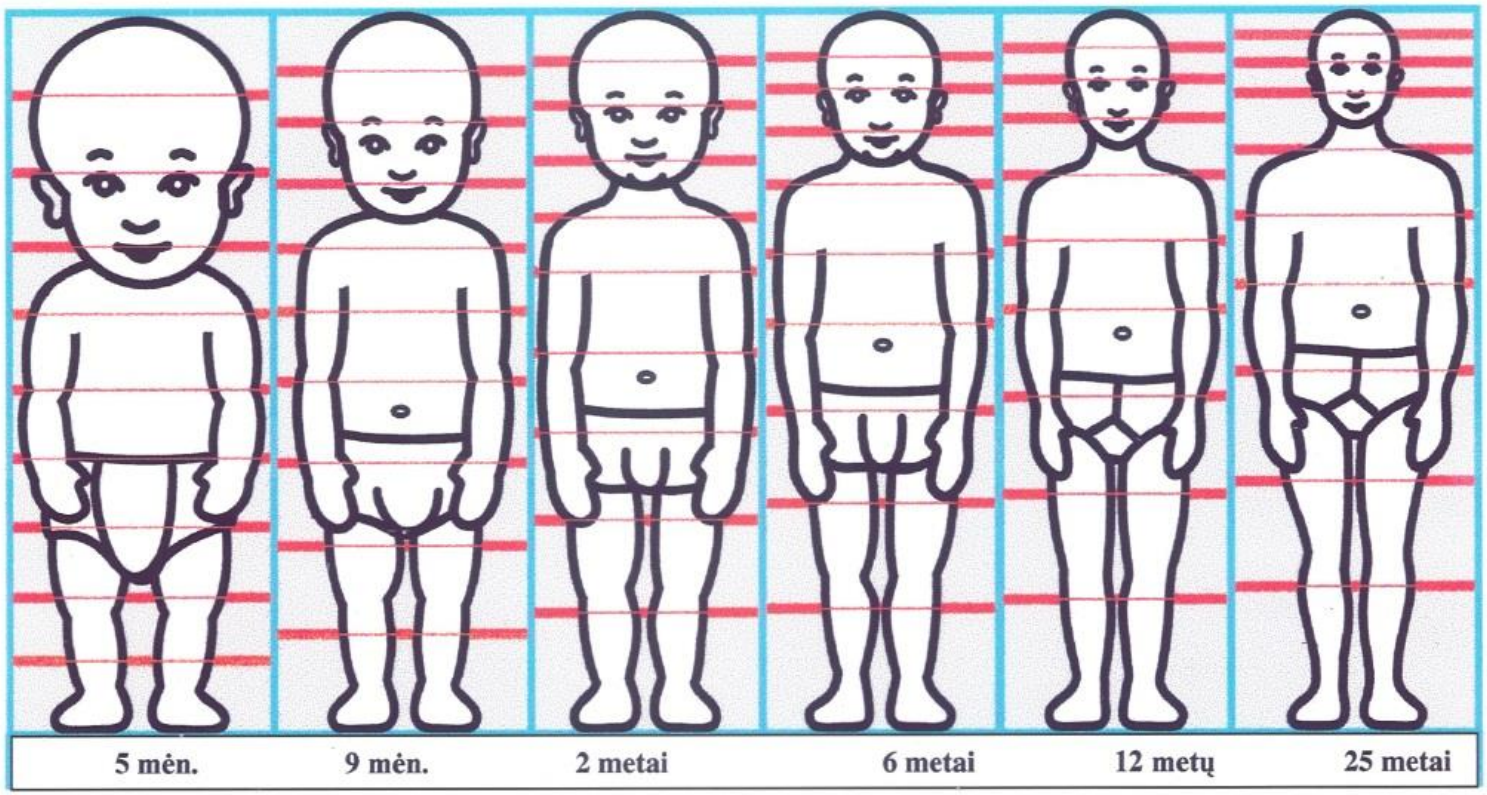
# Vaikų klinikinė farmakologija

Prof. Dr. Jolanta Gulbinovič




**Pav. Vaikas – tai ne suaugusio žmogaus maža kopija**

Ar vaikai serga tomis pačiomis ligomis ir taip pat kaip suaugusieji?

Kaip gydyti vaikus?
Ar tinka suaugusiųjų vaistai vaikams?

Ar suaugusiųjų vaistai tokie pat efektyvūs ir saugūs vaikams?

Ar vaistai ištirti klinikiniuose tyrimuose?

Kokią dozę skirti?

Kokią vaisto formą skirti?

Kiek laiko gydyti?

# Terapiniai našlaičiai

PEDIATRICS Vol. 104 No. 3 September 1999 583

**Editorial Comment: Therapeutic Orphans**

Harry Shirkey, MD

<...> However, many of the drugs released since 1962 carry an "orphaning" clause, eg, "Not to be used in children . . . is not recommended for use in infants and young children since few studies have been conducted in this age group... clinical studies have been insufficient to establish any recommendations for use in infants and children . . . should not be given to children."

Despite such clear cautions, many physicians have ignored the warnings and have prescribed the restricted drugs. It requires little imagination to wonder what a jury of laymen would decide after a defending physician admitted in court to the use of a drug despite such a clear warning.<...>

- Vaikams neskirti
- Nerekomenduojama skirti kūdikiams ir mažiems vaikams, nes šios grupės tirtos tik keliuose tyrimuose
- Klinikinių tyrimų duomenų nepakanka, kad galima būtų rekomenduoti vaikams
- Nepaisant rekomendacijų, vaikai gydomi neregistruotais vaistais (*unlicensed*) arba vaistais, vartojami ne pagal produkto informaciją (*off-label*)

## 1. VAISTINIO PREPARATO PAVADINIMAS

Xydalba 500 mg milteliai infuzinio tirpalo koncentratui

## 4. KLINIKINĖ INFORMACIJA

### 4.1 Terapinės indikacijos

Xydalba skirtas gydyti suaugusiųjų ūminėms bakterijų sukeltoms odos ir odos struktūrų infekcinėms ligoms (ŪBOOSIL) (žr. 4.4 ir 5.1 skyrius).

Būtina atsižvelgti į oficialias tinkamo antibakterinių vaistinių preparatų vartojimo rekomendacijas.

### 4.2 Dozavimas ir vartojimo metodas

Dozavimas

*Vaikų populiacija*

Dalbavancino saugumas ir veiksmingumas vaikams nuo gimimo iki 18 metų dar neištirtas. Turimi duomenys pateikiami 5.2 skyriuje, tačiau dozavimo rekomendacijų pateikti negalima.

ARTICLE

# Off-label Drug Use in Hospitalized Children

*Samir S. Shah, MD; Matthew Hall, PhD; Denise M. Goodman, MD, MS; Pamela Feuer, MD; Vidya Sharma, MBBS, MPH; Crayton Fargason, Jr, MD; Daniel Hyman, MD, MMM; Kathy Jenkins, MD, MPH; Marjorie L. White, MD; Fiona H. Levy, MD; James E. Levin, MD, PhD; David Bertoch, MHA; Anthony D. Slonim, MD, DrPH*

**Objectives:** To describe the magnitude of off-label drug use, to identify drugs most commonly used off-label, and to identify factors associated with off-label drug use in children hospitalized in the United States.

**Design:** Retrospective cohort study.

**Setting:** Administrative database containing inpatient resource utilization data from January 1 to December 31, 2004, from 31 tertiary care pediatric hospitals in the United States.

**Participants:** Hospitalized patients 18 years or younger.

**Main Exposures:** Institution and patient characteristics.

**Main Outcome Measures:** Off-label drug use was defined as use of a specific drug in a patient younger than the Food and Drug Administration–approved age range for any indication of that drug.

**Results:** At least 1 drug was used off-label in 297 592 (78.7%) of 355 409 patients discharged during the study. Off-label use accounted for $270 275 849 (40.5%) of the total dollars spent on these medications. Medications classified as central or autonomic nervous system agents or as fluids or nutrients, or gastrointestinal tract agents were most commonly used off-label, whereas antineoplastic agents were rarely used off-label. Factors associated with off-label use in multivariate analysis were as follows: undergoing a surgical procedure, age older than 28 days, greater severity of illness, and all-cause in-hospital mortality.

**Conclusions:** Most patients hospitalized at tertiary care pediatric institutions receive at least 1 medication outside the terms of the Food and Drug Administration product license. Substantial variation in the frequency of off-label use was observed across diagnostic categories and drug classes. Despite the frequent off-label use of drugs, using an administrative database, we cannot determine which of these treatments are unsafe or ineffective and which treatments result in substantial benefit to the patient.

*Arch Pediatr Adolesc Med. 2007;161:282-290*

# *Off-label* kategorijos

| ***Off-label* kategorija** | **Apibūdinimas** |
|---|---|
| Amžius | Vaistas nerekomenduojamas jaunesniems kaip tam tikro amžiaus asmenims (PCS) |
| Svoris | Vaistas nerekomenduojamas tam tikro svorio vaikams |
| Informacijos vaikams nebuvimas | Nėra informacijos apie vaisto skyrimą vaikams |
| Pediatrinių klinikinių tyrimų duomenų nebuvimas | Nurodyta, kad nėra informacijos apie vaisto efektyvumą ir saugumą vaikams |
| Kontraindikacijos | Nurodyta, kad vaistas kontraindikuotinas vaikams |
| Indikacijos | Vaistas skiriamas kitoms negu registruotos indikacijos |
| Vartojimo būdas | Vaistas vartojamas kitais negu registruota būdais |

I

*(Aktai, kuriuos skelbti privaloma)*

# EUROPOS PARLAMENTO IR TARYBOS REGLAMENTAS (EB) NR. 1901/2006

**2006 m. gruodžio 12 d.**

**dėl pediatrijoje vartojamų vaistinių preparatų, iš dalies keičiantis Reglamentą (EEB) Nr. 1768/92, Direktyvą 2001/20/EB, Direktyvą 2001/83/EB ir Reglamentą (EB) Nr. 726/2004**

**(Tekstas svarbus EEE)**

EUROPOS PARLAMENTAS IR EUROPOS SĄJUNGOS TARYBA,

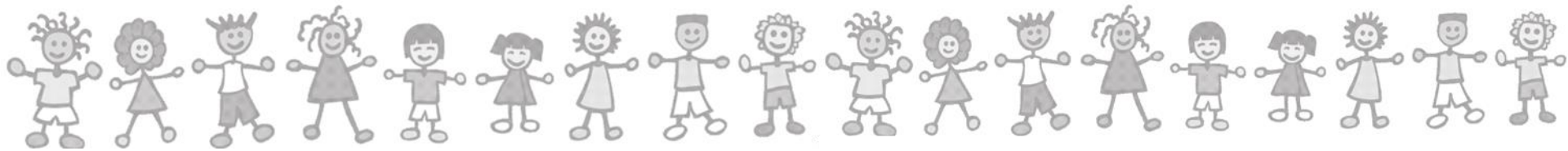
atsižvelgdami į Europos bendrijos steigimo sutartį, ypač į jos 95 straipsnį,

atsižvelgdami į Komisijos pasiūlymą,

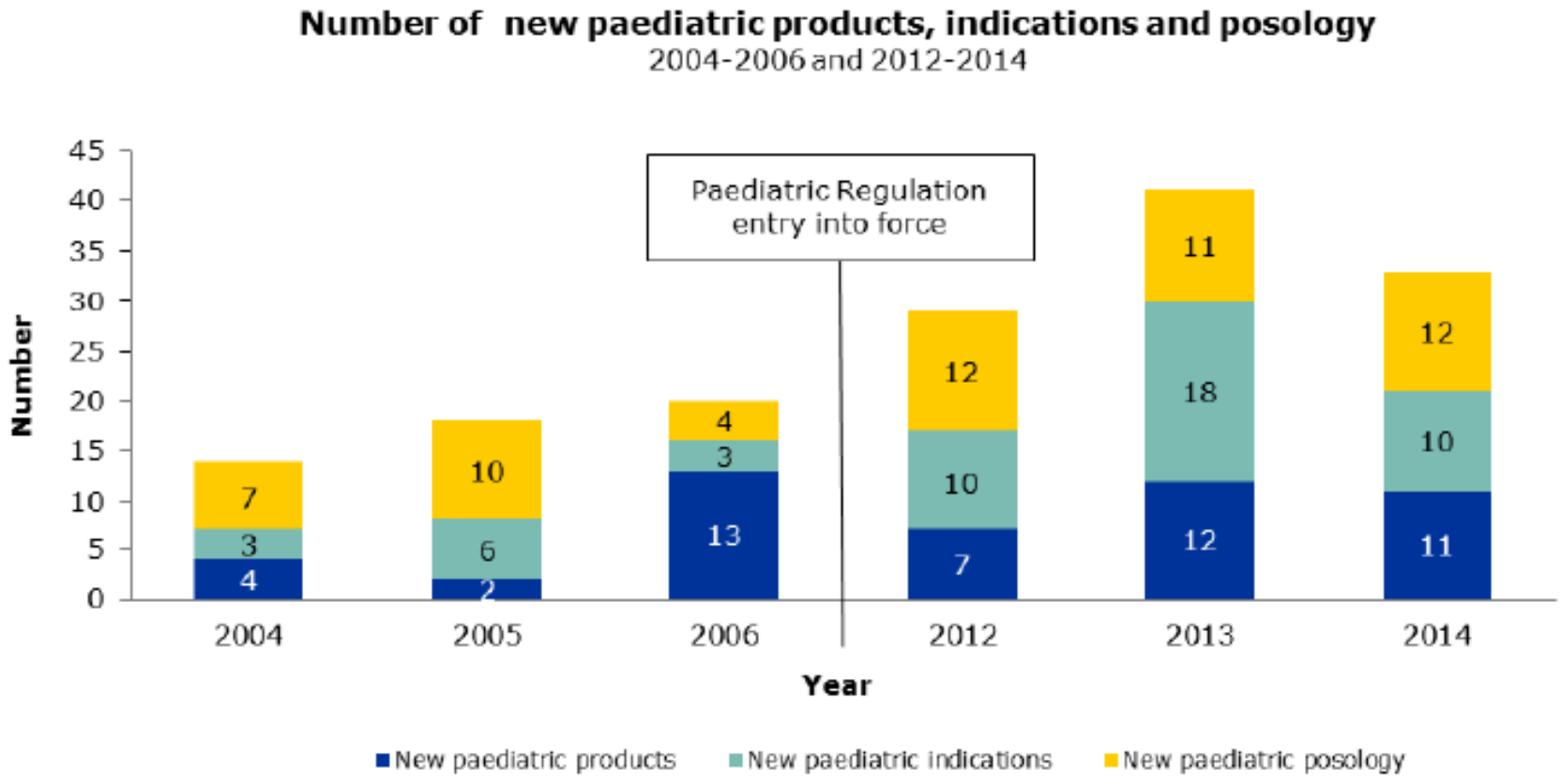
atsižvelgdami į Europos ekonomikos ir socialinių reikalų komiteto nuomonę (1),

pasikonsultavę su Regionų komitetu,

(4) Šio reglamento tikslas — palengvinti vaikų populiacijai skirtų vaistinių preparatų kūrimą ir jų prieinamumą, užtikrinti, kad dėl vaikų populiacijos gydymui vartojamų vaistinių preparatų būtų atliekami aukštos kokybės etiški moksliniai tyrimai, vaikų populiacijai vartoti skirtiems vaistiniams preparatams būtų išduoti tinkami leidimai prekiauti, ir pagerinti informacijos apie vaistinių preparatų vartojimą įvairioms vaikų populiacijoms teikimą. Šie tikslai turėtų būti pasiekti neįtraukiant vaikų populiacijos į bereikalingus klinikinius tyrimus ir išvengiant delsimo išduodant leidimus vaistiniams preparatams, skirtiems kito amžiaus gyventojų grupėms.

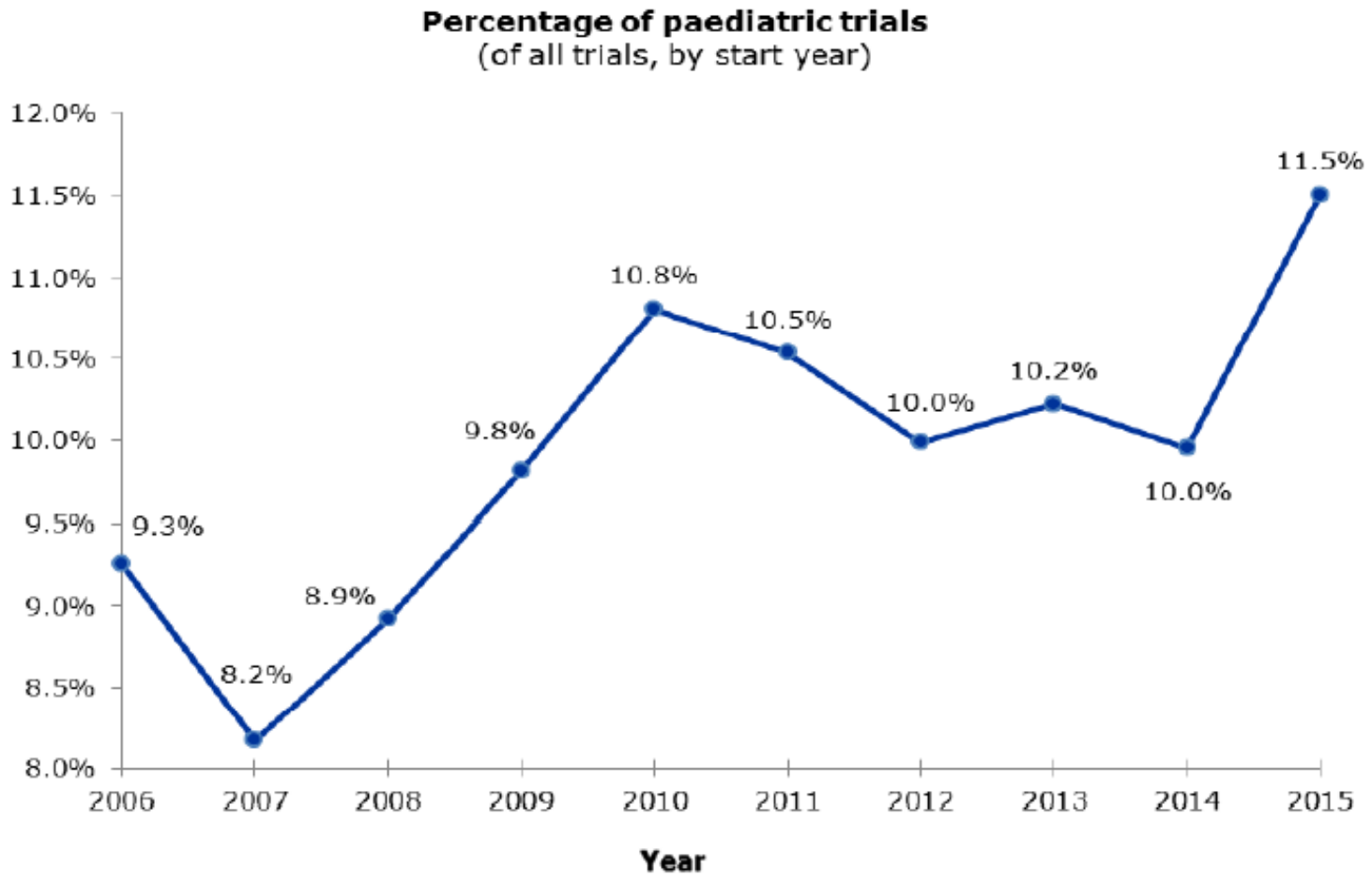


# Centralizuotai registruoti vaistai vaikams




Source: EMA database (SIAMED)

# Vaikų klinikinių tyrimų proporcija

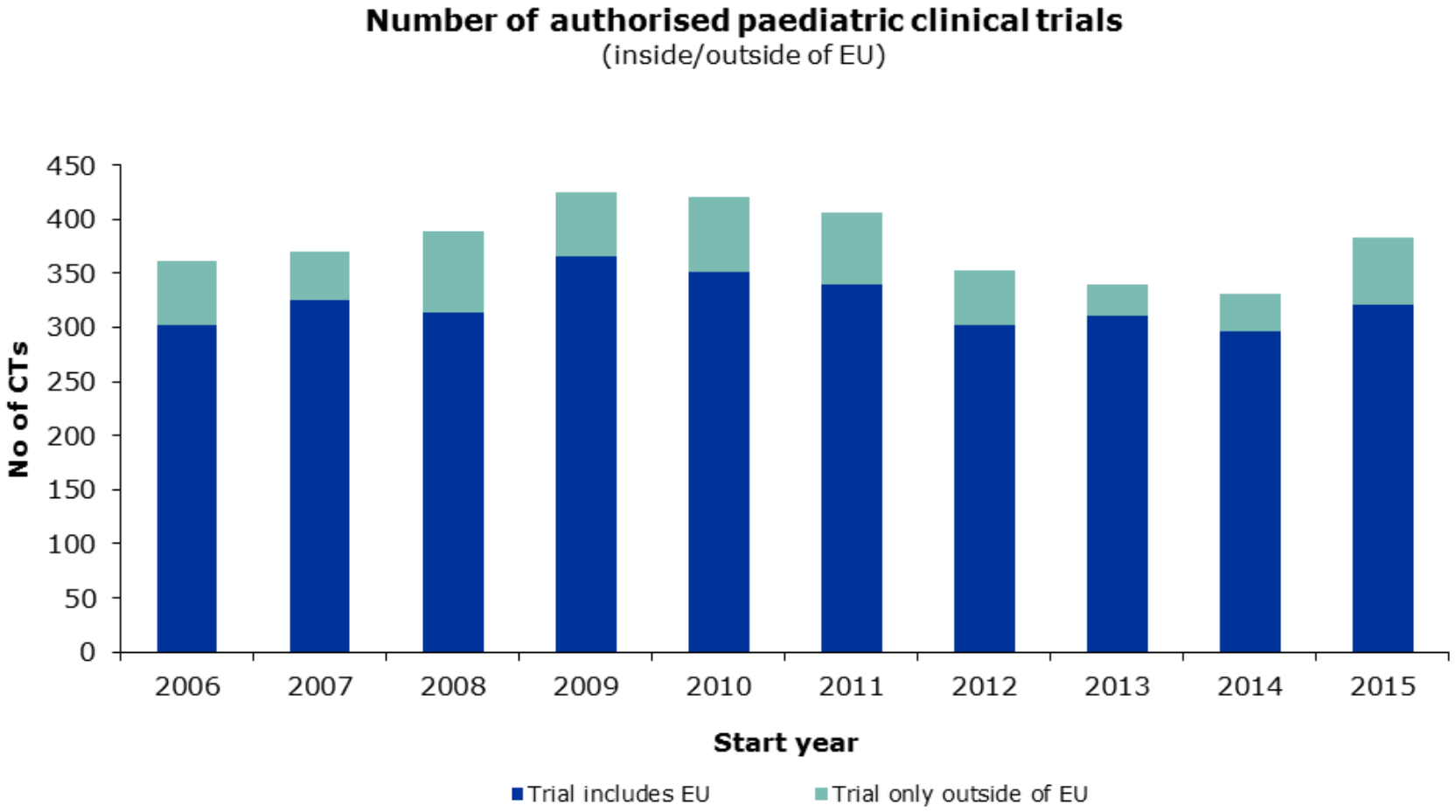



Note: A paediatric trial is a trial that includes at least one participant below 18 years of age.

Source: EudraCT database

Ref. Ares(2016)6395061 - 14/11/2016

# Patvirtintų vaikų klinikinių tyrimų skaičius




Ref. Ares(2016)6395061 - 14/11/2016

# Ar problema išspręsta?

- Gydytojai vis dar neišvengiamai priversti vaikams skirti jiems neregistruotų vaistų
- Tokie vaistai sudaro apie 40% visų bendrosios praktikos gydytojų paskyrimų ir iki 90% paskyrimų ligoninėse
- Tai lemia suboptimalų gydymą, kelia vaikams galima perdozavimo, nepageidaujamų reakcijų riziką, taip pat nepakankamą efektyvumą dėl galimai per mažos dozės
- Be to, vaistą skiriantis gydytojas paliekamas nežinioje, jam sunku nurodyti tinkamą dozę jų pacientams

van der Zanden TM, et al. Arch Dis Child 2017;102:357–361

# Klinikinis atvejis

- Neišnešiotas naujagimis, 32 sav. gestacinis amžus, 4 sav. 1,7 kg
- Hospitalinė infekcija
- Iš kraujo auga *Pseudomonas aeruginosa,* jautri  piperacilinui su tazobaktamu

- Dozavimas (Preparato charakteristikų santrauka)

***Vaikų populiacija (2–12 metų)***

| Dozė pagal svorį ir vartojimo dažnis | Indikacija/būklė |
|---|---|
| 80 mg piperacilino/10 mg tazobaktamo/ kg kūno svorio/kas 6 valandas | Karščiuojantys vaikai, kuriems pasireiškė neutropenija, kurie karščiuoja, kaip įtariama, dėl bakterijų sukeltų infekcijų*. |
| 100 mg piperacilino/12,5 mg tazobaktamo/kg kūno svorio/kas 8 valandas | Intraabdominalinės infekcijos komplikacijos*. |

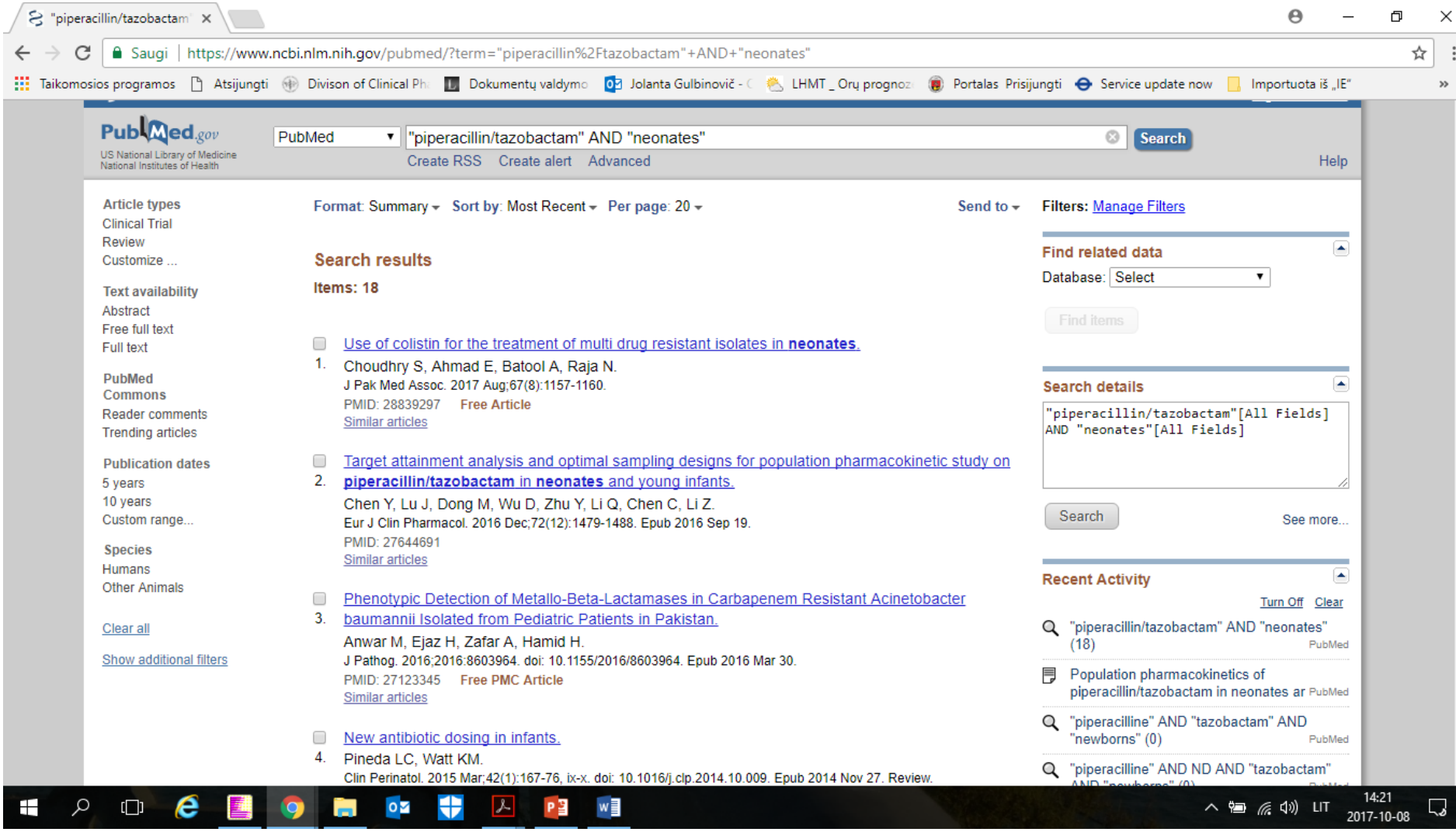
# Vaistų dozavimas vaikams

Von Harnack lentelė

| Amžius | Suaugusiojo dozės dalis |
|---|---|
| 1 mėn. | 1/10 |
| 6 mėn. | 1/5 |
| 12 mėn. | 1/4 |
| 3 metai | 1/3 |
| 7 metai | 1/2 |
| 12 metai | 2/3 |

Dozės faktorius (mg/kg)

| Amžius metais | Koeficienttas |
|---|---|
| 0-1 | 1,8 |
| 1-6 | 1,6 |
| 6-10 | 1,4 |
| 10-14 | 1,2 |
| Suaugusieji | 1,0 |


"piperacillin/tazobactam"
Saugi
https://www.ncbi.nlm.nih.gov/pubmed/?term="piperacillin%2Ftazobactam"+AND+"neonates"
Taikomosios programos
Atsijungti
Divison of Clinical Ph
Dokumentų valdymo
Jolanta Gulbinovič -
LHMT _ Orų prognoz
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Species
Humans
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Items: 18
1. Use of colistin for the treatment of multi drug resistant isolates in neonates.
Choudhry S, Ahmad E, Batool A, Raja N.
J Pak Med Assoc. 2017 Aug;67(8):1157-1160.
PMID: 28839297 Free Article
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2. Target attainment analysis and optimal sampling designs for population pharmacokinetic study on piperacillin/tazobactam in neonates and young infants.
Chen Y, Lu J, Dong M, Wu D, Zhu Y, Li Q, Chen C, Li Z.
Eur J Clin Pharmacol. 2016 Dec;72(12):1479-1488. Epub 2016 Sep 19.
PMID: 27644691
Similar articles
3. Phenotypic Detection of Metallo-Beta-Lactamases in Carbapenem Resistant Acinetobacter baumannii Isolated from Pediatric Patients in Pakistan.
Anwar M, Ejaz H, Zafar A, Hamid H.
J Pathog. 2016;2016:8603964. doi: 10.1155/2016/8603964. Epub 2016 Mar 30.
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4. New antibiotic dosing in infants.
Pineda LC, Watt KM.
Clin Perinatol. 2015 Mar;42(1):167-76, ix-x. doi: 10.1016/j.clp.2014.10.009. Epub 2014 Nov 27. Review.
Find related data
Database: Select
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"piperacillin/tazobactam"[All Fields] AND "neonates"[All Fields]
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Population pharmacokinetics of piperacillin/tazobactam in neonates ar PubMed
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"piperacilline" AND ND AND "tazobactam"
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2017-10-08

Eur J Clin Pharmacol. 2013 Jun;69(6):1223-33. doi: 10.1007/s00228-012-1413-4. Epub 2013 Jan 26.

# Population pharmacokinetics of piperacillin/tazobactam in neonates and young infants.

Li Z[1], Chen Y, Li Q, Cao D, Shi W, Cao Y, Wu D, Zhu Y, Wang Y, Chen C.

⊕ Author information

## Abstract

**OBJECTIVES:** To develop population pharmacokinetic (PK) models for piperacillin/tazobactam in neonates and infants of less than 2 months of age in order to determine the appropriate dosing regimen and provide a rational basis for the development of preliminary dosing guidelines suitable for this population.

**METHODS:** A two-stage, open-label study was conducted in neonates and infants less than 2 months of age in the neonatal intensive care unit (NICU). A total of 207 piperacillin and 204 tazobactam concentration-time data sets from 71 patients were analyzed using a nonlinear mixed-effect modeling approach (NONMEM VII). PK models were developed for piperacillin and tazobactam. The final models were evaluated using both bootstrap and visual predictive checks. External model evaluations were made in 20 additional patients.

**RESULTS:** For neonates and young infants less than 2 months of age, the median central clearance was 0.133 and 0.149 L/h/kg for piperacillin and tazobactam, respectively. Postmenstrual age (PMA) was identified as the most significant covariate on central clearance of piperacillin and tazobactam. However, the combination of current bodyweight (BW) and postnatal age proved to be superior to PMA alone. BW was the most important covariate for apparent central volume of distribution. Both internal and external evaluations supported the prediction of the final piperacillin and tazobactam PK models. The dosing strategy 44.44/5.56 mg/kg/dose piperacillin/tazobactam every 8 or 12 h evaluated in this study achieved the pharmacodynamic target (free piperacillin concentrations >4 mg/L for more than 50 % of the dosing interval) in about 67 % of infants.

**CONCLUSIONS:** Population PK models accurately described the PK profiles of piperacillin/tazobactam in infants less than 2 months of age. The results indicated that higher doses or more frequent dosing regimens may be required for controlling infection in this population in NICU.

# Vaikų vaistų žinynas (Nyderlandai)

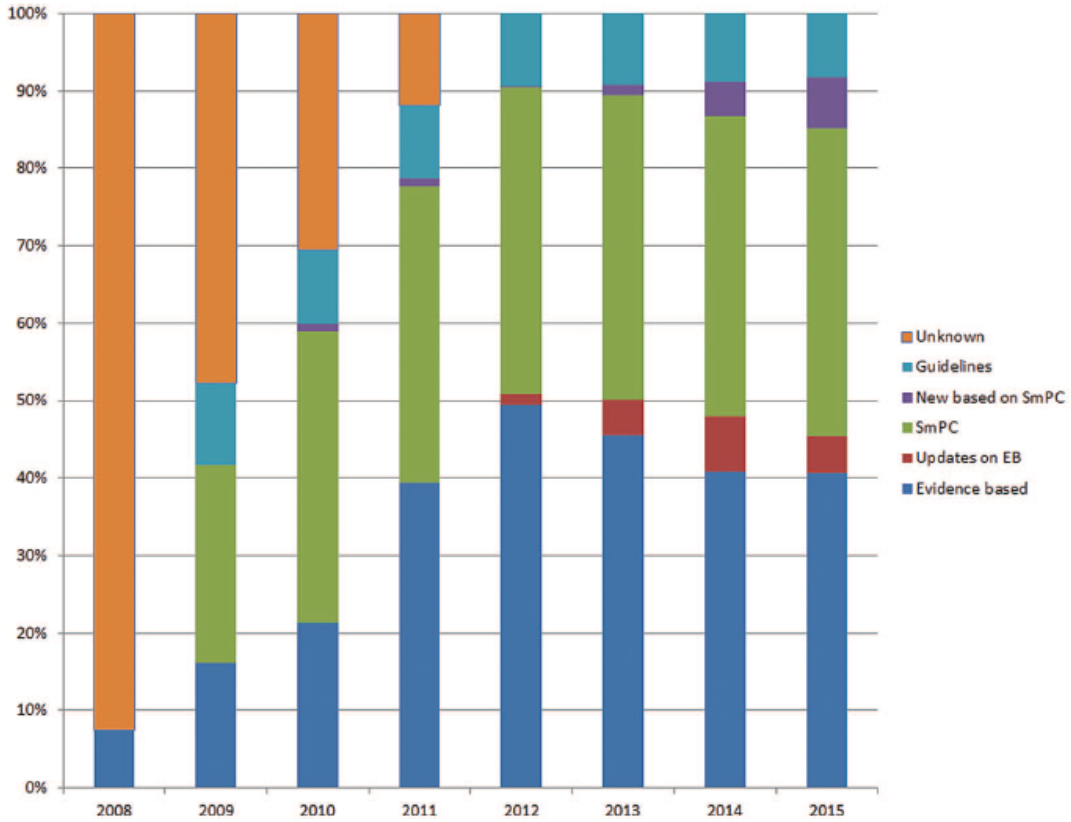



**Figure 1** Improving the knowledge base. EB, evidence based; SmPC, Summary of Product Characteristics.

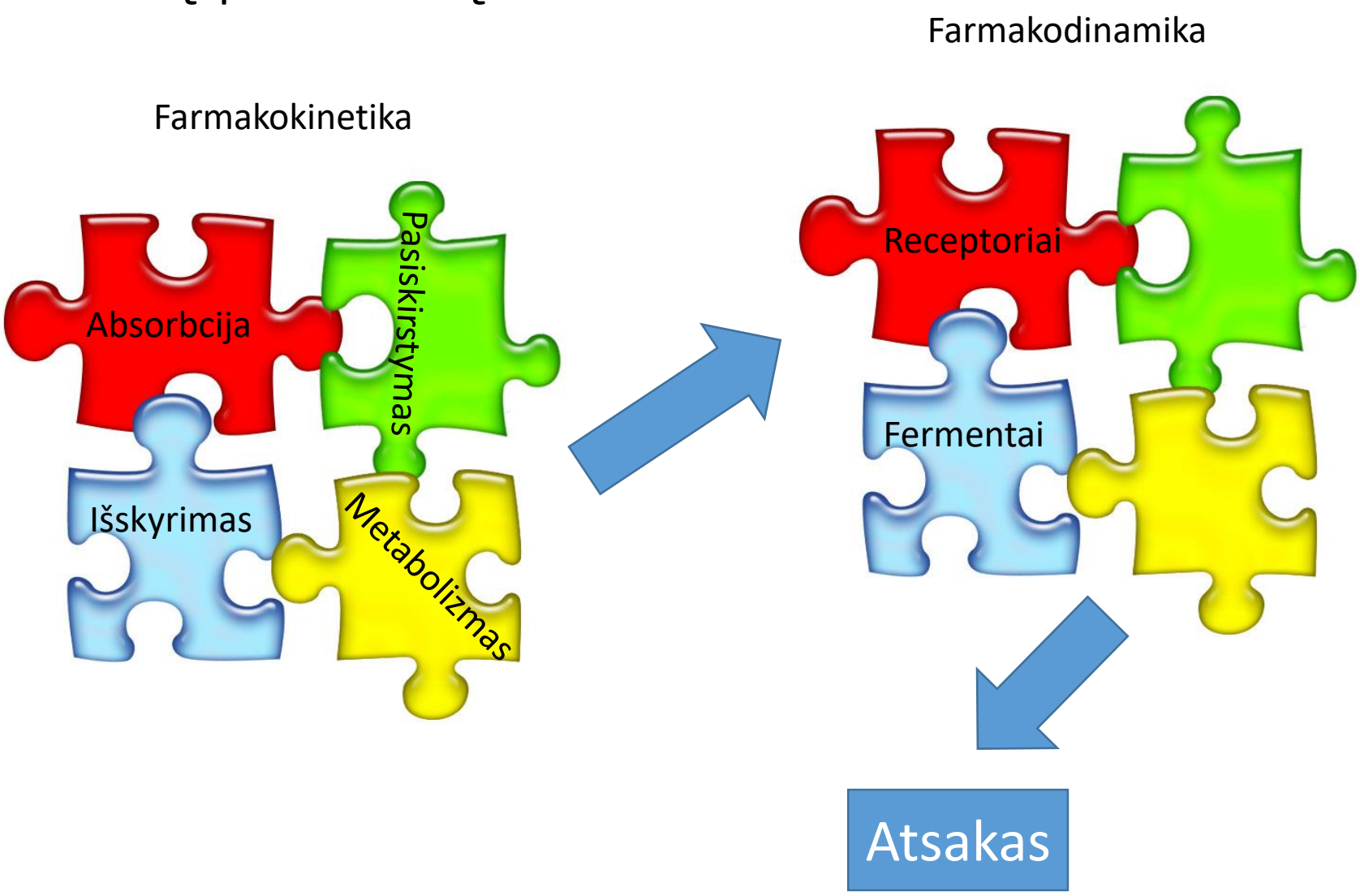
van der Zanden TM, et al. Arch Dis Child 2017;102:357–361

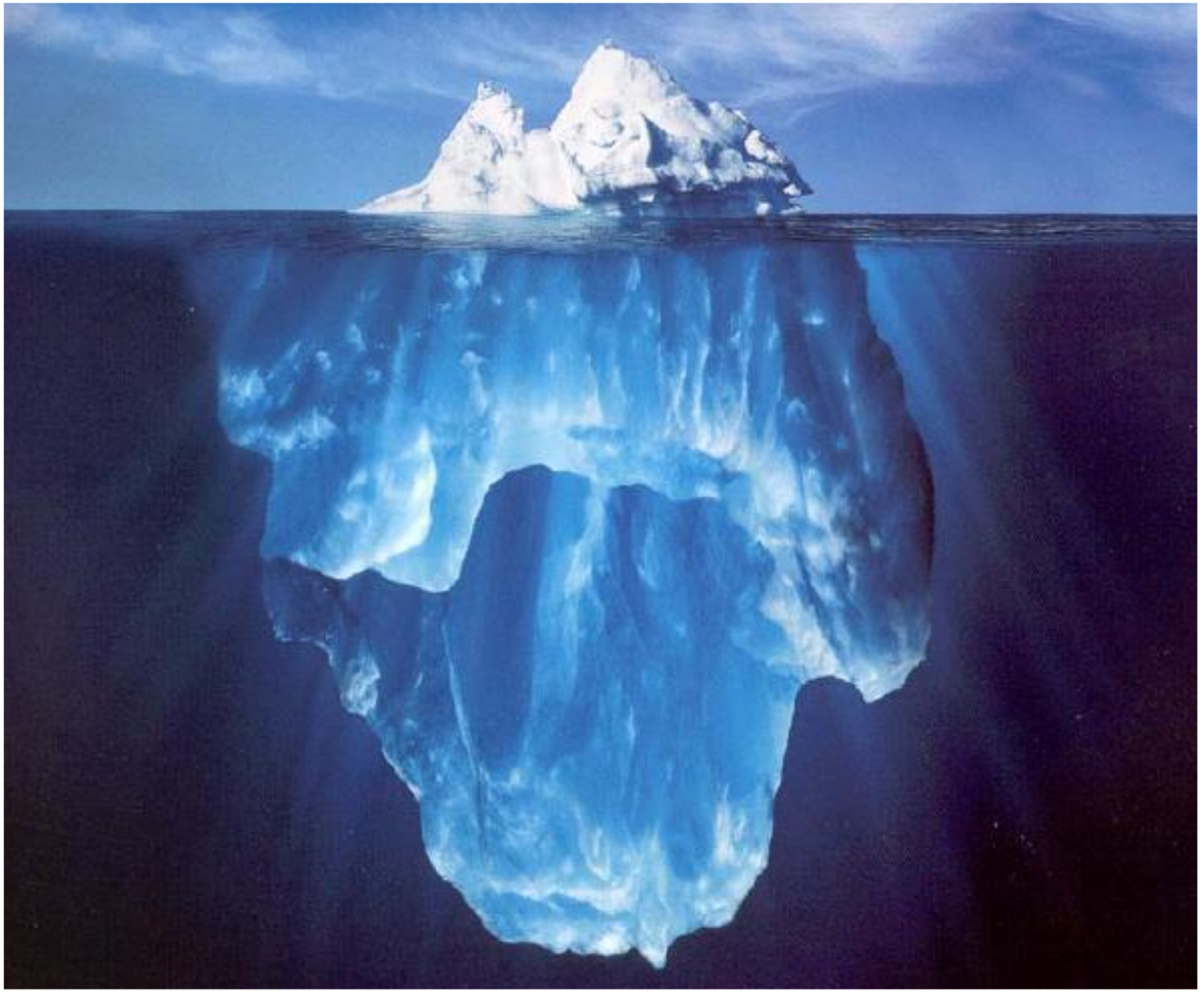
# Vaistų poveikis vaikams – kintantis

Ontgenezė

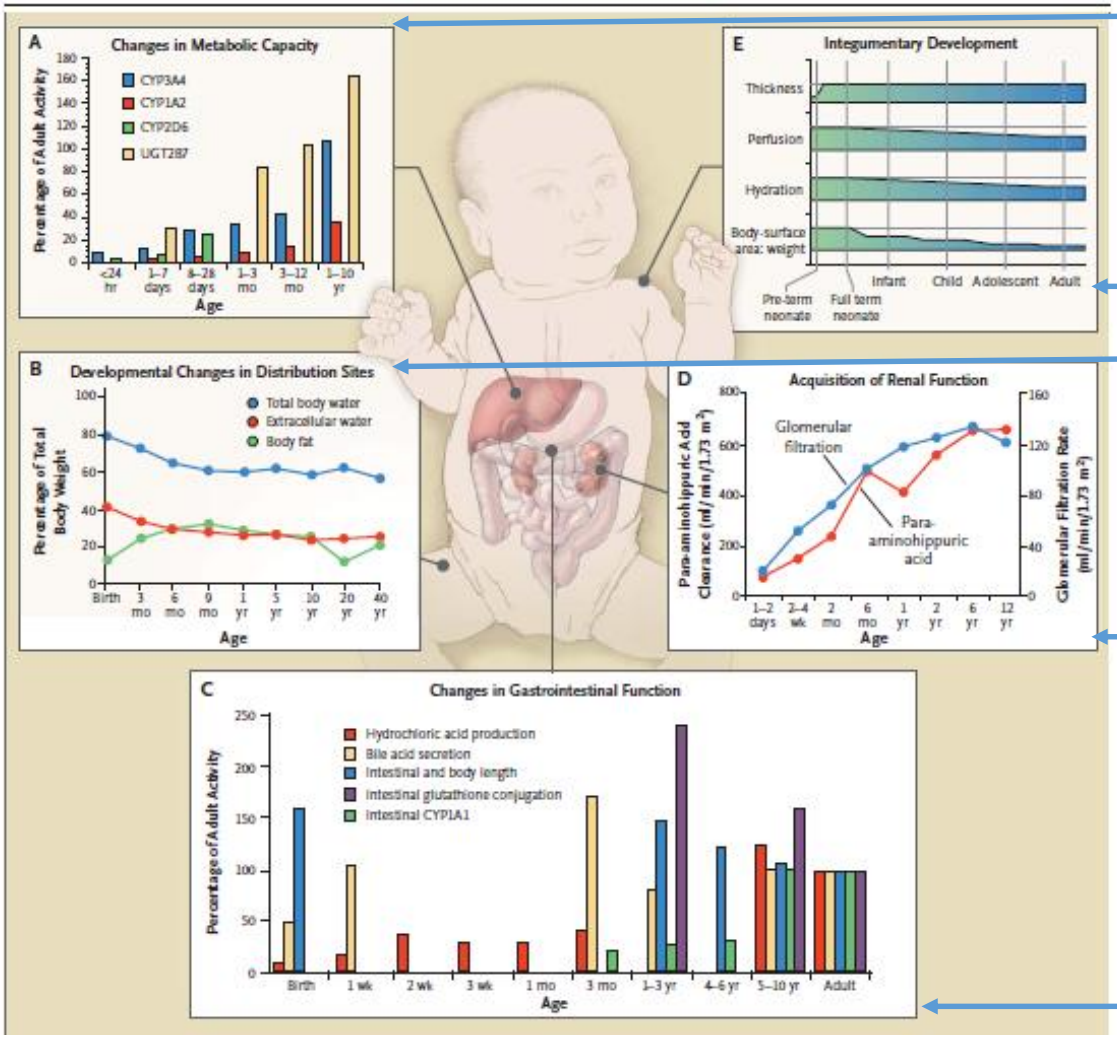
Farmakogenetika

# Vaistų poveikio įvairumas





# Vaikų farmakoterapija
# „šaudymas į judantį taikinį“...




Metabolizmas

Dangalai/oda

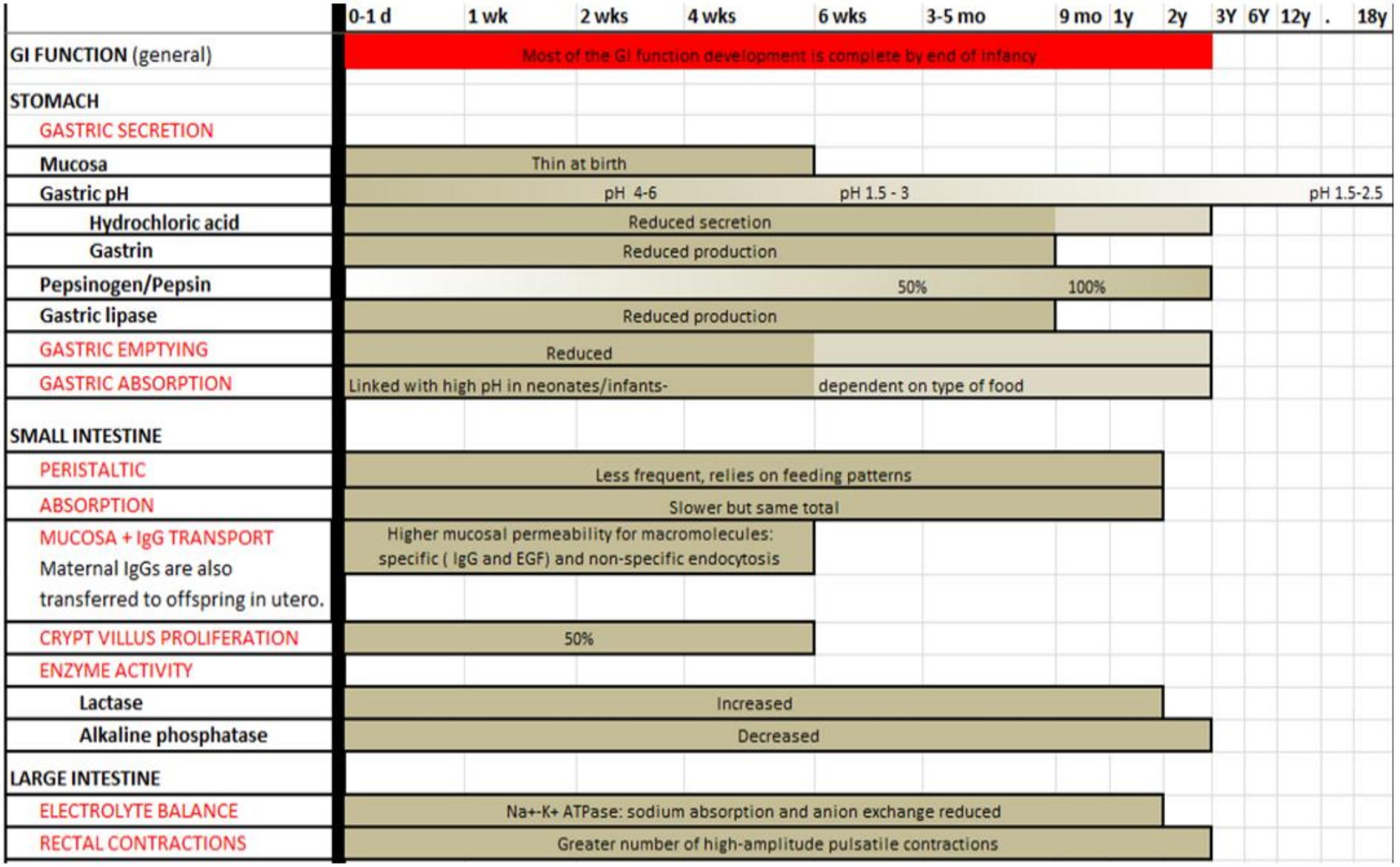
Vaistų pasiskirstymo vietos

Inkstų funkcija

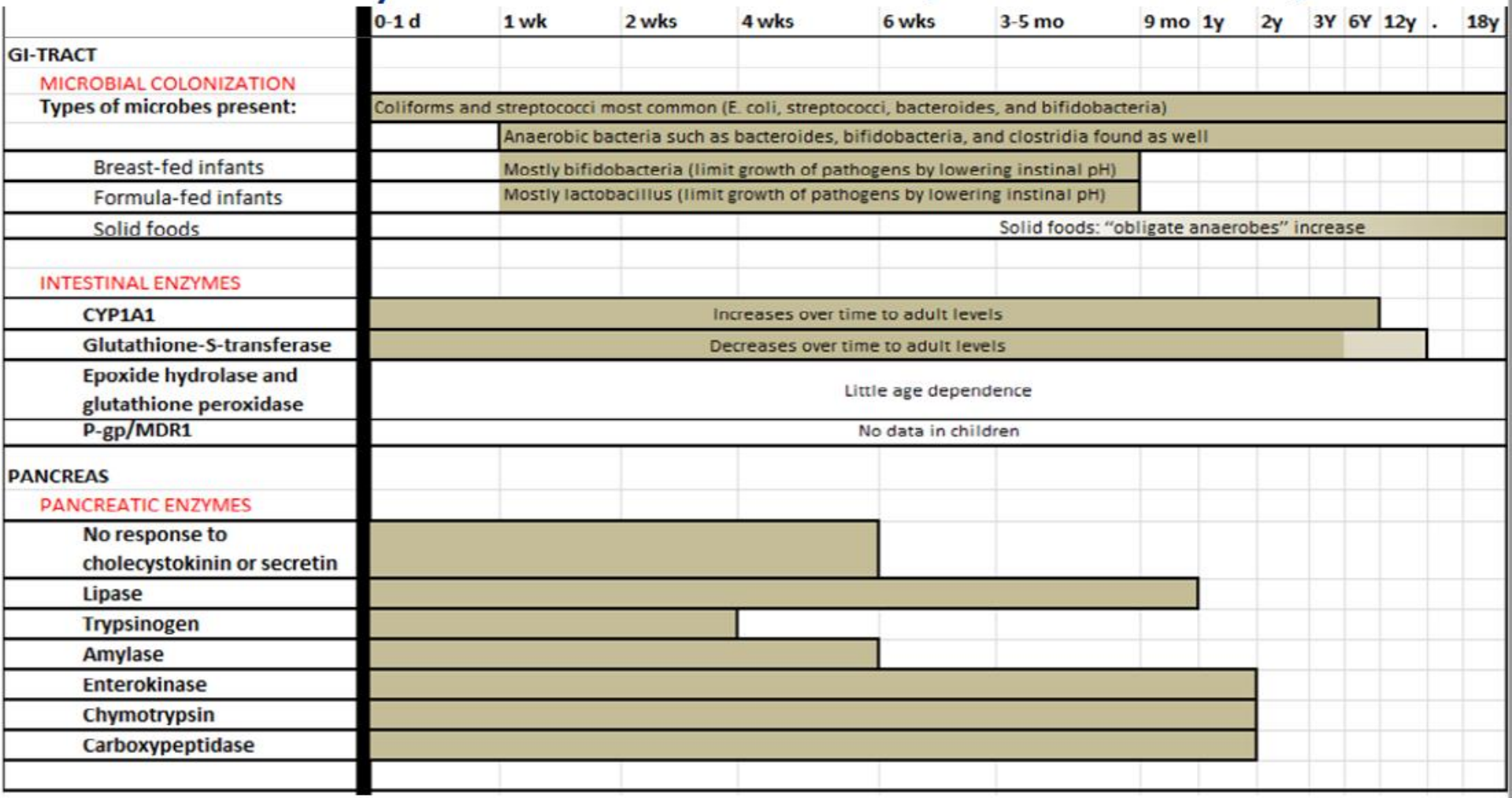
Virškinimo trakto funkcija

N Engl J Med 2003;349:1157-67

# GI-system maturation (under construction)



# GI-system maturation (under construction)

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- Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Delopmental pharmacology--drug disposition, action, and therapy in infants and children. N Engl J Med. 2003 Sep 18;349(12):1157-67. Review.
- Walthall K, Cappon GD, Hurtt ME, Zoetis T. Postnatal development of the gastrointestinal system: a species comparison.Birth Defects Res B Dev Reprod Toxicol. 2005 Apr;74(2):132-56.

# Liver maturation

| | Age (after birth) and maturation period / Hepato-biliary system and metabolic pathways | 1 month | 2 months | 3 months | 4 months | 5 months | 6 months | 12 months | 15 months | 2 years | 5 years |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Phase I Enzymes | CYP3A4 (midazolam, itraconazole) | | | | | | | | | | |
| | CYP1A2 (caffeine, theophylline) | | | | | | | | | | |
| | CYP2D6 (dextromethorphan) | | | | | | | | | | |
| | CYP2C9/CYP2C19 (benzodiazepines, proton pump inhibitors) | | | | | | | | | | |
| | CYP2E1 (acetaminophen, halothane, ethanol) | | | | | | | | | | |
| | FMO (chlorpromazine, promethazine) | | | | | | | | | | |
| Phase II Enzymes | Glucuronidation UGT1A (acetaminophen) | | | | | | | | | | |
| | Glucuronidation UGT2B (chloramphenicol, morphine) | | | | | | | | | | |
| | Sulfation SULT1A1/SULT1A3 (acetaminophen; iodothyronines and catecholamines in foetus) | | | | | | | | | | |
| | NAT2 (caffeine, isoniazid) | | | | | | | | | | |
| | Bile flow (reaching up to the adult levels) | | | | | | | | | | |

Reference:
Mulberg AE, Silber SA, van den Anker JN; Paediatric Drug Development: Concepts and Applications; Developmental hepatic pharmacology in paediatrics; 2009; p. 243.

# Renal system maturation

| Renal system Function / Age subsets | 0 – 1 year | 1 – 2 years | 2 – 3 years | Up to 18 years |
|---|---|---|---|---|
| **Glomerular filtration rate (GFR)** | Due to haemodynamic changes during and just after birth, GFR increases rapidly in the first two weeks of life. Afterwards, GFR corrected for body surface area increases more slowly to reach adult levels **between 1 to 2 years of age.** | | | |
| **Tubular secretion** | The renal tubular secretion capacity increases over the first months of life and then declines to reach the adult level (per unit of body area) at **~ 7 months to 1 year of age.** The organic anion pathway matures faster than the organic pathway. | | | |
| **Tubular reabsorption** | The development and maturation of the glomerular permeability functions and the renal tubular reabsorption are gradual and continuous processes from **birth** to **adolescence**. The key stage of their maturation is at **~ 1 and 3 years of age.** | | | |

**References:**

1. **Guideline on the investigation of medicinal products in the term and preterm neonate. CHMP and PDCO, EMEA, London 25 June 2009.**
2. **Paediatric Drug Development. Mulberg AE, Silber SA, Van den Anker JN. John Wiley & Sons, 2009.**

# Brain maturation

| Brain/brain elements | Period of maturation (postnatal months and years of age) | 1 m | 6 m | 12 m | 18 m | 24 m | 3 y | 4 y | 5 y | 6 y | 7 y | 8 y | 9 y | 10 y | 11 y | 12 y | 13 y | 14 y | 15 y | 16 y | 17 y | 18 y |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Neural tube differentiation | Up to 1st month of age | | | | | | | | | | | | | | | | | | | | | |
| Blood brain barrier | Until 6th month of age | | | | | | | | | | | | | | | | | | | | | |
| Proliferation and organization of synapses | 50% at 2 yrs; 100% at 4 yrs | | | | | | | | | | | | | | | | | | | | | |
| Myelination | 50 % of corpus callosum at 18 months; up to 20-30 yrs | | | | | | | | | | | | | | | | | | | | | |
| Brain size | 80% at 2 yrs; 90% at 5 yrs; remodelling of white and gray matter up to 20-30 yrs | | | | | | | | | | | | | | | | | | | | | |
| Cortical gray matter maturation (motor & sensory systems, memory, audio-visual input, object recognition) | 1. Frontal lobe: 11 yrs girls & 12.1 yrs boys<br>2.Temporal lobe: 16.7 yrs girls & 16.2 yrs boys<br>3. Parietal lobe: 10.2 years girls and 11.8 yrs boys | | | | | | | | | | | | | | | | | | | | | |
| Subcortical gray matter maturation (control of movement and muscle tone, higher cognitive functions, attention, affective states) | Nucleus caudatus size peak: 7.5 yrs girls & 10.0 yrs boys | | | | | | | | | | | | | | | | | | | | | |
| Amygdala and hippocampus maturation (emotion, language, memory) | Between 4 yrs and 18 years | | | | | | | | | | | | | | | | | | | | | |
| White matter maturation | 1. Lobar white matter volumes increase up to 30 years<br>2. Corpus callosum: between 4 yrs and 18 years (integrating left & right hemispheres; unification of sensory fields, memory storage and retrieval, attention & arousal, enhancing language and auditory functions) | | | | | | | | | | | | | | | | | | | | | |
| Prefrontal cortex maturation | Up to the late adolescence – 17-18 yrs | | | | | | | | | | | | | | | | | | | | | |
| Neurotransmitter system maturation (NMDA receptors) | Up to 3 years of age | | | | | | | | | | | | | | | | | | | | | |
| Cholinergic and serotonergic systems | Through childhood and adolescence, in individuals possibly into adulthood | | | | | | | | | | | | | | | | | | | | | |

1. Volpe JJ, Neurology of the newborn, 5th ed., Elsevier Health Sciences, Philadelphia 2008, p5
2. Benes F, The development of the pre-frontal cortex, the maturation of neurotransmitter systems and their interactions, in: Handbook of developmental cognitive neuroscience (Nelson CA, Luciana M, eds) , MIT press, 2001

# Lung maturation (under construction)

| Development of the Pulmonary System | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Fertilization | | | | | | | | Birth | | | | | | | | |
| | Age subset | Embryogenesis | | Foetal development | | | | | | Neonate/ Infant | Child | | | | | | | |
| | | 0 w | 5 w | 10 w | 15 w | 20 w | 25 w | 20 w | 35 w | 40 w | 1y | 2y | 3y | 4y | 5y | 6y | 7y | 8y |
| Stage | Embryonic | | | | | | | | | | | | | | | | | |
| | Pseudo-glandular | | | | | | | | | | | | | | | | | |
| | Canalicular | | | | | | | | | | | | | | | | | |
| | Saccular | | | | | | | | | | | | | | | | | |
| | Alveolar (proliferation) | | | | | | | | | | | | | | | | | |
| | Microvascular maturation | | | | | | | | | | | | | | | | | |
| | Alveolar (expansion) (Normal lung growth period) | | | | | | | | | | | | | | | | | |

References:


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# Vaistų klinikiniai tyrimai pediatrijoje

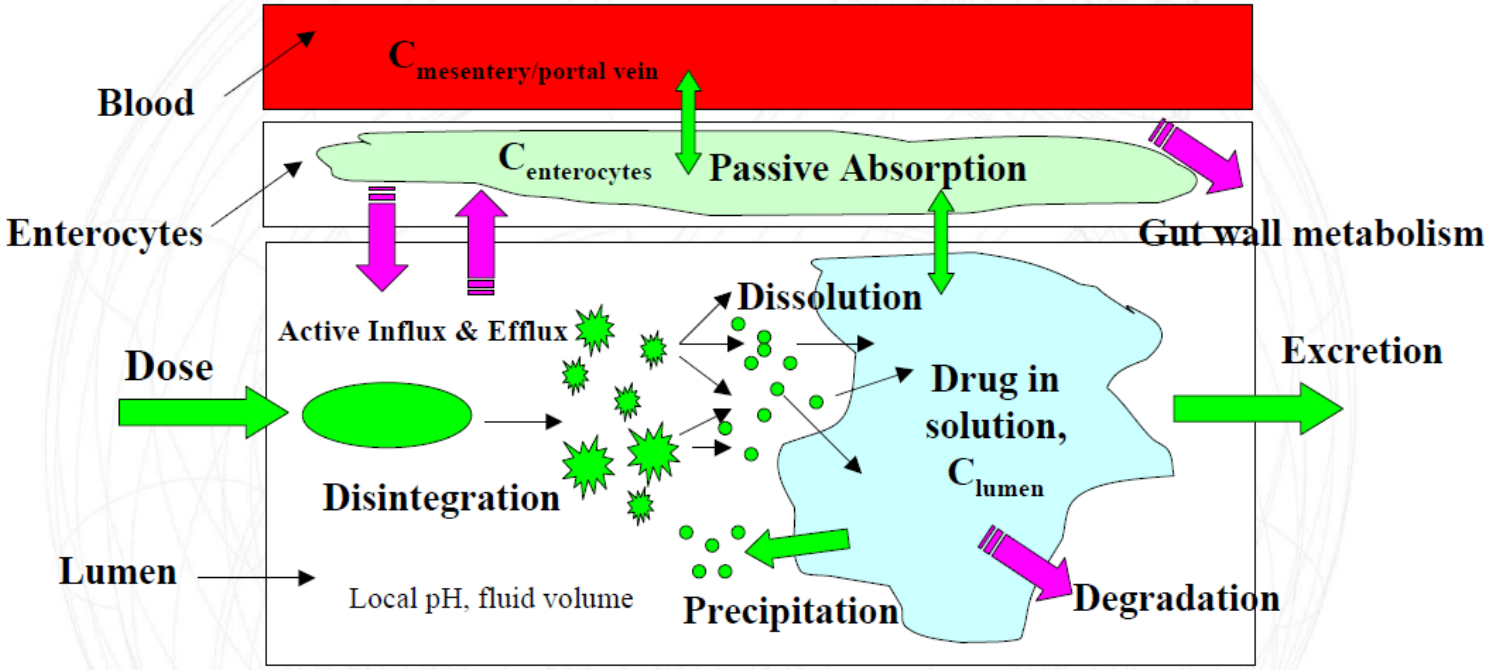
## Problemos

- Etinės problemos
- Nedidelis sergamumas
- Sunku surinkti reikiamą pacientų skaičių
- Reikia tirti visų amžiaus grupių pacientus
- Didelės išlaidos

## Sprendimai

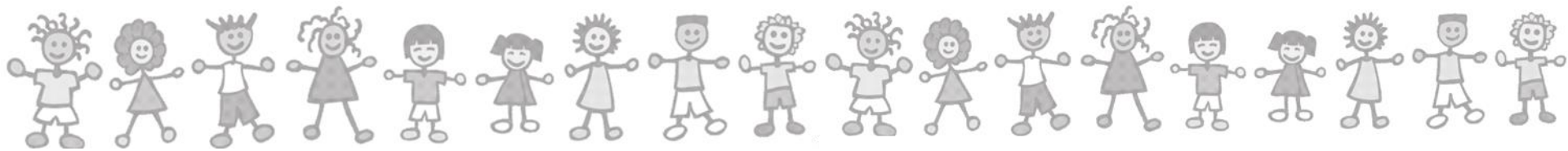
- Nemokamas mokslinis patarimas
- Patento pratęsimas
- Rinkos apsauga
- Nauji tyrimo metodai
  - Duomenų ekstrapoliavimas
  - Klinikinių tyrimų simuliacija

# Processes Involved in Oral Absorption

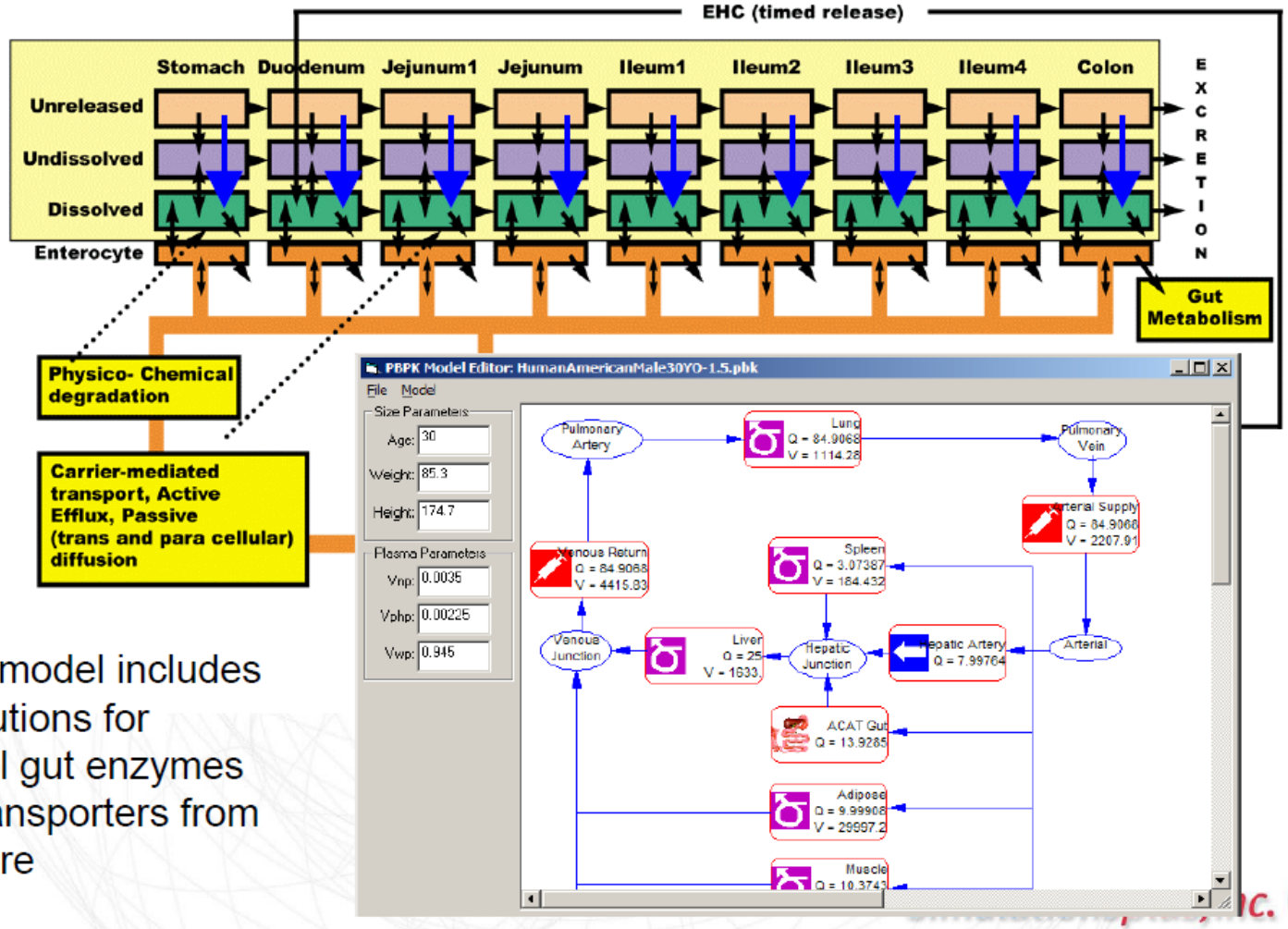



**These phenomena are repeated in each of the compartments of the gastrointestinal tract**



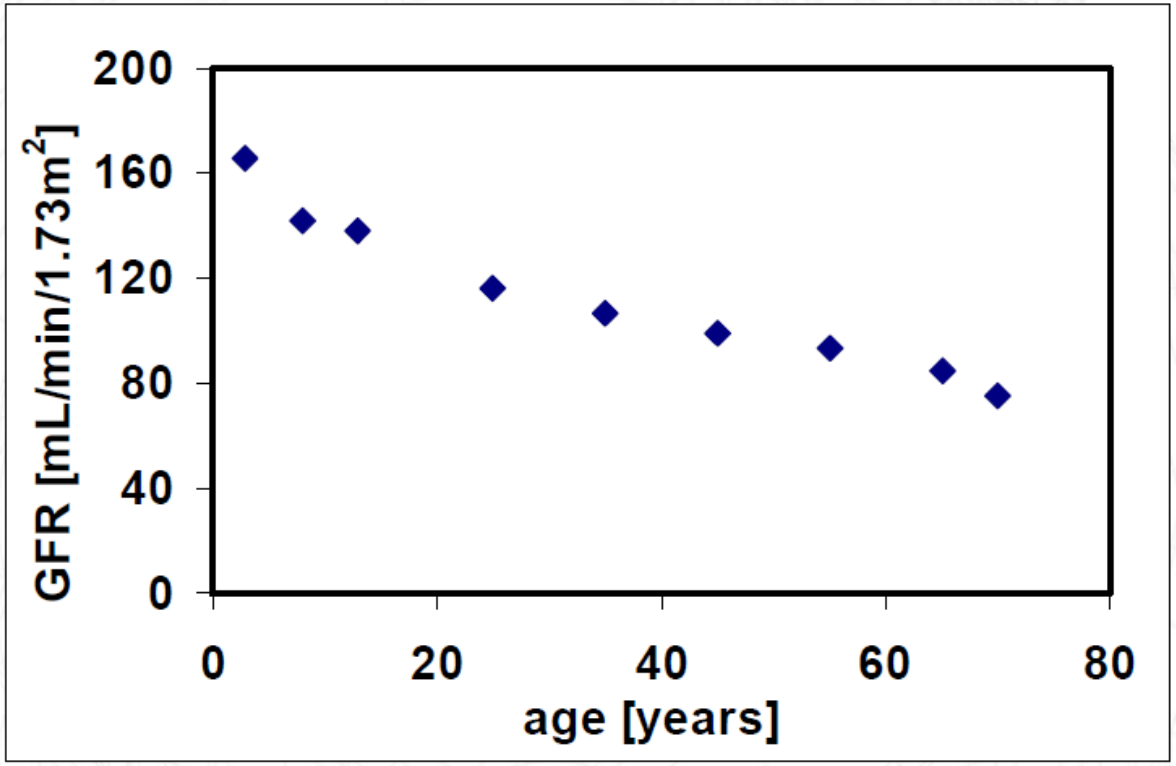


# ACAT-PBPK Combined Model



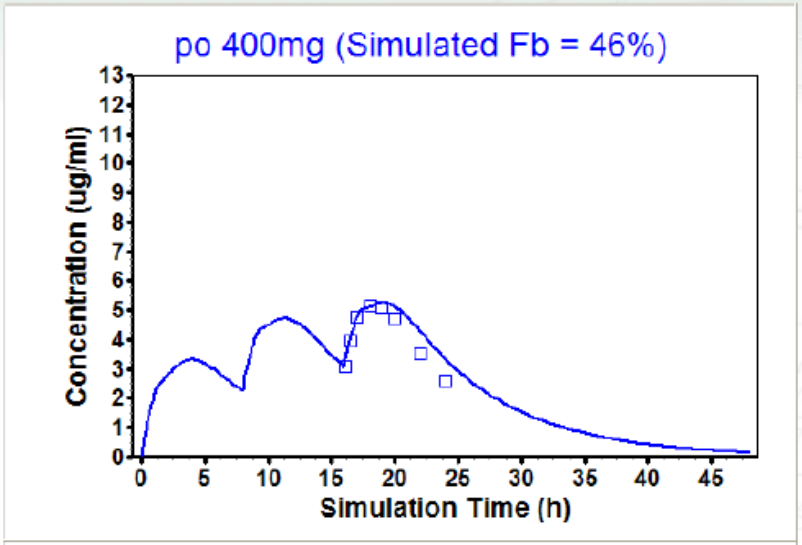

ACAT model includes distributions for several gut enzymes and transporters from literature

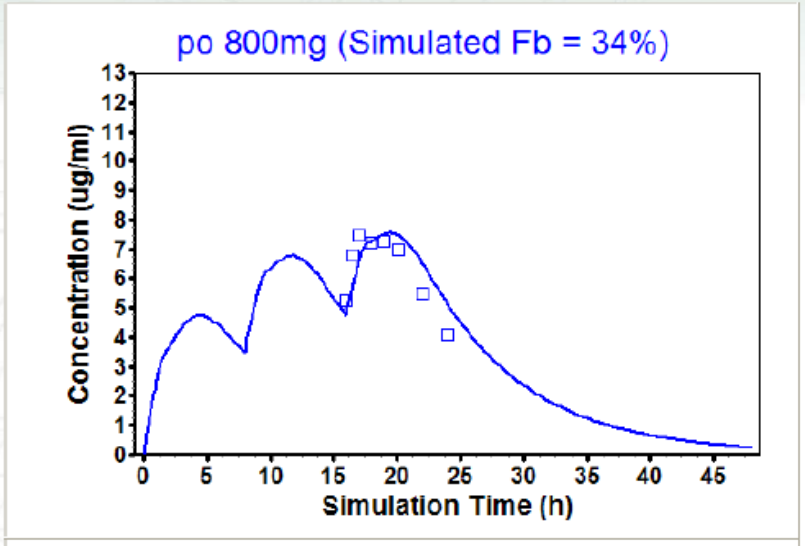
# Gabapentin CL Modeled as Function of Glomerular Filtration Rate

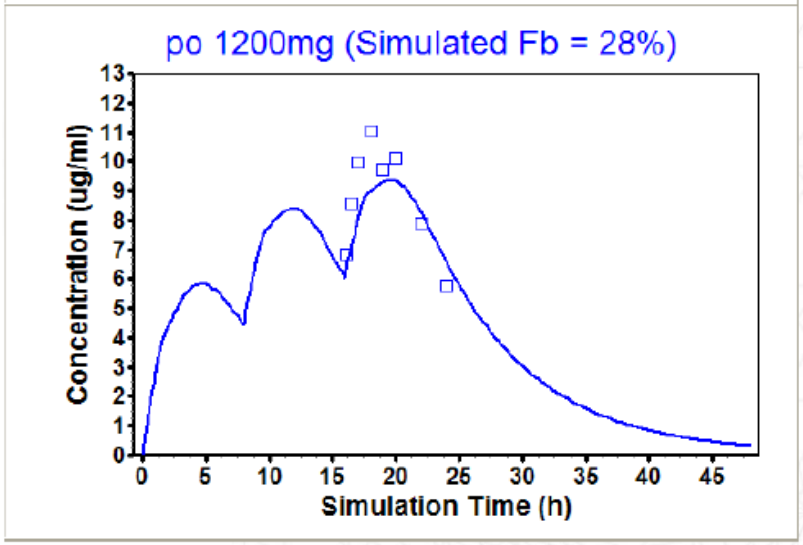


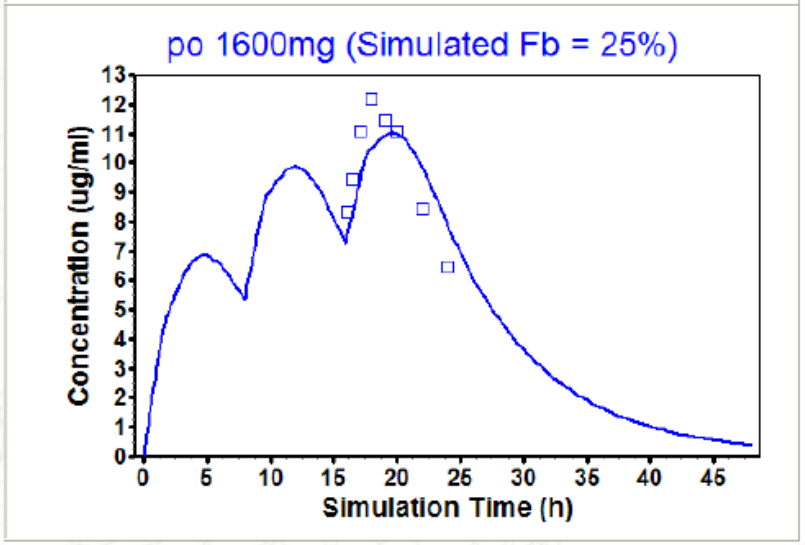

Mego S. 36th Annual Scientific Meeting of the Australian and New Zealand Society of Nuclear Medicine (poster)
Stevens L. FAQ about GFR Estimates (National Kidney Foundation publication)

# Gabapentin Nonlinear Dose Dependence in Adults

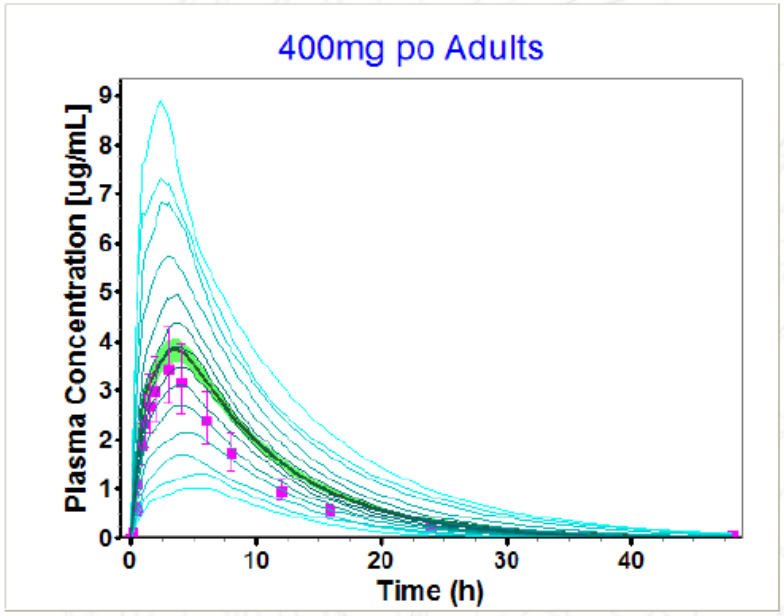


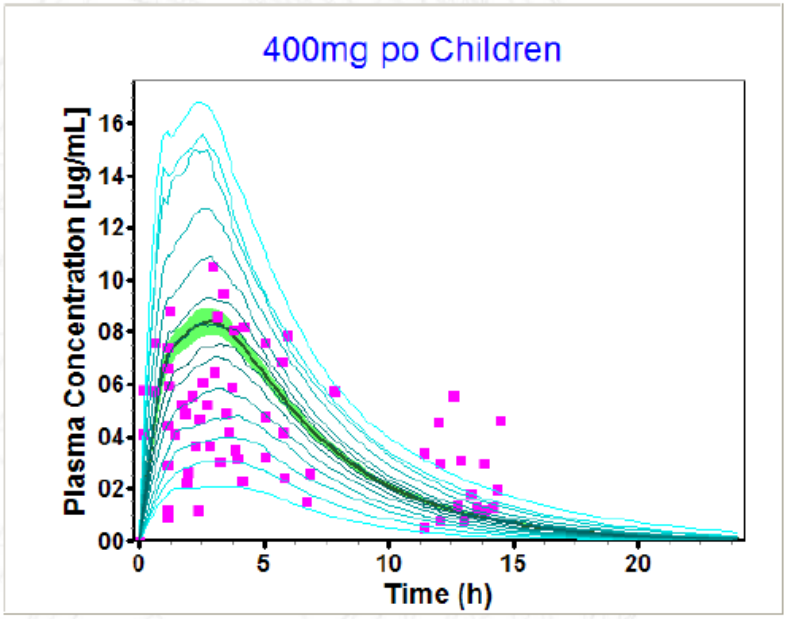



# Adult and Pediatric Population Simulations




400 mg solution: 41 yo adult female




400 mg tablet, 7 yo children

# Išvados

- Vaistų farmakokinetika ir farmakodinamika vaikams gali skirtis nuo suaugusiųjų (kitų amžiaus grupių vaikų) dėl skirtingos organų brandos
- Daugelio naujų (ir ne tik) vaistų poveikis vaikams nežinomas
- Skiriant neregistruotą vaistą vaikams, būtina įvertinti naudą ir riziką, stengti kuo tiksliau parinkti dozę atsižvelgiant į amžių, kūno masę, kūno paviršiaus plotą, inkstų funkciją, brandą, stebėti atsaką į vaistą
- Skirti vaikams tinkamą vaisto formą, vartojimo būdą
- Vengti polifarmacijos