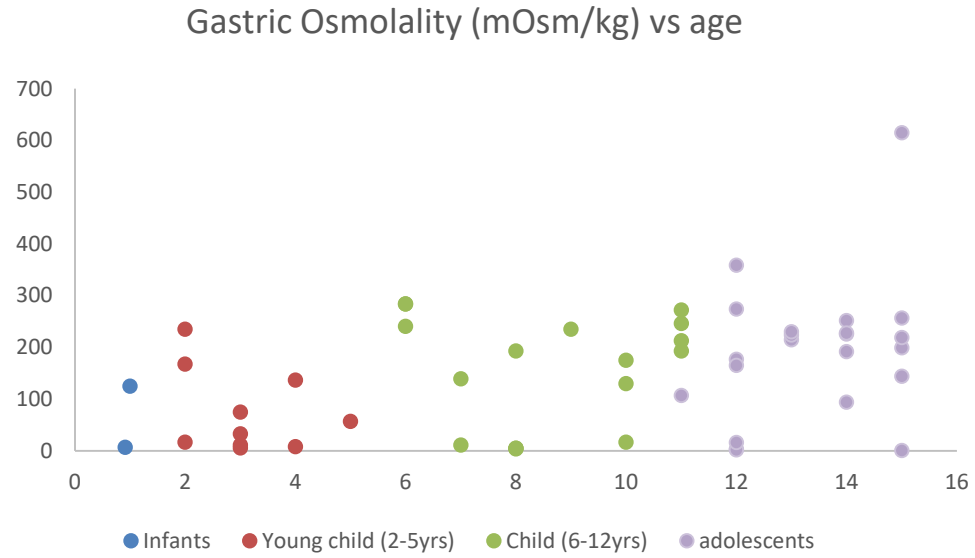


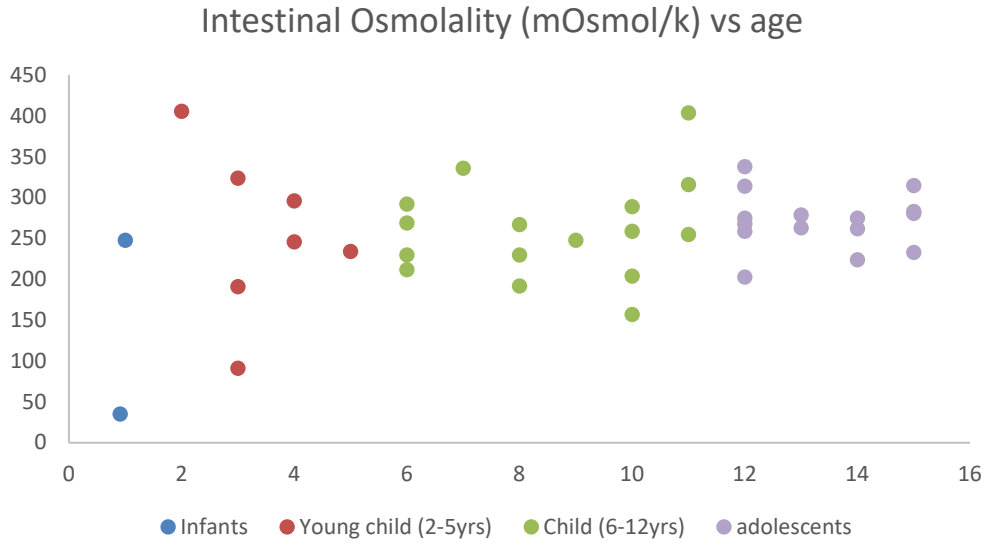
Jens Van Den Abeele, Maissa Rayyan, Ilse Hoffman, Els Van de Vijver, Wei Zhu, Patrick Augustijns. Gastric fluid composition in a paediatric population: Age-dependent changes relevant for gastrointestinal drug disposition. European Journal of Pharmaceutical Sciences, Volume 123, 2018, Pages 301-311,

Preliminary data: osmolality

	Gastric Osmolality	Intestinal Osmolality
max	615	631
mean	157	271
min	1	91







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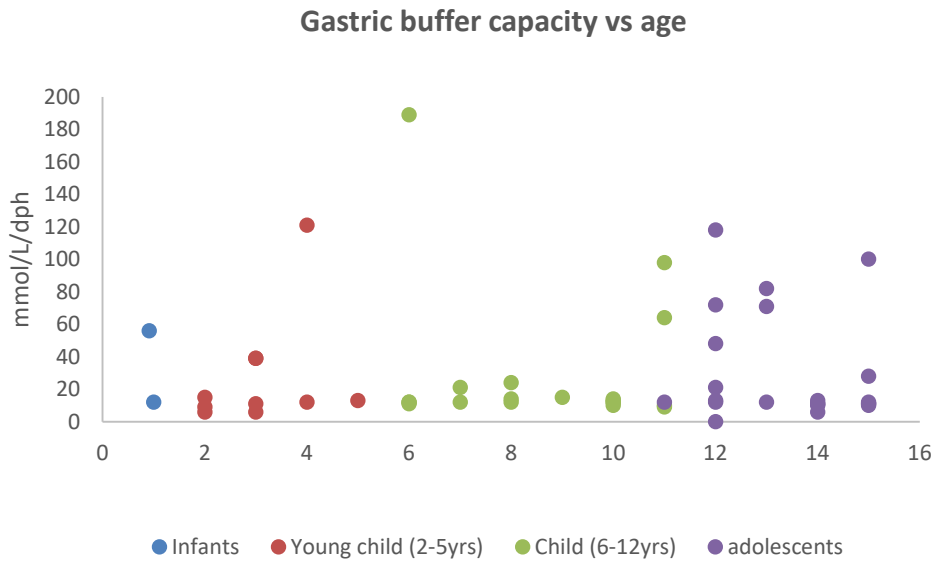
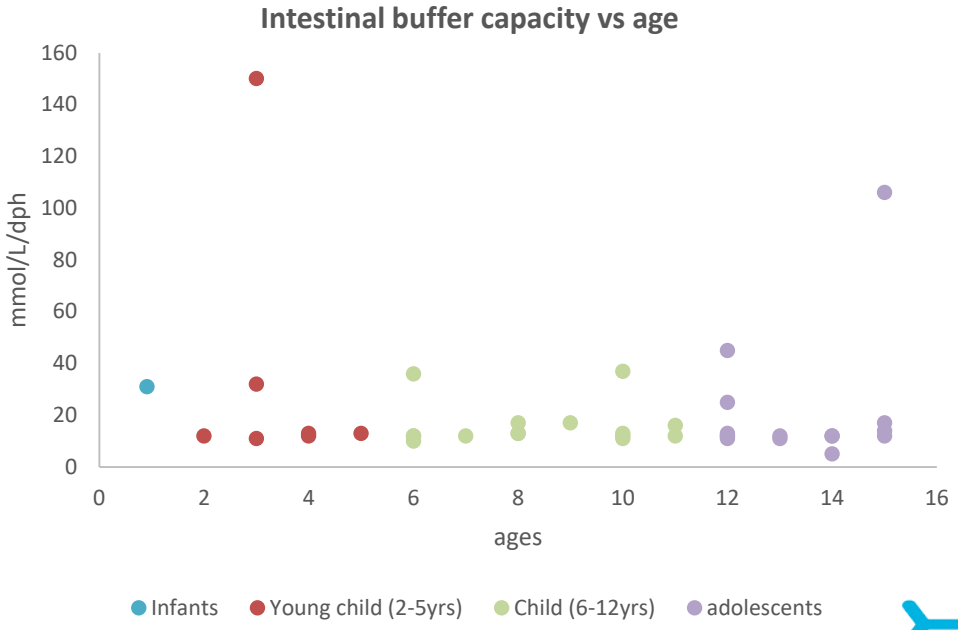
Buffer capacity





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Bile salt quantification

- Method development is ongoing
- Preliminary data with HPLC ELS was not sufficiently sensitive

- HPLC with ELS detector

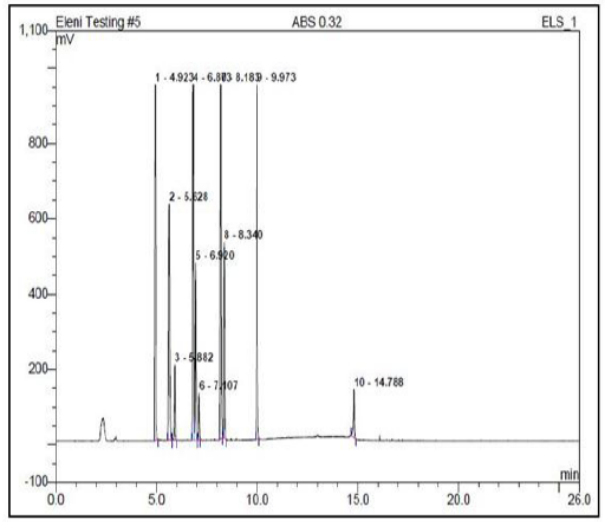

Figure 1. Separation of bile salts mixture at 0.32 mM

Column: C18

Detector: ELS

Mobile Phase: A: Water + 0.05% TFA and B: MeCN+ 0.05% TFA

Method:

Eluent B started running at time 0 at 30%. At t=7 min, eluent B changed to 100% until t_1=11 min. When t_2=11.100 min, eluent B came back to 70%. After 2 minutes, eluent A was equal to eluent B=50%. At t_3=16 min, eluent B decreased and reached 30%. This lasted until the completion of the method at t_{total}= 26 minutes. The column temperature was 45 degrees (for better separation of the bile salts)

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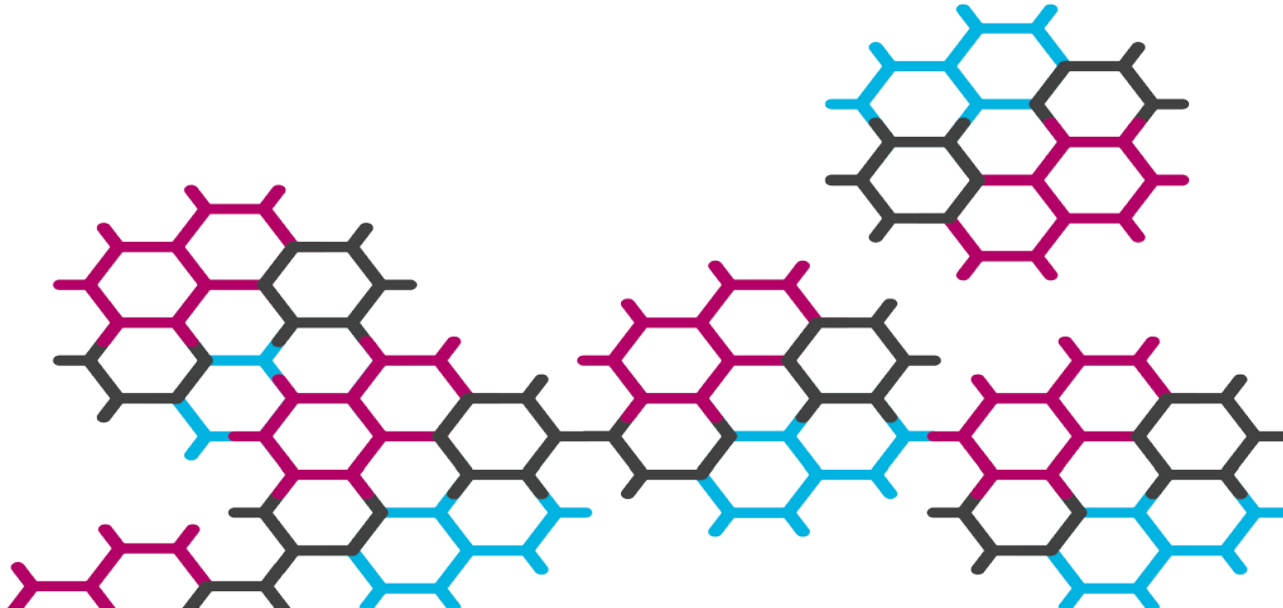
Manufacture of simulated paediatric intestinal fluid

- Also looking at microstructure and colloid self-assembly for a range of poorly soluble drugs
  - Impact of bile salt composition
  - Impact of addition of lecithin and oleic acid/sodium oleate



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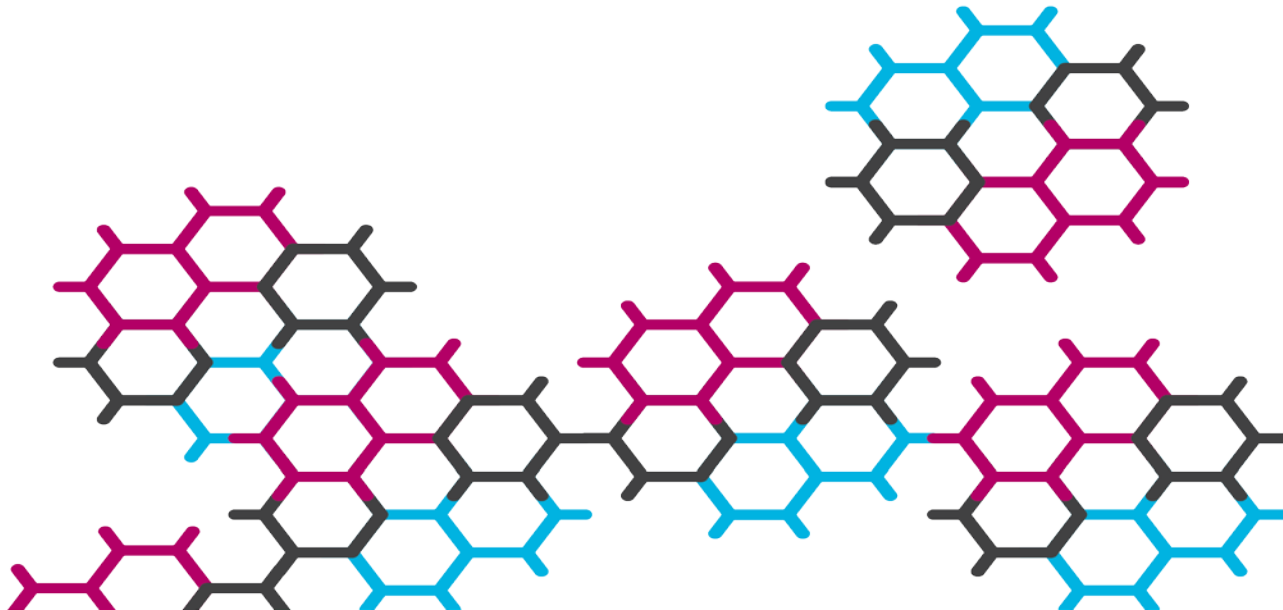
Intestinal biopsy/tissue samples

- Ongoing work to quantify the expression of transporters and enzymes
- Provide age-related data on expression in biopsies available



Preliminary associated work

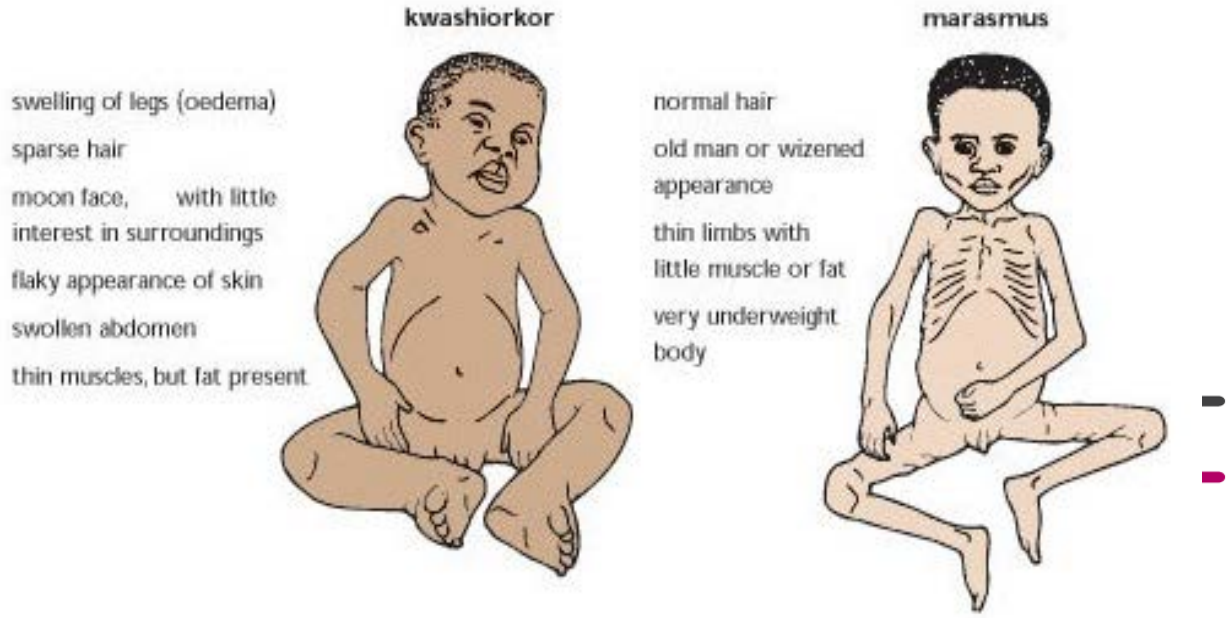
- Malnutrition occurs due to deficiencies, excesses or imbalances in intake of proteins, calories and other essential micronutrients
- It is a major health problem in infants and older children worldwide.
- WHO- In 2018, globally there were 149 million children under 5 years of age who were stunted, 49 million wasted

ELSEVIER
European Journal of Pharmaceutics and Biopharmaceutics
Volume 137, April 2019, Pages 9-22

Review article

A review of GI conditions critical to oral drug absorption in malnourished children

Lisa Freerks [a], Eleni Papadatou Soulou [b], Hannah Batchelor [b], Sandra Klein [a]



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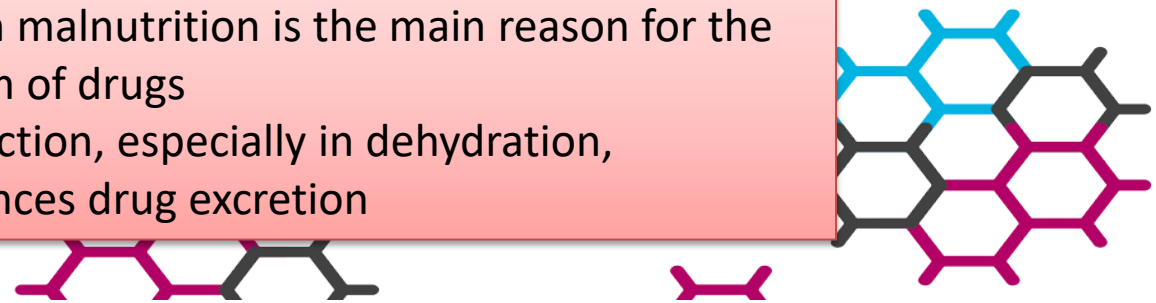
Consequences of malnutrition on pharmacokinetics

Absorption
- alteration of nutrient /drugs transport
- mucosal and villous atrophy
- modification of permeability of the intestinal mucosa
- altered activity of small-intestine enzymes

Distribution
- Changes in body's fat/lean mass ratio may also lead to an alteration of drug distribution,
- ↓ protein-binding capacity. Reduced plasma protein, mainly albumin
- ↑ in the free drug concentration – leads to drug toxicity

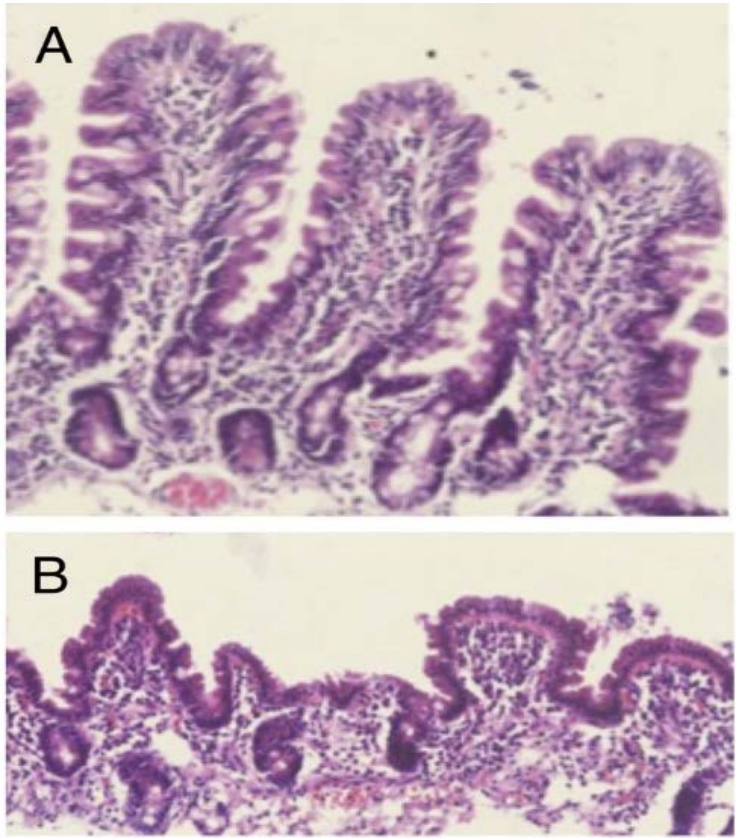
Biotransformation and excretion
- liver dysfunction in malnutrition is the main reason for the altered metabolism of drugs
- impaired renal function, especially in dehydration, significantly influences drug excretion



Protein deficiency -↓ mixed function oxidase, ↑ Glucuronyl transferase, ↓ Glucuronyl, ↓ Glutathione-S-transferase
Carbohydrate- ↓ mixed function oxidase, ↑ Glucuronyl transferase, Glucuronyl-No change, ↓ Glutathione-S-transferase

(Krishnaswamy 1987)

- Many studies (Table 2) have shown GI morphological changes such as villous atrophy (reduced villous height, number), thinned mucosa, increased intestinal permeability, loss of tight junction proteins and increased pore size leading to delayed absorption of drugs or plasma concentrations resulting in therapeutic failure.



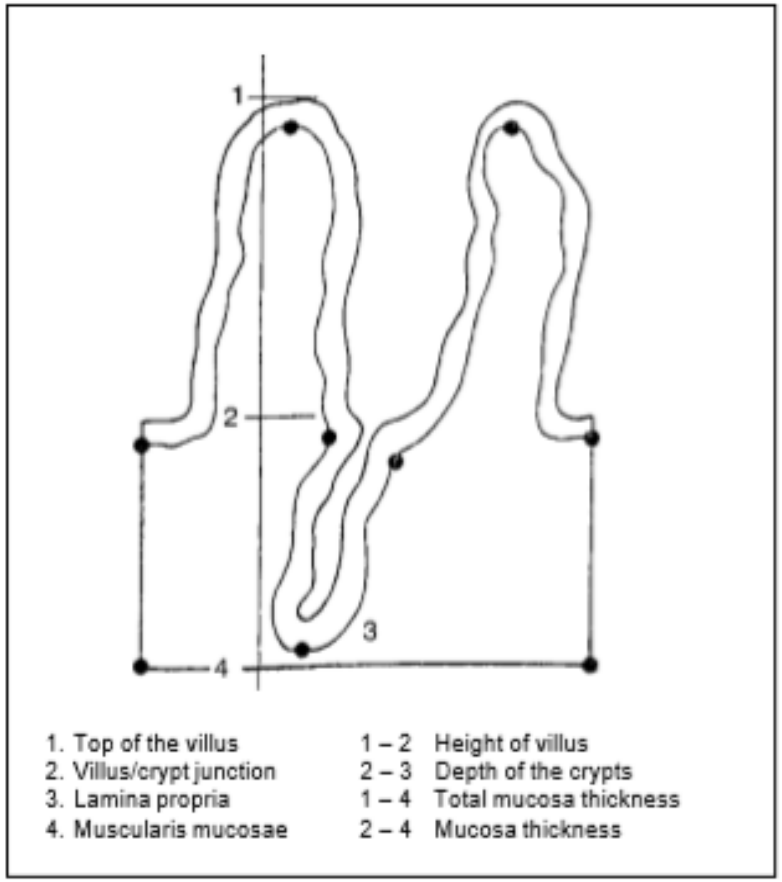
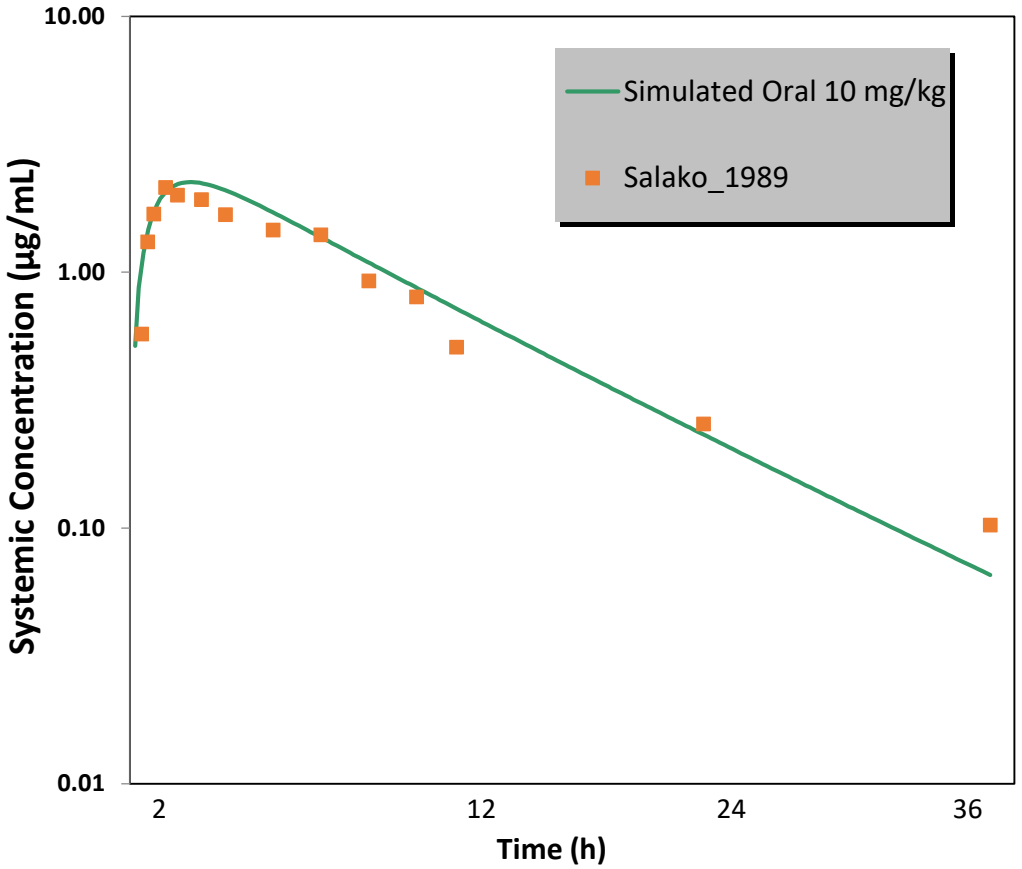
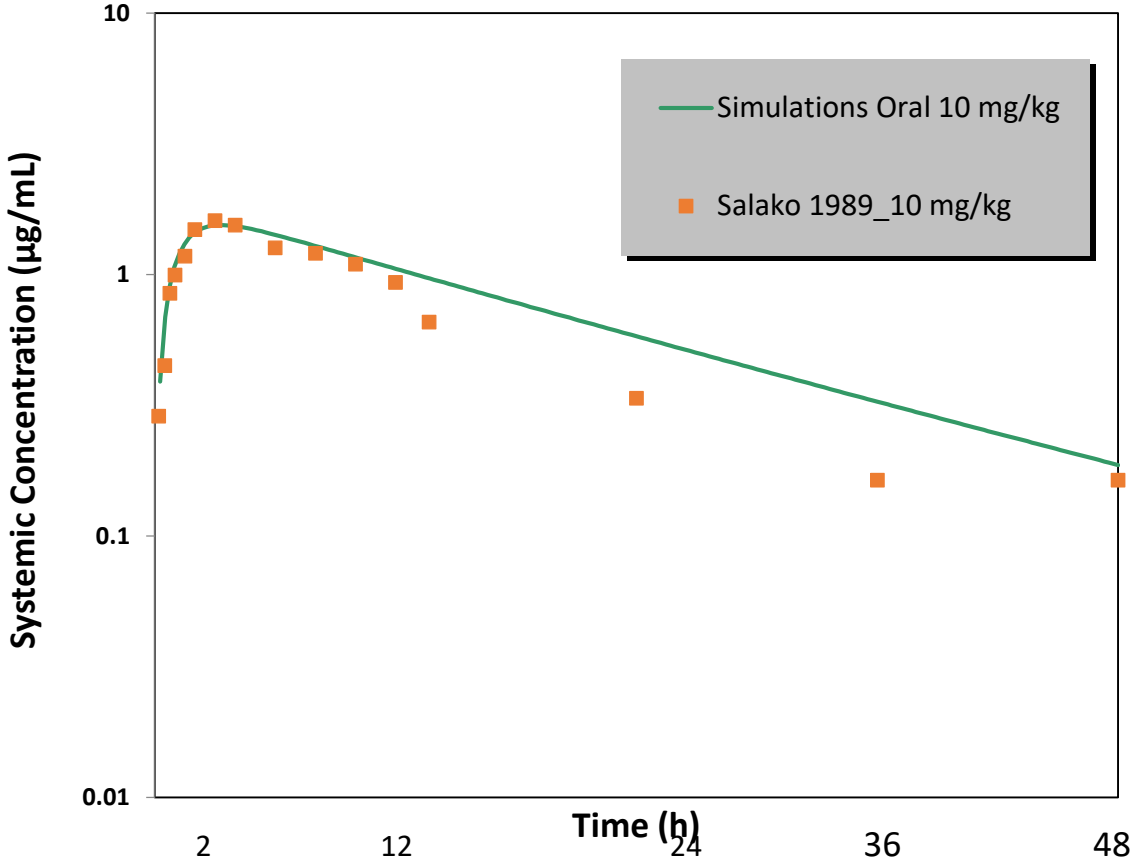


Fig.1: Histological sections (Owino et al., 2016) from distal duodenal biopsy specimens (A) Healthy children; normal mucosa with **long villi and short crypts depth (3:1 height to depth ratio)** (B) Malnourished children; **villus shortening and reduction in villus height:crypt depth ratio (>1:1)** (C) Characteristics small intestinal mucosa at 100 times magnification (Pires et al., 2002)

Mean Values of Systemic concentration in plasma of Quinine HCL over Time in Healthy children (n=7)



Mean Values of Systemic concentration in plasma of Quinine HCL over Time in Kwashiorkar children (n=6)

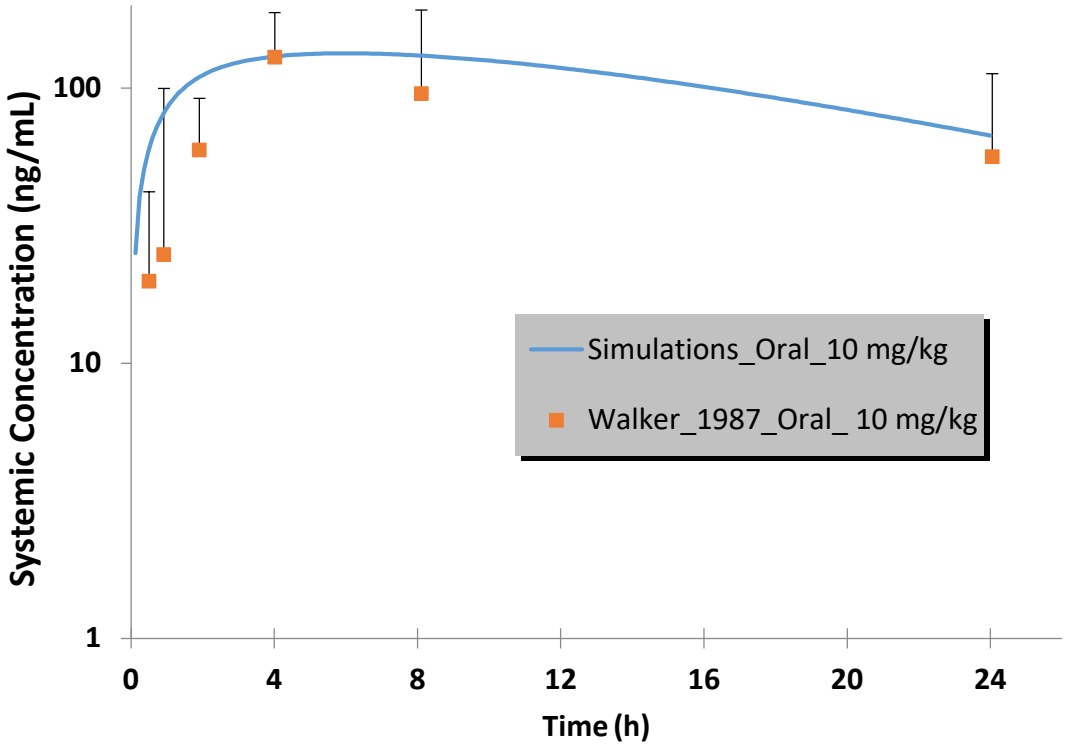


Summary Statistics			Mean		
	From (h)	To (h)	TMax (h)	CMax (µg/mL)	AUC (µg/mL.h)
CPlasma (µg/mL) - Kwas	0.00	48.00	3.37	1.55	33.09
CPlasma (µg/mL) - Healthy	0.00	36.00	2.72	2.20	26.02

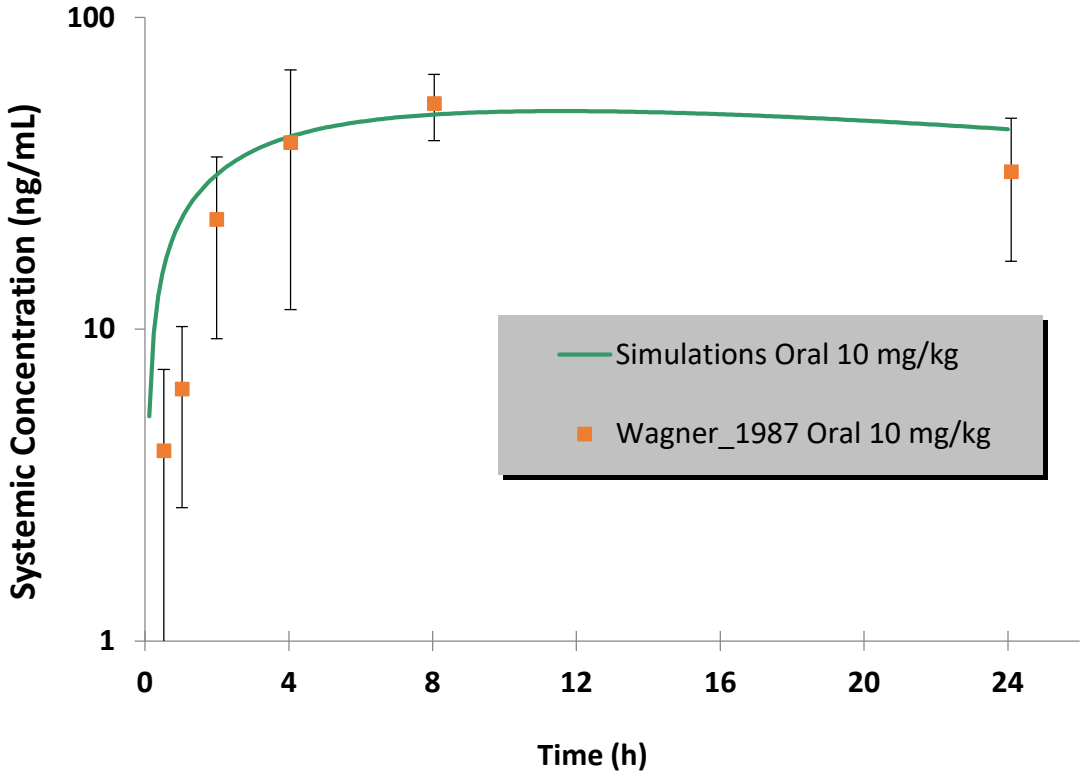
Age- 1-3 years,
n=6-7
Oral, fasted,
single dose 10
mg/kg

1.26 FOLD INCREASE IN AUC PROFILE IN KWASHIORKAR CHILDREN

Mean Values of Systemic concentration in plasma of Chloroquine in Healthy Children (n =6)



Mean Values of Systemic concentration in plasma of Chloroquine in Malnourished (Kwashiorkar) children (n =5)

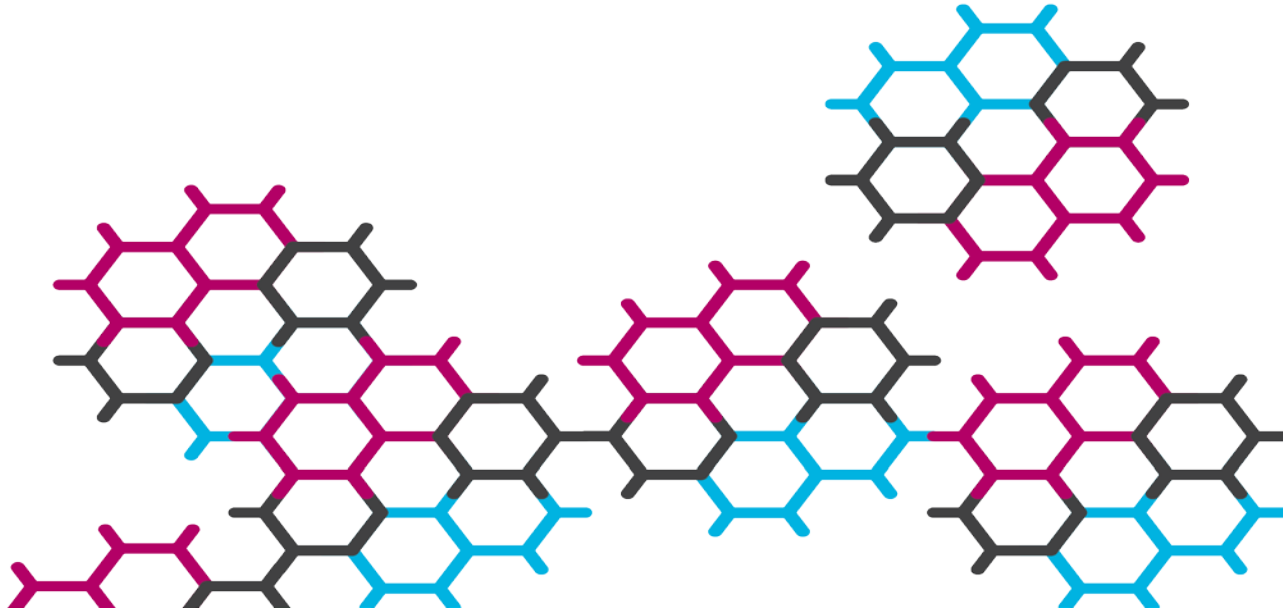


Summary Statistics			Mean		
	From (h)	To (h)	TMax (h)	CMax (ng/mL)	AUC (ng/mL.h)
CPlasma (ng/mL)- Healthy	0.00	24.00	6.00	133.83	2542.27
CPlasma (ng/mL)-Kwas	0.00	24.00	11.65	50.11	1069.38

2.4 & 2.7 FOLD DECREASE IN AUC & Cmax of CQ IN KWASHIORKAR CHILDREN

Summary

- There is much to be learned about the composition of fluids in the GI tract of children
- Understanding absorption is complex
- The lack of available clinical data limits evaluation of new *in vitro* and *in silico* models.



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Acknowledgements

Eleni Papadatou-Soulou
Gopal Pawar
Jan Goelen

Thank-you

Questions

Oral Drug Absorption in Pediatrics: What we know and where are we going?

Building a pediatric absorption model

Pediatric drug absorption - Evidence from the literature

Slower absorption in premature neonates but ↑ bioavailability Paracetamol
Anderson et al 2002

Slower absorption e.g. Oral Ciprofloxacin
Pentola et al 1992

↓ Bioavailability due to ↑ gastric pH e.g. Oral ketoconazole
van den Anker et al 1993

Bioavailability same but slower absorption e.g. Oral digoxin, phenobaritone sulphonamides
Heimann 1980

No Change in F or Ka e.g. Pleconaril 1993
Kearns et al 1999, 2000

↓ rate conversion pro drug e.g Famciclovir to penciclovir)
Blumer et al 2010

↑↓ Bioavailability due to ↓ 1st pass and ↓ absorption e.g. Oral Zidovudine
Capparelli et al 2003, Boucher et al 1993

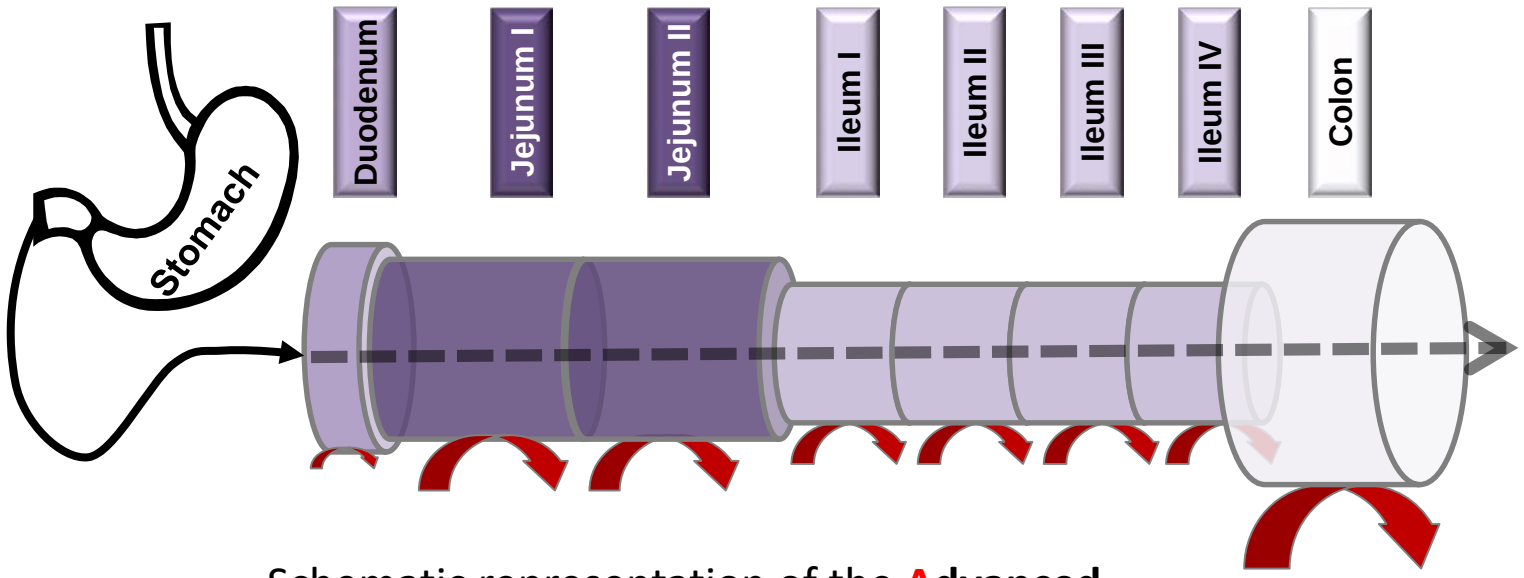
Ka for acetaminophen / theophylline / indomethacin reaches adult levels 1 week after birth
Somani et al 2015

↑ Bioavailability due to ↓ 1st pass e.g. Oral midazolam
de Wildt et al 2002

CERTARA

Drug absorption model

Jamei *et al.* 2009, Darwich *et al.* 2010 and Harwood *et al.*, 2013



Schematic representation of the **A**dvanced **D**issolution, **A**bsorption & **M**etabolism (ADAM) model, displaying the mechanistic segmentation of the GI tract into 9 sections with segregated blood flows to each section

Can we parameterize this model for pediatrics?

Pediatric absorption model development

- ☑ Stomach volume
- ☑ **Gastric emptying**
  - ☑ No significant effect of age on mean gastric residence time
  - ☑ Food type effects significant
- ☑ Intestinal length/diameter
  - ☑ ↑ as function of age
- ☑ Transit times
  - ☑ No change with age (Maharaj DMD 2016; 44: 1080)
- ☑ Permeability
- ☑ **pH**
  - ☑ Gastric: ↑ in early postnatal period
- ☑ **Intestinal CYP3A ontogeny**
  - ☑ ↑ in expression and activity with age
- ☑ **Bile production** and composition
- ☑ **Salivary production** and flow
  - ☑ Age related change
- ☑ **Intestinal transporter ontogeny**
  - ☑ Some information on P-gp
  - ☑ Little information on BCRP, MRP2
- ☑ GI tract fluid dynamics

- ❑ Intestinal UGT/other drug-metabolizing enzyme ontogeny
- ❑ Unstirred water layer characteristics
- ❑ and others

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Gastric emptying

- Several review articles state that the ‘Time of gastric emptying is delayed immediately after birth for both full and preterm neonates. It approaches adult values within first 6-8 months of life’

Morselli 1976 → Beneditti and Baltes, 2003 → Kearns et al 2003 → Smits et al 2012

Data collection for meta analysis

- Total number of studies evaluated: 174
- Total number of studies used in analysis: 49
- Total number of individuals the data represents: 1991
- Preterm neonates of 28 weeks gestation through to adults
- Median age (range) in months: 1.47(0.011-744)
- Food types: Aqueous, breast milk, formula, semi-solid, solid
- Other covariates: age, weight, volume, gestational age

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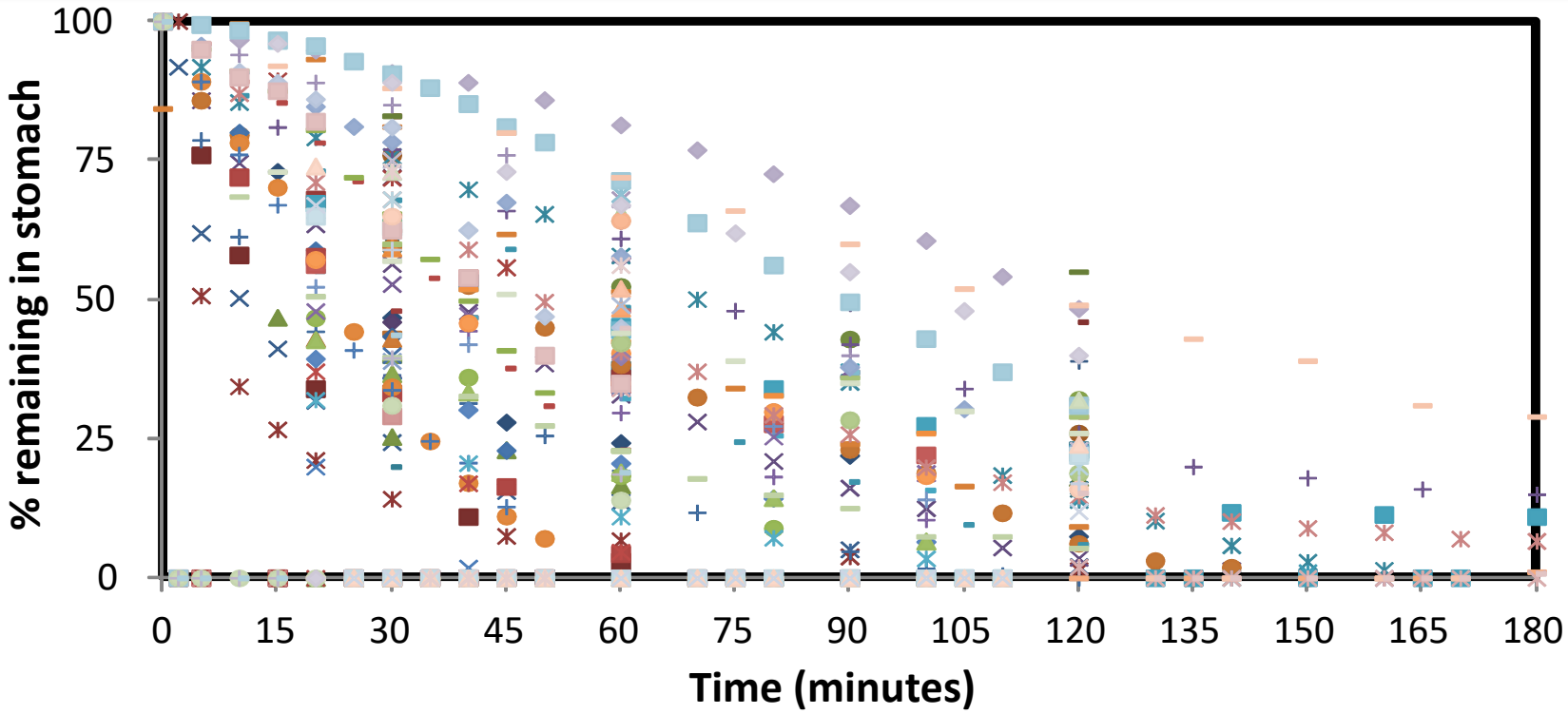
Modelling gastric emptying



$$y_{ij} = (D_i - PR_i) \times e^{-\left(t_{ij}/\gamma_{1i}\right)^{\beta_{1i}}} + PR_i \times e^{-\left(t_{ij}/\gamma_{2i}\right)^{\beta_{2i}}}$$

- Double Weibull function was used to model data
  - Allowed incorporation of biphasic nature of emptying, but makes no assumptions about relative speed of either phase

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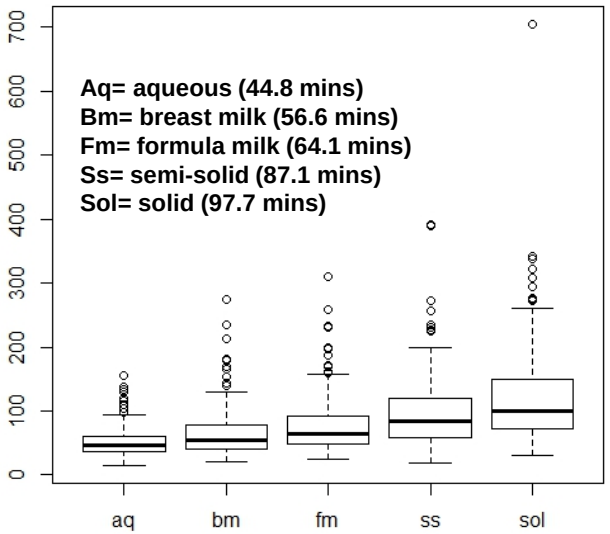
Gastric emptying meta-analysis:

No significant effect by postnatal or gestational age, weight or volume of intake but **Food Type a significant COVARIATE**

Mean gastric residence time (mins)

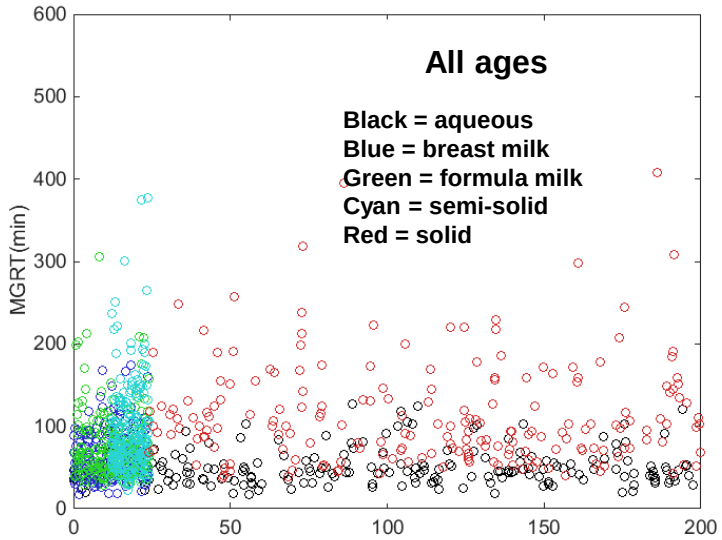


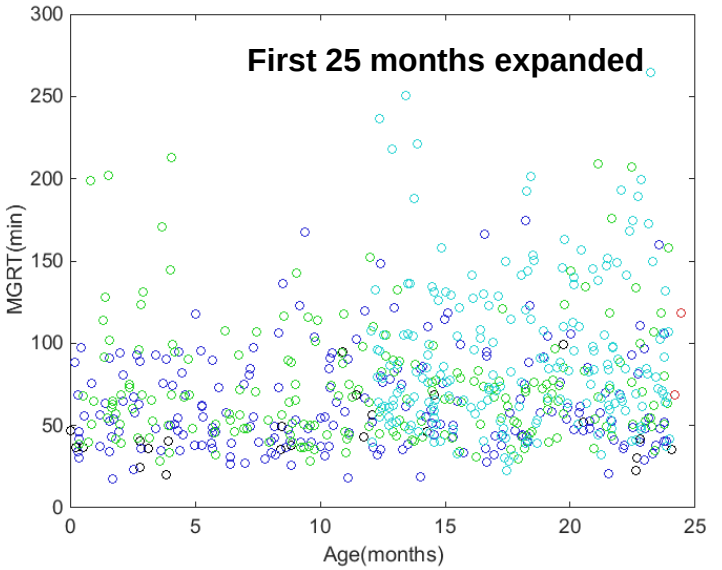
Biopharm Drug Dispos. **2015; 35:245-257**

Does age affect gastric emptying time? A model-based meta-analysis of data from premature neonates through to adults.

Bonner JJ[1], Vajjah P, Abduljalil K, Jamei M, Rostami-Hodjegan A, Tucker GT, Johnson TN.

No discernible relationship between mean gastric residence time and age





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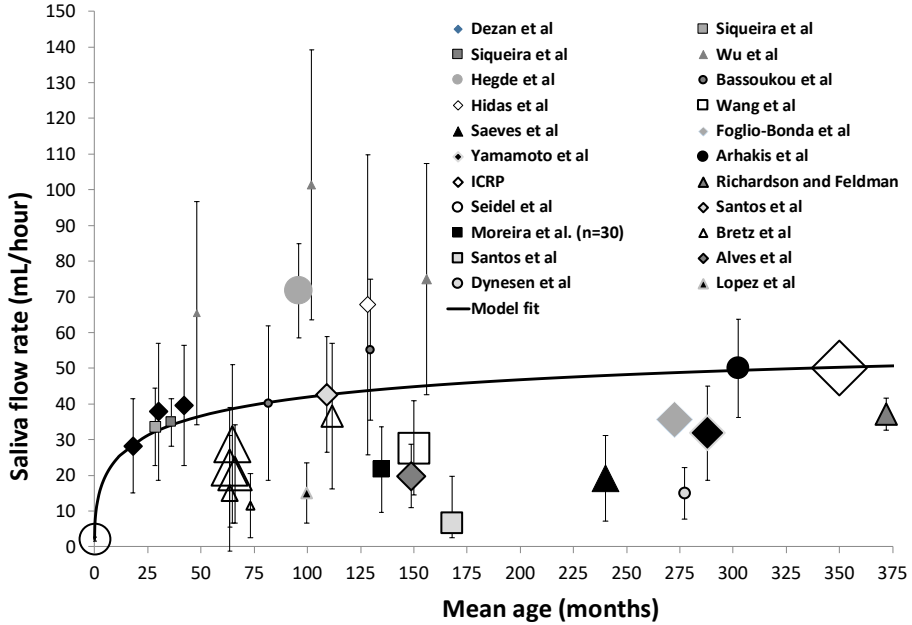
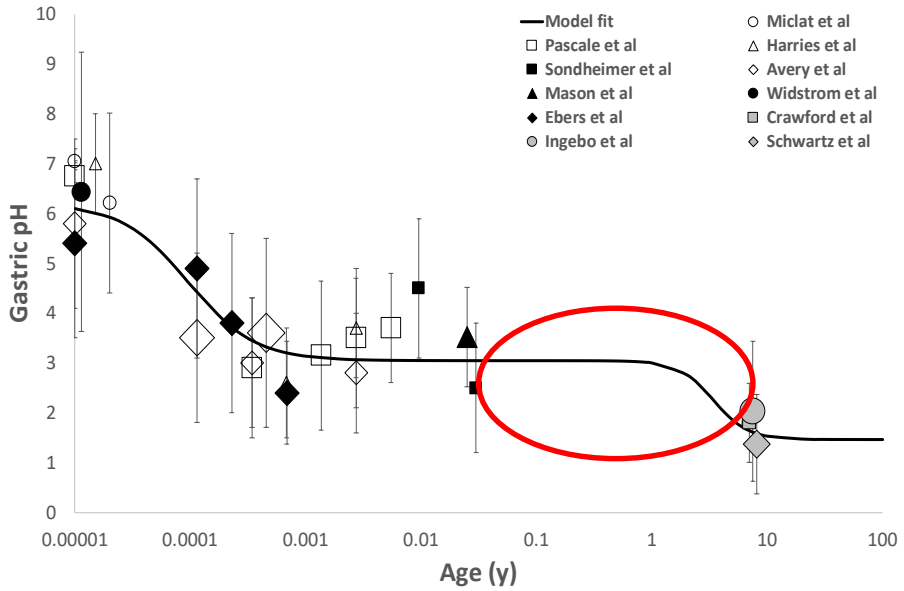
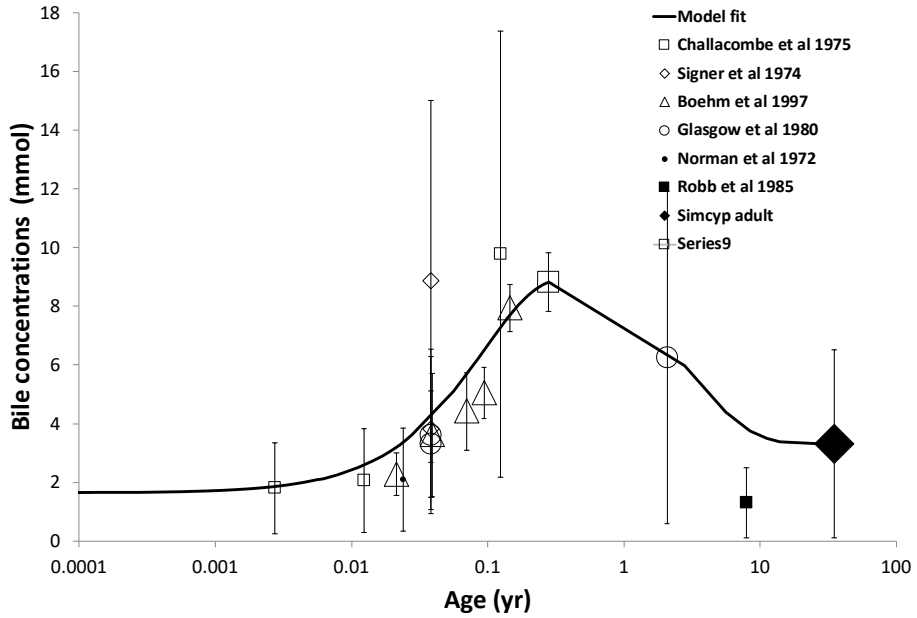
Other age related changes







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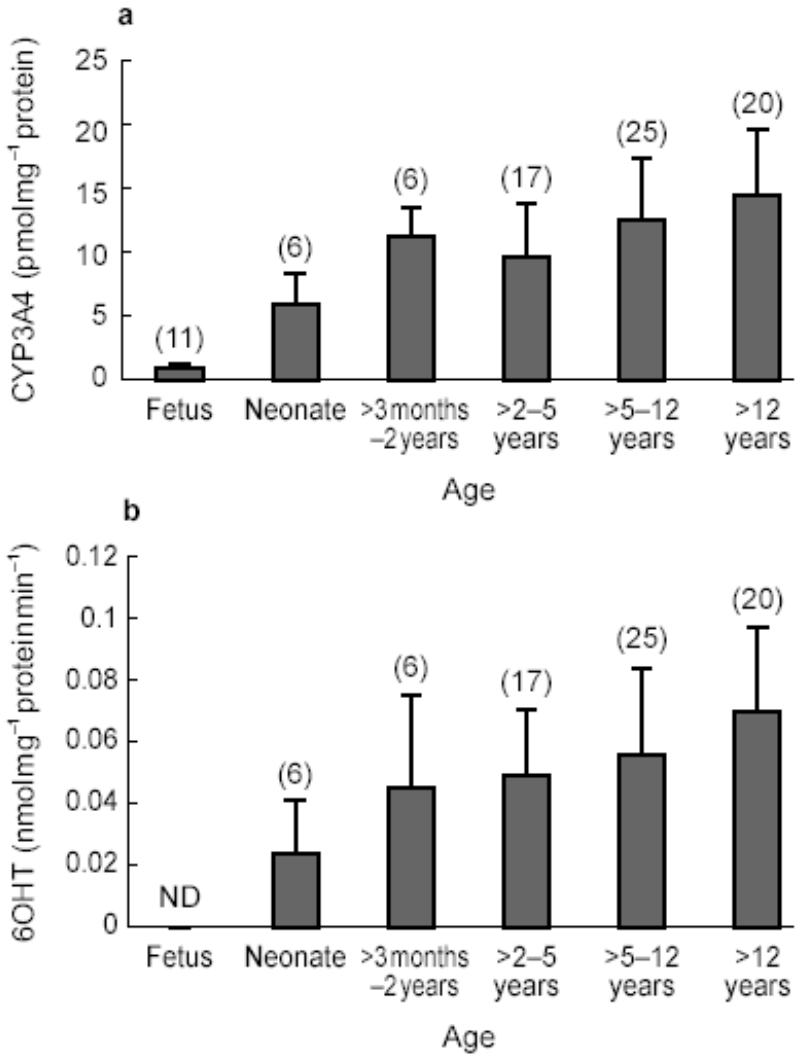
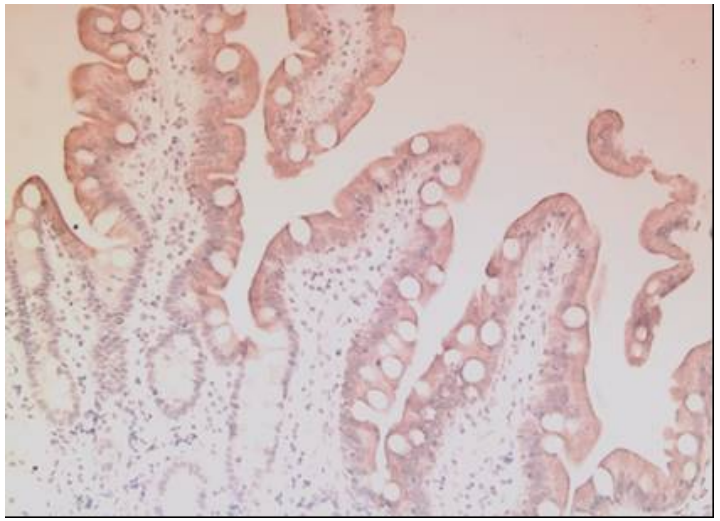
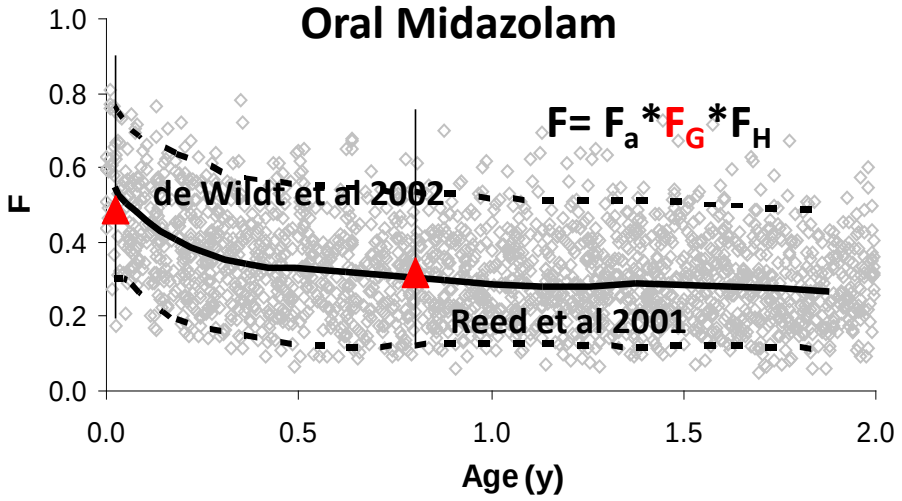
Ontogeny of CYP3A enzymes in the Gut





Johnson *et al* BJCP 2001



$$\text{Expression} = \frac{(1 - F_{birth}) \cdot Age^{n}}{Age_{50}^{n} + Age^{n}} + F_{birth}$$

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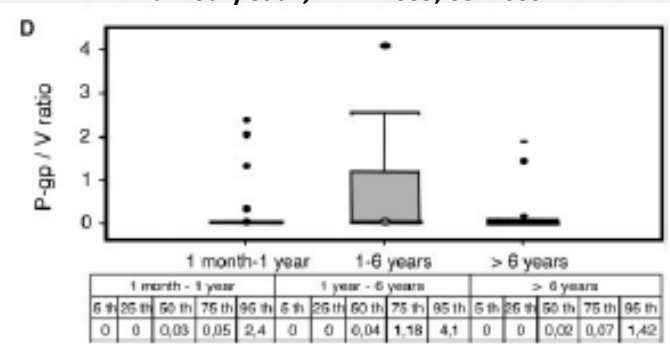
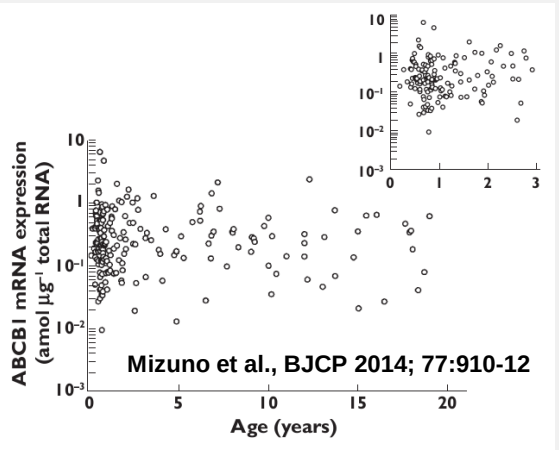
Intestinal transporter ontogeny

P-gp mRNA data

Fakhoury *et al.*, DMD 2005; 33: 1603

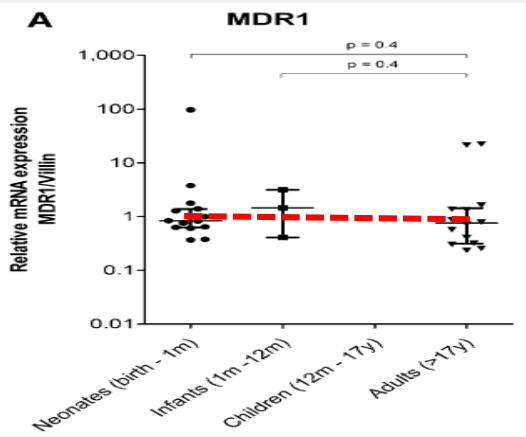


1 month - 1 year					1 year - 6 years					> 6 years				
5 th	25 th	50 th	75 th	95 th	5 th	25 th	50 th	75 th	95 th	5 th	25 th	50 th	75 th	95 th
0	0	0,03	0,05	2,4	0	0	0,04	1,18	4,1	0	0	0,02	0,07	1,42



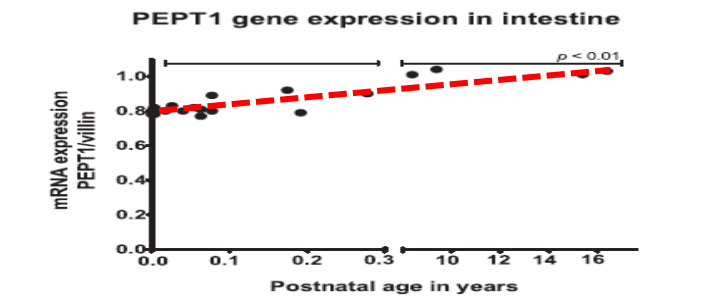
Mizuno et al., BJCP 2014; 77:910-12

Mooij *et al.*, DMD 2014; 42: 1268



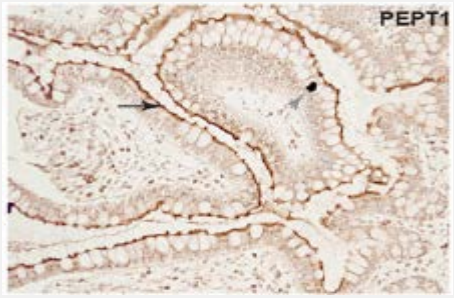
There appears to be no change with intestinal P-gp expression with age

PepT1 mRNA/IHC data



Mooij *et al.*, DMD 2016; 44: 1014

Paediatric



Adolescent

SLC transporters link between mRNA and activity? H^+ (pH) driving force

Application of Paediatric ADAM model (Ketoconazole)

Development and applications of a physiologically-based model of paediatric oral drug absorption

European Journal of Pharmaceutical Sciences 115 (2018) 57–67

T.N. Johnson[a,*], J.J. Bonner[a], G.T. Tucker[b], D.B. Turner[a], M. Jamei[a]

Ketoconazole BCS class 2 drug – high permeability, low solubility – model accounts for bile mediated solubility and supersaturation / precipitation

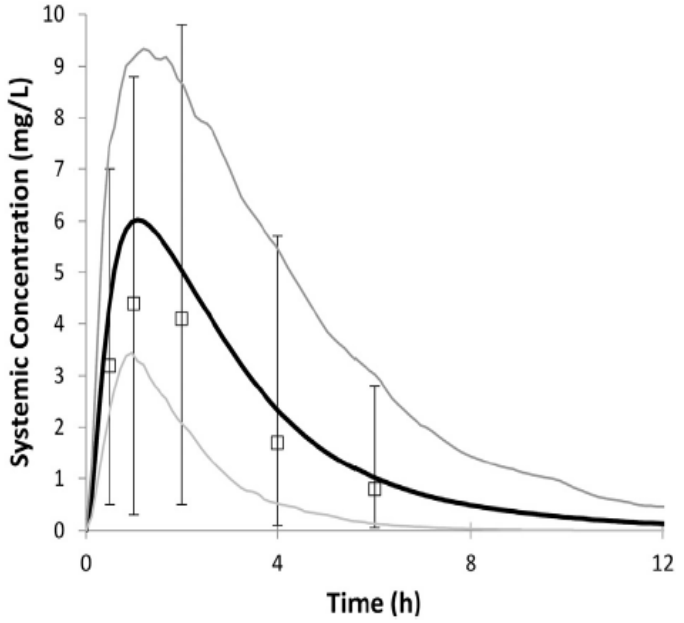


Fig. 6. A comparison of predicted mean (black lines with 95% confidence limits in grey) and observed (data points and bars indicating absolute range; (Ginsburg et al., 1983)) plasma drug concentration – time profiles of ketoconazole given as a 5 mg/kg as a suspension to children aged 2 to 12.5 years.

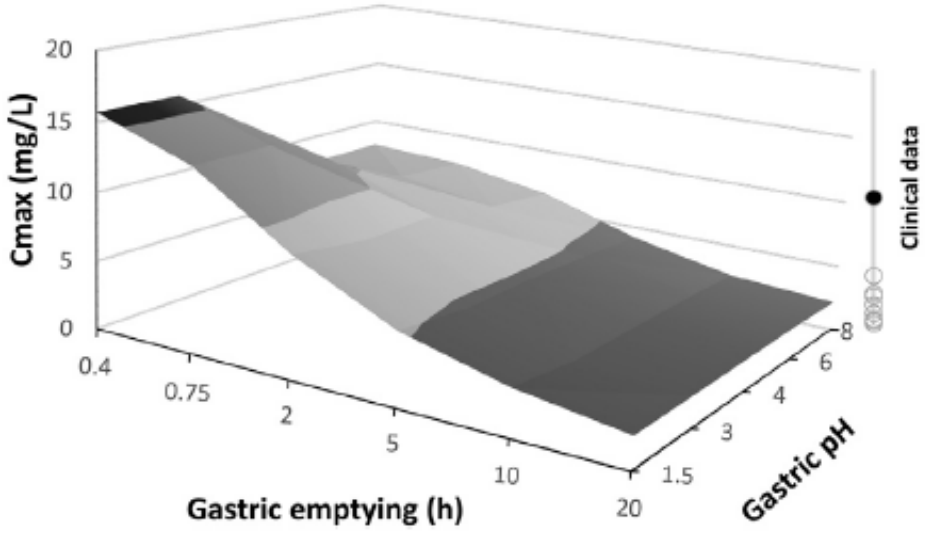


Fig. 7. Sensitivity analysis of the effects of changing both gastric emptying time and gastric pH on C_{max} values of ketoconazole after administration of a 10 mg/kg suspension dose to neonates. The open circles are clinical data (van den Anker et al., 1994) and the filled black circle is the typical C_{max} after administration of a 400 mg dose to adults.

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Applications of Paediatric Absorption models

Development of physiologically based pharmacokinetic model to evaluate the relative systemic exposure to quetiapine after administration of IR and XR formulations to adults, children and adolescents

Trevor N. Johnson[a], Diansong Zhou[b], and Khanh H. Bui[b,*] *Biopharm. Drug Dispos.* 35: 341–352 (2014)

Case study 1

Physiologically Based Pharmacokinetic Models in the Prediction of Oral Drug Exposure Over the Entire Pediatric Age Range—Sotalol as a Model Drug

Feras Khalil[1] and Stephanie Läer[2,3] *The AAPS Journal (© 2014)*
DOI: 10.1208/s12248-013-9555-6

Exploratory Investigation of the Limiting Steps of Oral Absorption of Fluconazole and Ketoconazole in Children Using an *In Silico* Pediatric Absorption Model Journal of Pharmaceutical Sciences 105 (2016) 2794–2803

Rodrigo Cristofoletti [1, 2], Naseem A. Charoo [3, 4], Jennifer B. Dressman [2, *]

Investigating Oral Absorption of Carbamazepine in Pediatric Populations

The AAPS Journal (© 2017)
DOI: 10.1208/s12248-017-0149-6

Philip Kohlmann,[1] Cordula Stillhart,[1] Martin Kuentz,[2] and Neil Parrott[3,4]

Pharmacokinetics of rivaroxaban in children using physiologically based and population pharmacokinetic modelling: an EINSTEIN-Jr phase I study

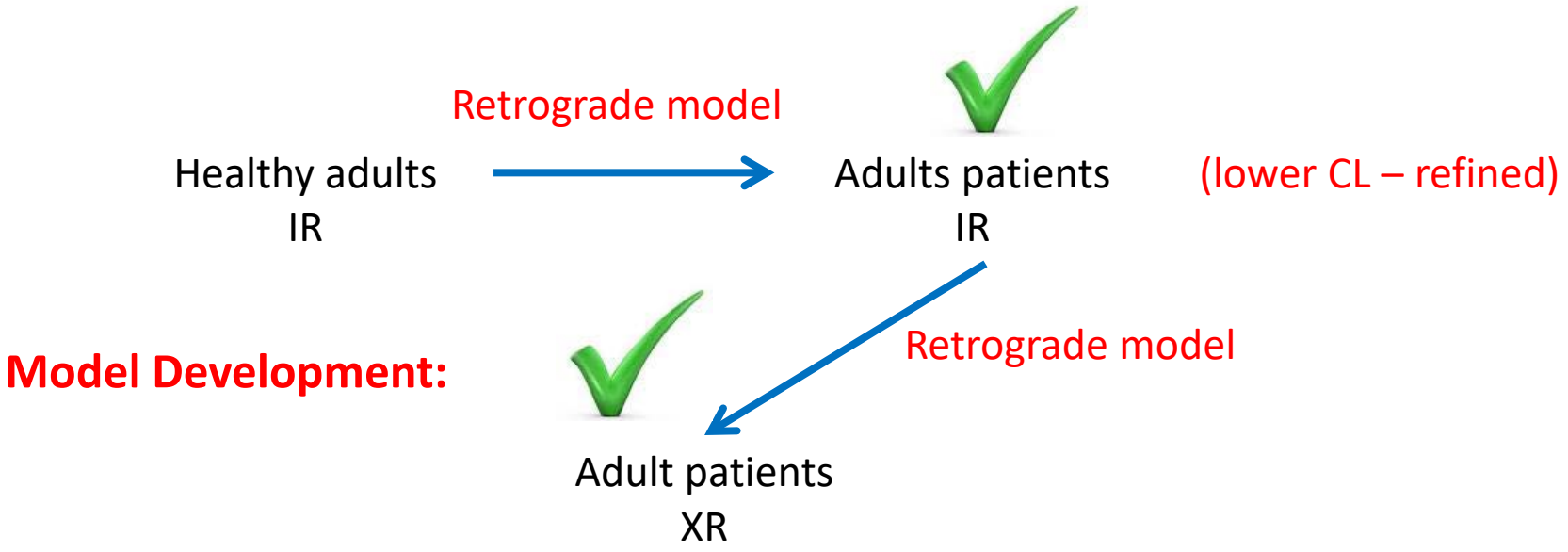
Willmann *et al. Thrombosis Journal* (2018) 16:32
https://doi.org/10.1186/s12959-018-0185-1

Stefan Willmann[1*], Kirstin Thelen[1], Dagmar Kubitz[1], Jan Stampfuss[4], Rolf Burghaus[1], Wolfgang Mück[4]

Case study 1: Quetiapine example – bridging between formulations

- Antipsychotic Drug (BCS class 2)
- Immediate release formulation (IR) – BD
- Developed extended release (XR) – QD

AIM: Predict exposure of new formulation in paediatric patients (>10y)



ADAM input data: Dissolution Profile
For sustained release formulations

Quetiapine example

Figure 2. Simulated mean plasma drug concentration-time profile (solid black line) during dosing of 150 mg IR quetiapine bid (A) and 300 mg XR qd (B) in adults. The corresponding mean and individual observed data are shown by black filled or grey unfilled circles, respectively. The grey dashed lines represent the 5th and 95th percentiles for the predicted values.

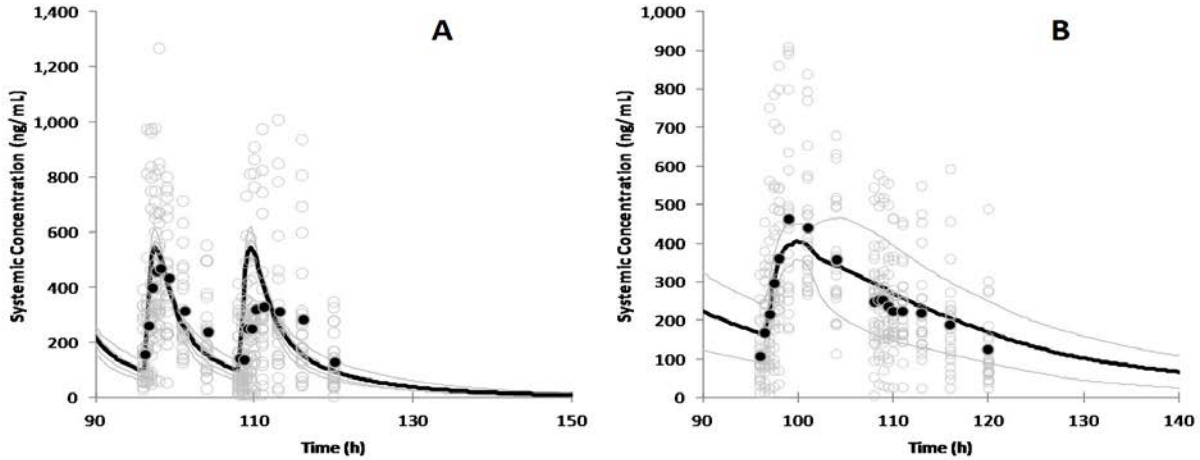
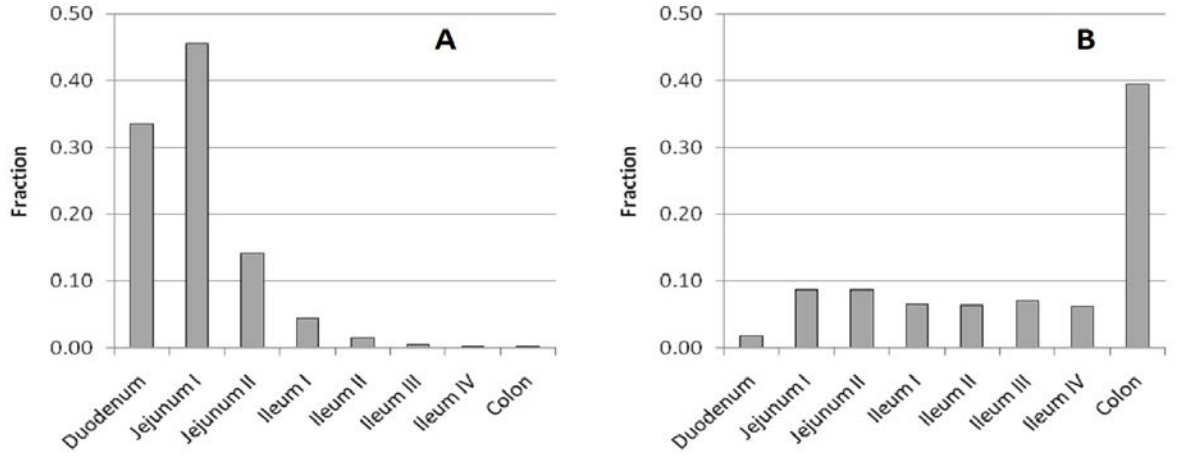
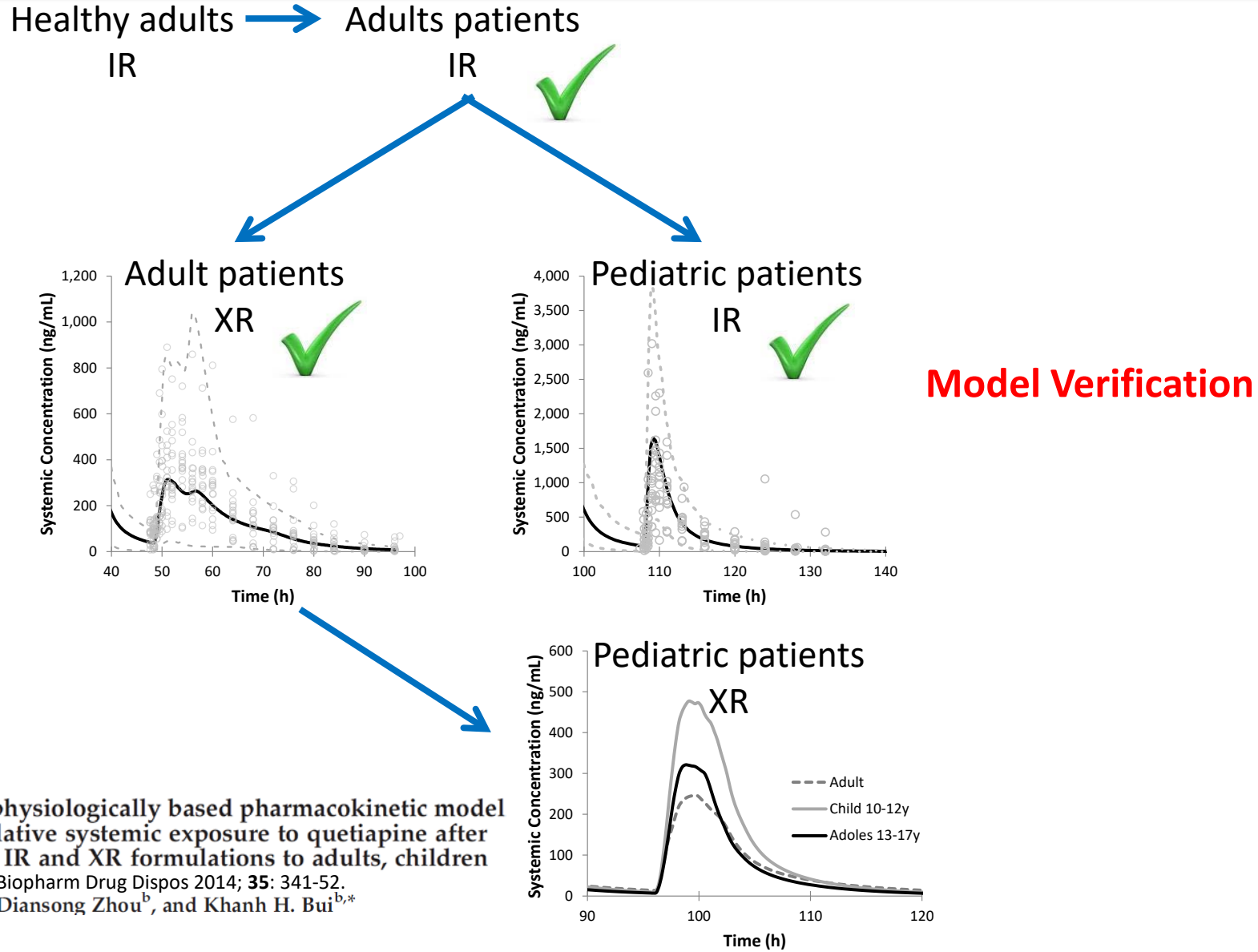


Figure 3. Regional distribution of the predicted fraction of dose absorbed in each segment of the GI tract following administration of the IR (A) and XR (B) formulation of quetiapine.



Quetiapine example



Model Verification

Development of physiologically based pharmacokinetic model to evaluate the relative systemic exposure to quetiapine after administration of IR and XR formulations to adults, children and adolescents Biopharm Drug Dispos 2014; **35**: 341-52.
Trevor N. Johnson[a], Diansong Zhou[b], and Khanh H. Bui[b,*]

Quetiapine example

Figure 4. Predicted mean plasma quetiapine concentration-time profiles after the last of 5 daily doses of the 300 mg XR formulation (A) and 150mg BID IR formulation (B) in adults, children and adolescents.

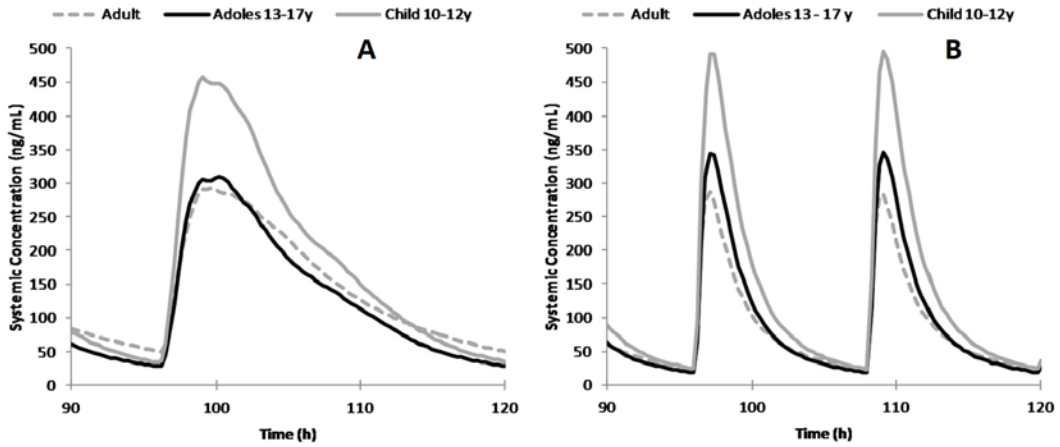
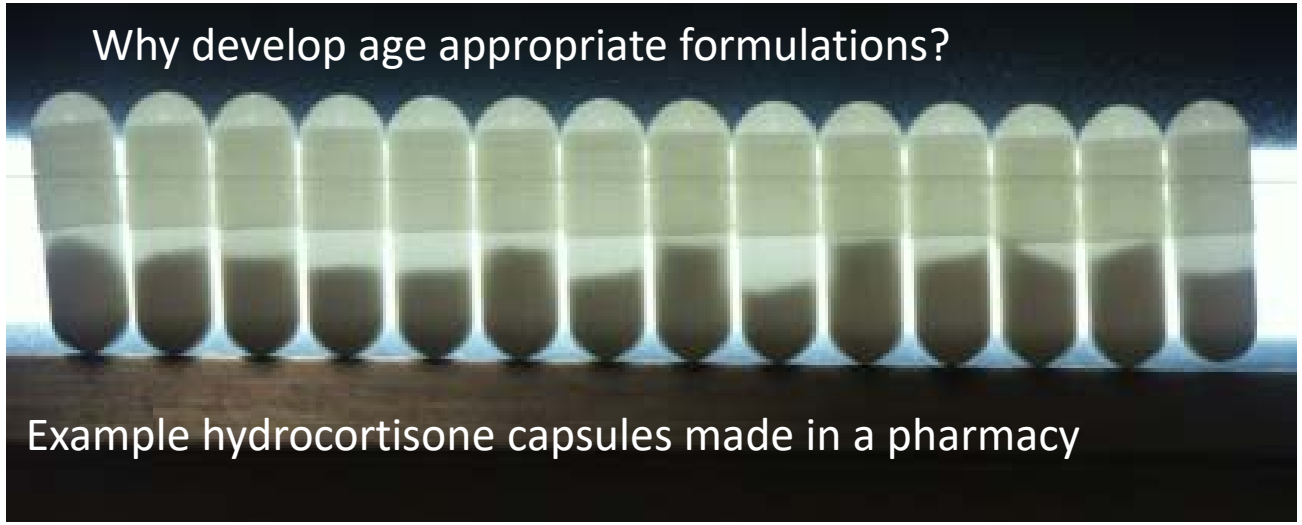


Table 2. Summary of predicted exposure to quetiapine after administration of 150 mg bid as an IR formulation in comparison with 300mg daily as the XR formulation in adults, adolescents and older children. All values are geometric means with the exception of t_{max} values which are medians.

300mg dose Minimal PBPK	**AUC_{0-24} (ng/ml/h)**			**C_{max} (mg/ml)**			**t_{max} (h)**		
	IR	XR	XR/IR	IR	XR	XR/IR	IR	XR	XR/IR
Adult	2464	2570	1.04	254	249	0.98	1.42	4.3	3.0
10 – 17y	3316	3738	1.13	393	447	1.14	1.61	4.5	2.8
13 – 17y	2974	2986	1.0	344	342	0.99	1.67	4.4	2.6
10 – 12y	3958	4227	1.07	517	523	1.01	1.65	4.6	2.8

Case study 2: Treating adrenal insufficiency in adults and children



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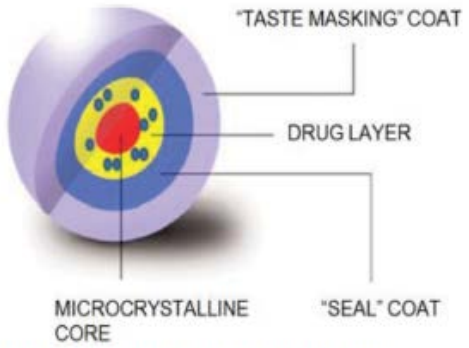
New Hydrocortisone formulations

1) **Infacort** granule formulation **(Taste mask)**

Development and Testing in Healthy Adults of Oral Hydrocortisone Granules With Taste Masking for the Treatment of Neonates and Infants With Adrenal Insufficiency

J Clin Endocrinol Metab, April 2015, 100(4):1681–1688

Martin J. Whitaker,* Sarah Spielmann,* Dena Digweed, Hiep Huatan, David Eckland, Trevor N. Johnson, Geoffrey Tucker, Heiko Krude, Oliver Blankenstein, and Richard J. Ross



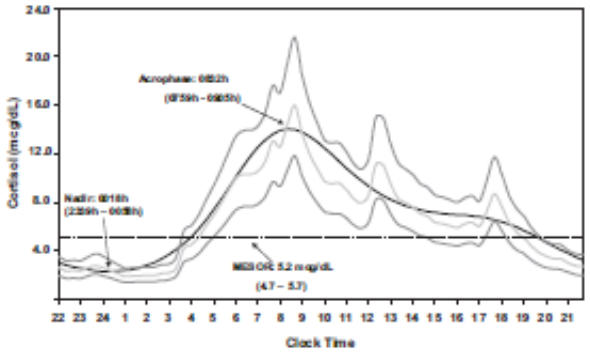
0.5, 1, 2, and 5 mg capsules

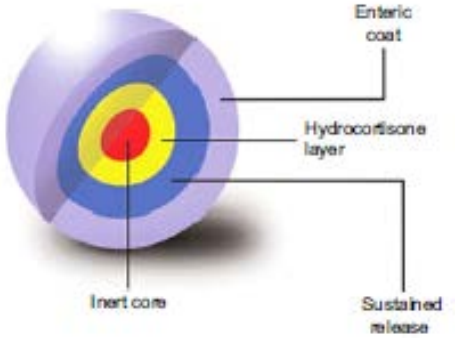
2) **Chronocort** EC granule formulation **(Diurnal variation)**

A Phase 2 Study of Chronocort, a Modified-Release Formulation of Hydrocortisone, in the Treatment of Adults With Classic Congenital Adrenal Hyperplasia

J Clin Endocrinol Metab, March 2015, 100(3):1137–1145

Ashwini Mallappa, Ninet Sinaii, Parag Kumar, Martin J. Whitaker, Lori-Ann Daley, Dena Digweed, David J. A. Eckland, Carol Van Ryzin, Lynnette K. Nieman, Wiebke Arlt, Richard J. Ross, and Deborah P. Merke





5, 10, and 20 mg capsules

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PBPK Modelling workflow

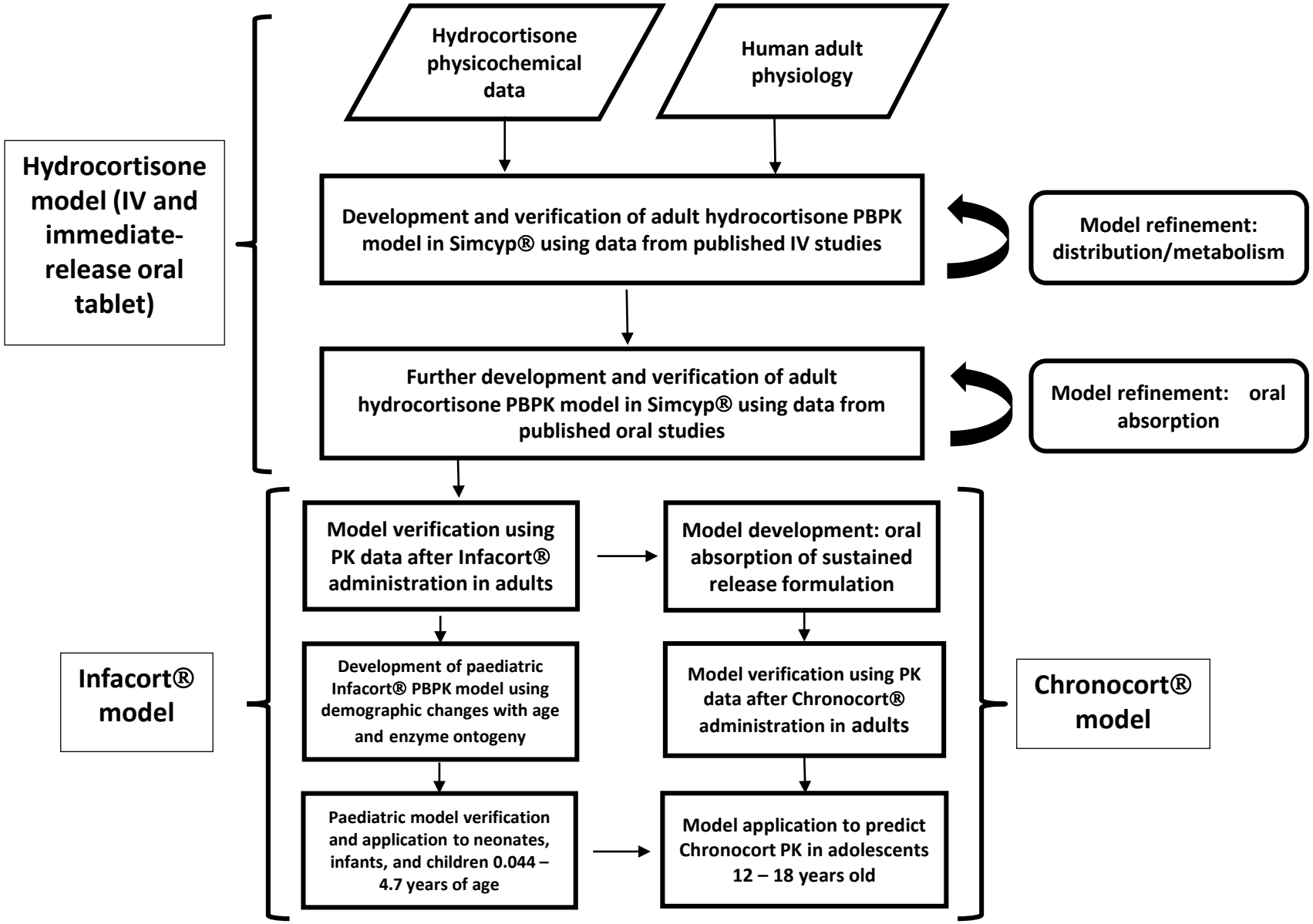
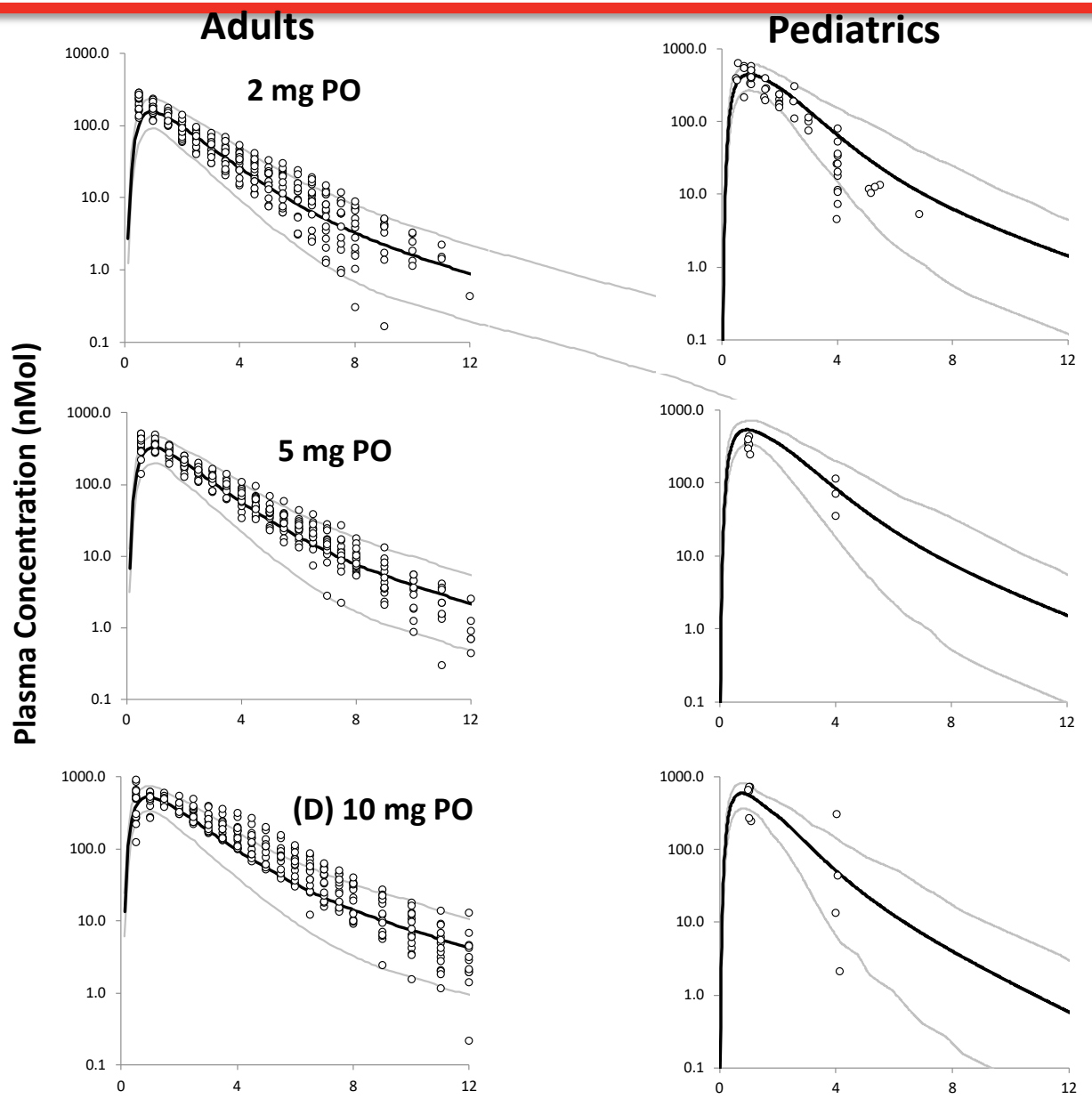


Figure 1. Oral Infacort PK in adults and pediatrics



0.16 mg/kg given to <u>children</u> 2 - 4.7 y (Cohort 1)

0.22 mg/kg given to <u>infants</u> 0.3 – 1.8 y (Cohort 2)

0.53 mg/kg given to <u>neonates</u> 0.044 – 0.071 y (Cohort 3)

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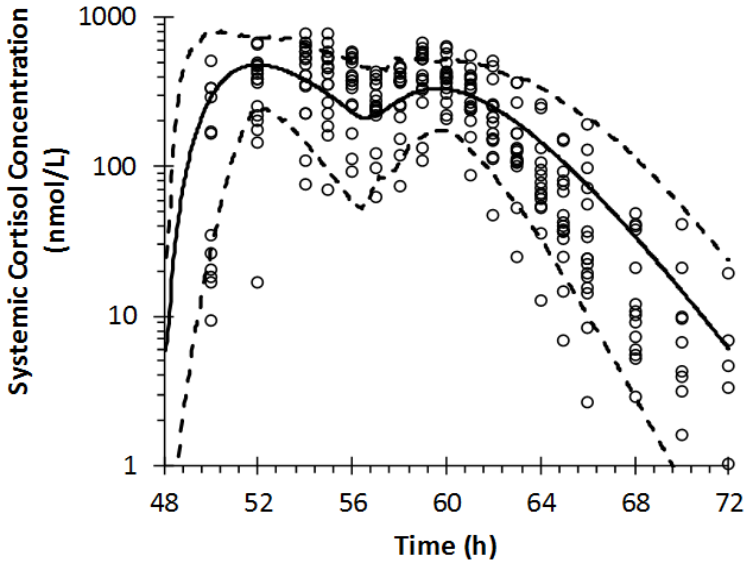
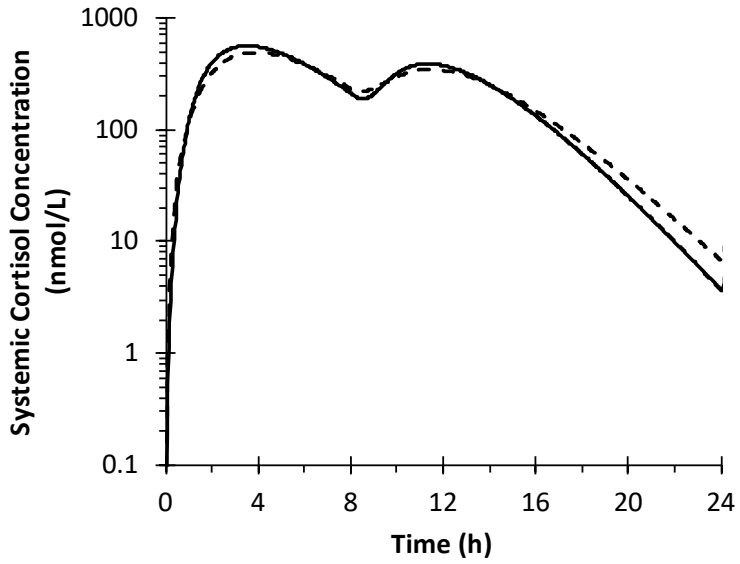
Chronocort PK in adults, dose projections in adolescents

Modelled as EC formulation with trigger pH = 7.2



20mg evening, 10mg morning in adults



11.6 mg/m^2 evening, 5.8 mg/m^2 morning adolescents aged 12 to 18 years (solid line). Adults (dotted line).

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Summary

- Beginning to apply PBPK absorption model to more complex formulations.
- Verification of model held back by lack of clinical absorption data with age particularly in young children.
- Various system parameters still need further data including:
  - Age gaps in existing data e.g. gastric pH.
  - Intestinal UGT and other drug-metabolizing enzyme ontogeny.
  - Unstirred water layer characteristics.
  - Luminal fluid dynamics with age.
  - Permeability changes with age.
  - Bile mediated solubility with age and fasted and fed intestinal fluid changes with age.
  - ….and others
- More research on effects of excipients (e.g. Adkinton et al. CPT 2018; 103: 402-408)
- Collaborations between academia, industry, regulators

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Acknowledgements

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  - **Xian Pan**
  - **Jennifer Bonner**
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- **Diurnal**
  - **Richard Ross**
  - **Martin Whitaker**

Images on slides 17 to 20 courtesy of Diurnal Limited

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