Population Pharmacokinetics of Isoniazid in Children with Tuberculous Meningitis

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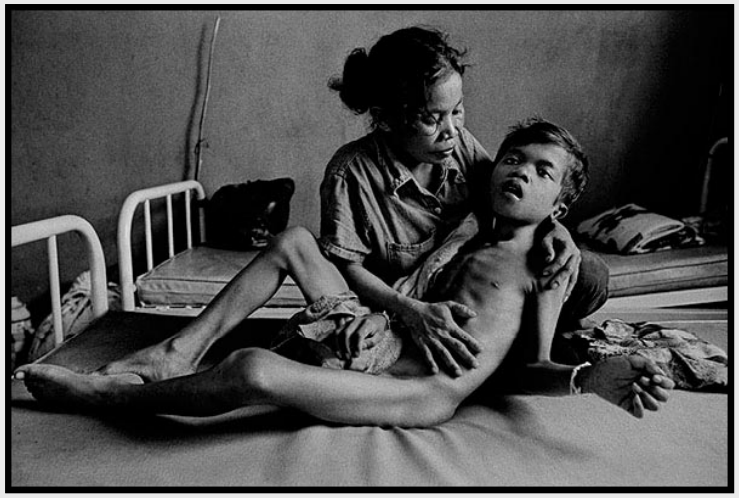

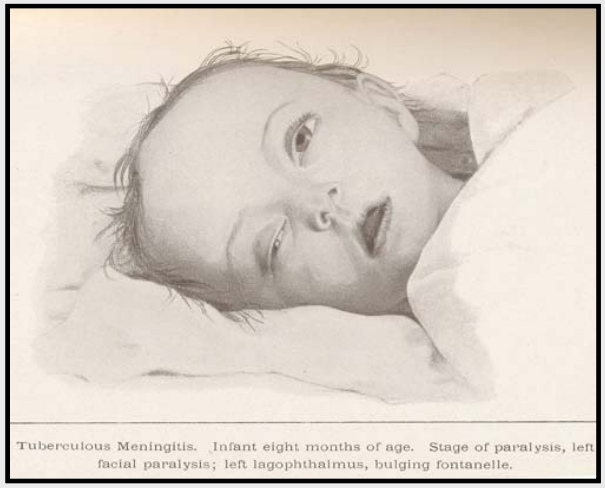

Tuberculous Meningitis. Infant eight months of age. Stage of paralysis, left facial paralysis; left lagophthalmus, bulging fontanelle.

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Outline

- Background
- Anti-tuberculosis drugs
- Objective
- Methods
- Pharmacokinetics of Isoniazid
- Planning for further study
- Conclusions
- Acknowledgement

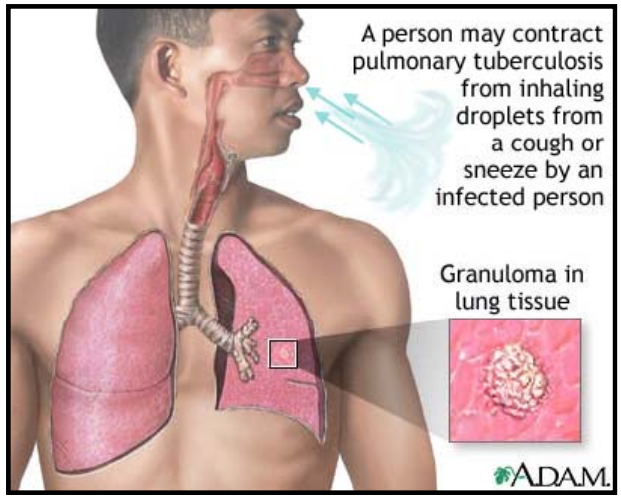
Background

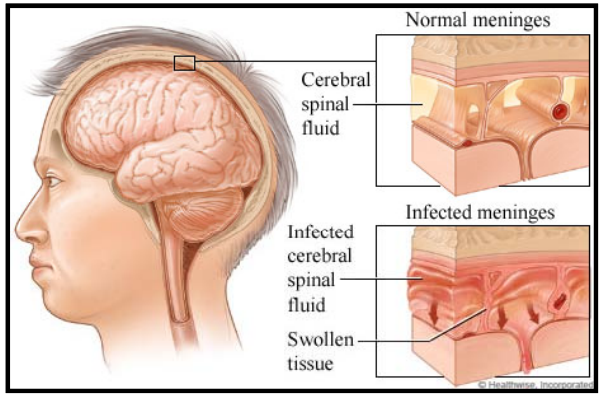
Tuberculosis

- Tuberculosis caused by *Mycobacterium tuberculosis*
- Airborne transmission
- Pulmonary tuberculosis
- Extrapulmonary tuberculosis (e.g. lymph nodes, skeletons, meninges)

Tuberculous meningitis (TBM)

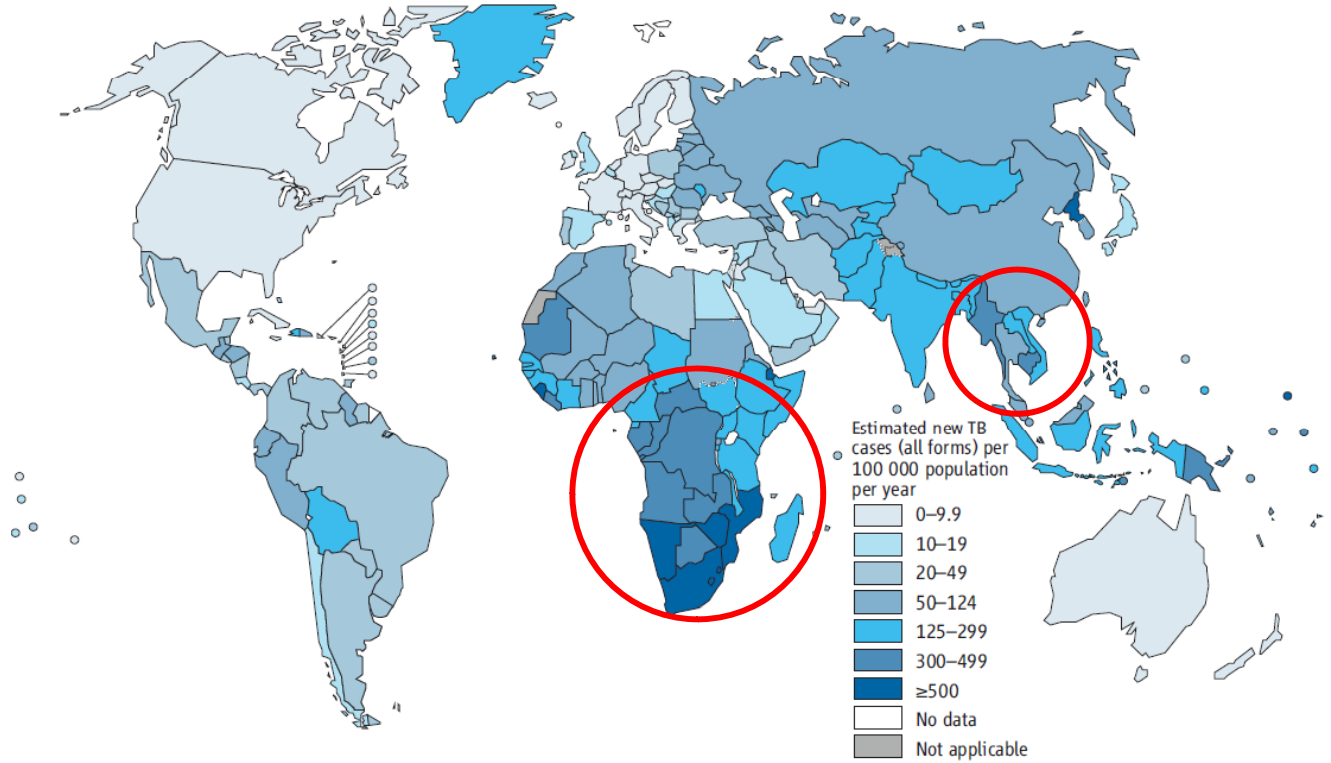
- The most common form of tuberculosis in the central nervous system
- Most often occur in young children but also found in adult, especially in HIV infected patients





Background

WHO estimated tuberculosis incidence rates,2012



- The incidence of tuberculosis among children was estimated at **530,000** cases, equivalent to about **6% of the total number of 8.6 million** incident cases in 2012
- Children aged <1 year has 10-20% risk of developing TBM after primary infection
- Early diagnosis and treatment are crucial to reduce the mortality

Anti-tuberculosis drugs

- Children with suspected or confirmed pulmonary tuberculosis

Isoniazid (H)
Rifampicin (R)
Pyrazinamide (Z)
Ethambutol (E)
2 months

→

Isoniazid (H)
Rifampicin (R)
4 months

- Children with suspected or confirmed tuberculous meningitis

Isoniazid (H)
Rifampicin (R)
Pyrazinamide (Z)
Ethambutol (E)
2 months

→

Isoniazid (H)
Rifampicin (R)
10 months

Anti-tuberculosis drugs

- Isoniazid is one of the essential first-line anti-tuberculosis agents that have a rapid early bactericidal activity

- Isoniazid is a lipophilic small molecule and considered to be the ideal agent for TBM treatment since it easily cross the blood-brain-barrier to the site of action

- Complex pharmacokinetic properties;
  - Polymorphic elimination (N-acetyltransferase 2, *NAT2*)
  - First-pass metabolism

- The information about pharmacokinetic properties of isoniazid in children with TBM is limited

Objective

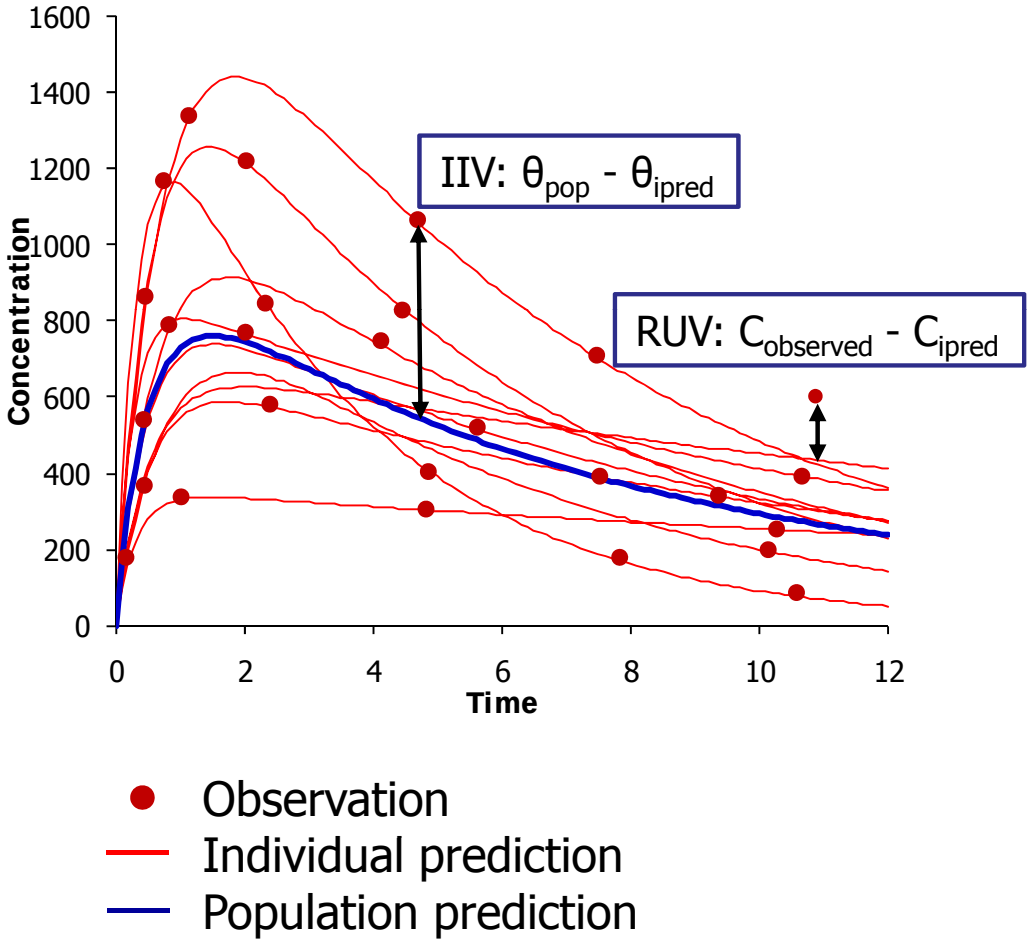
To investigate the pharmacokinetics of isoniazid in children with TBM

- 99 Vietnamese children with confirmed or suspected TBM
- Age from 2 months to 15 years
- Fixed dose combination tablet of isoniazid, rifampicin, and pyrazinamide + extra tablet for ethambutol
- Sparse sampling schedule at random time points
  - 4 plasma samples /patient
  - 2 cerebrospinal fluid (CSF) samples /patient

	Number of observations per patient			
Sample	DAY 1	DAY 14	DAY 30	DAY 90
Plasma	2	2	1	1
CSF	-	-	1	1

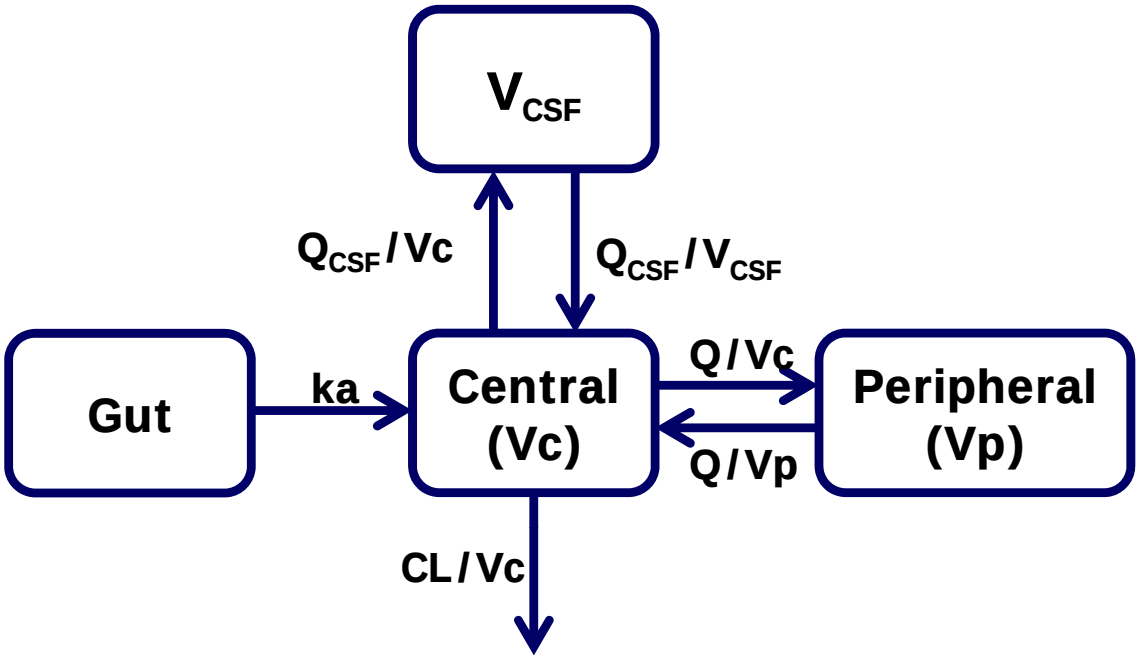
Methods

Nonlinear mixed-effects modeling



- Structural model
  - Absorption model
  - Distribution model
- Statistical model
  - Inter-individual variability
  - Residual unexplained variability
- Covariate model
  - Relationship between pharmacokinetic parameters and patient's demographic data (e.g. body weight, age)

Pharmacokinetics of Isoniazid



Maturation effect

$$MF = \frac{Age^{hill}}{AG50^{hill} + Age^{hill}}$$

Allometric scaling

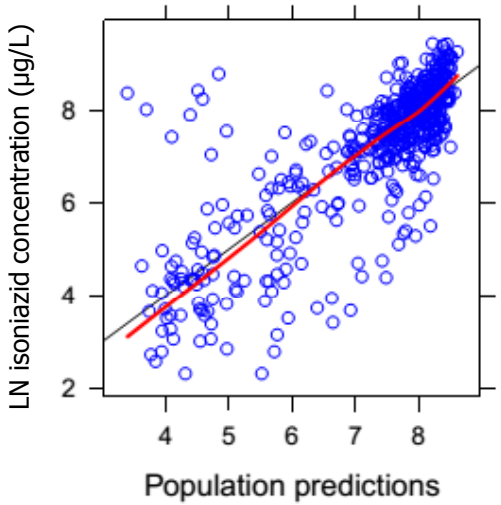
$$CL = CL_{std} \times \left(\frac{WT}{WT_{median}}\right)^{0.75}$$

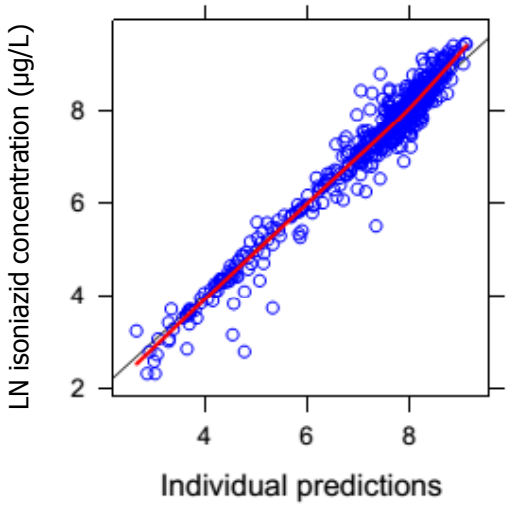
- 2-compartment distribution model for plasma
- 1-compartment distribution model for CSF
- The allometry was used to describe the PK parameter in children
- Clearance of isoniazid increased over time (increased by 30% in 48 h)
- Maturation of *NAT2* enzyme which influence isoniazid clearance complete during the 1st year of life.

Pharmacokinetics of Isoniazid

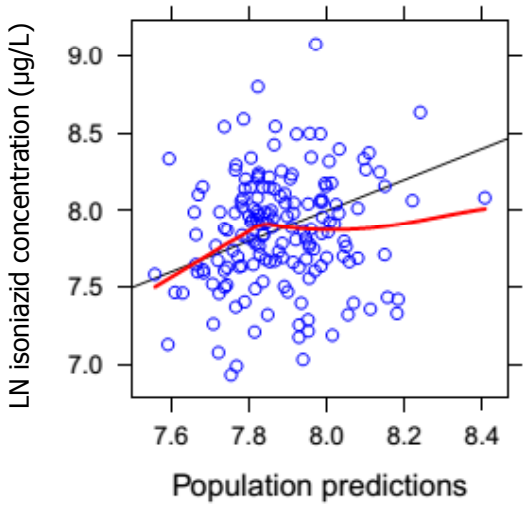
Goodness-of-fit plots

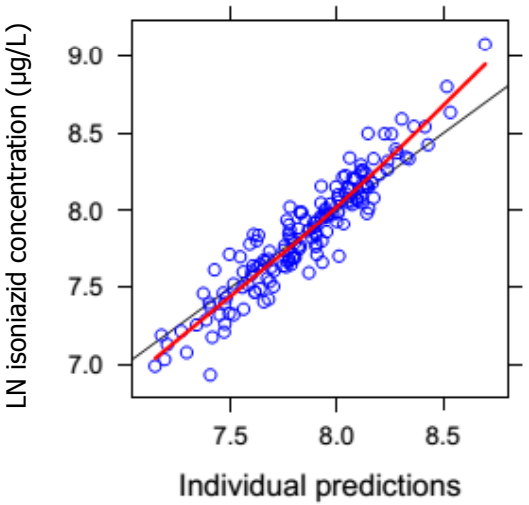
Plasma



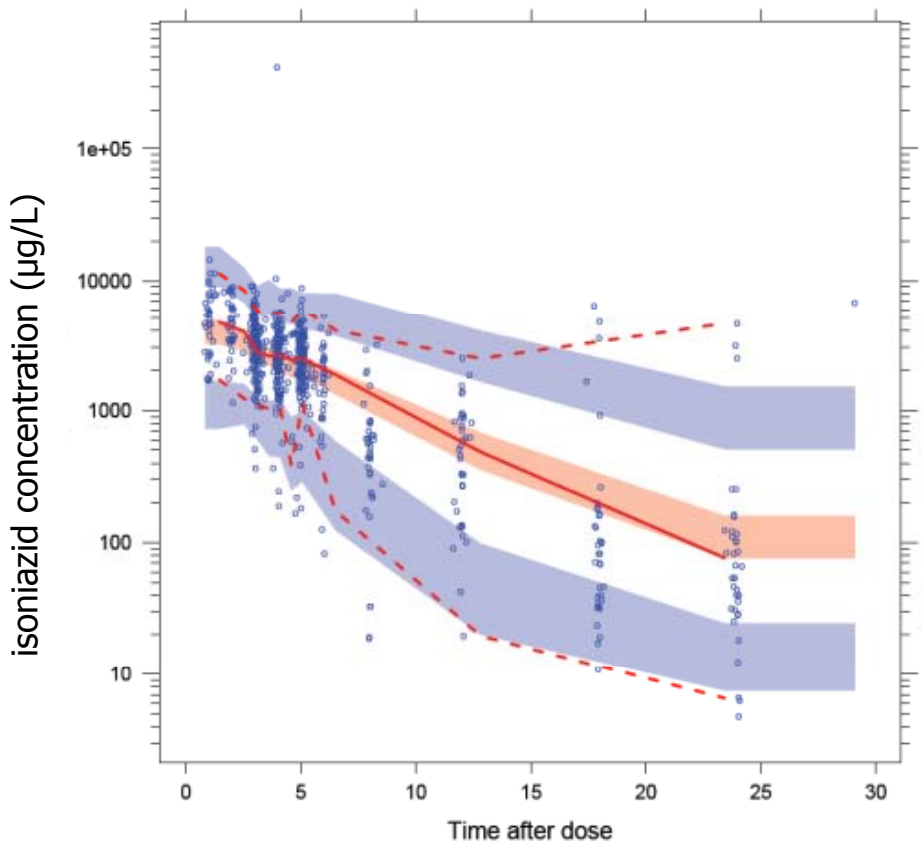


CSF

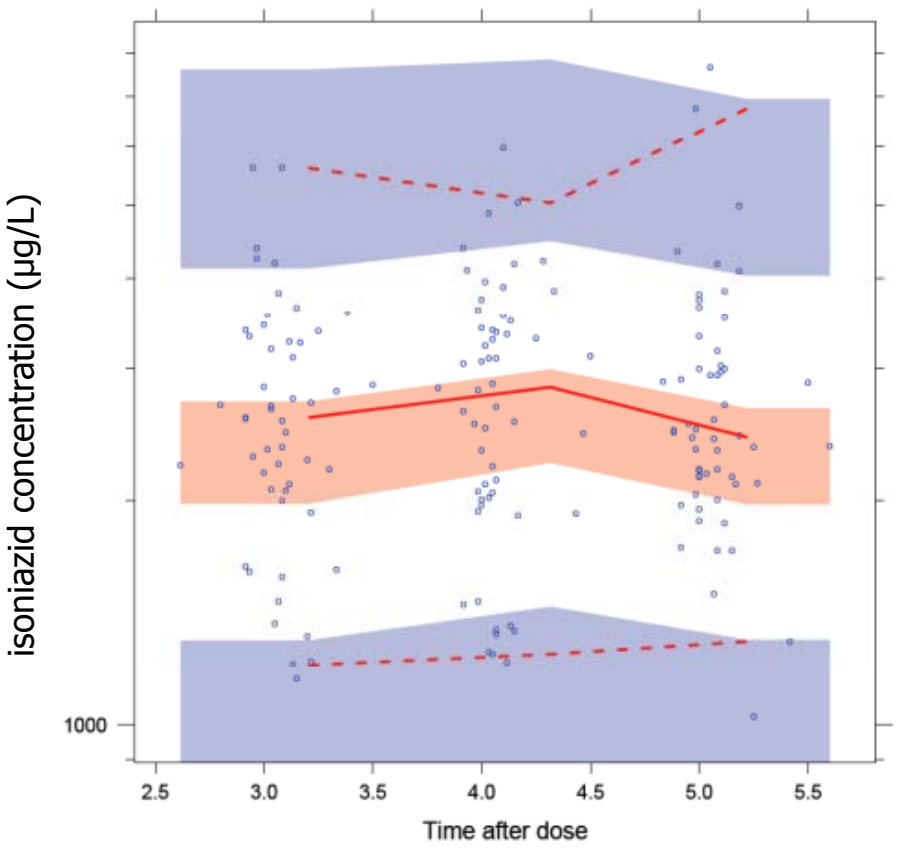




Pharmacokinetics of Isoniazid



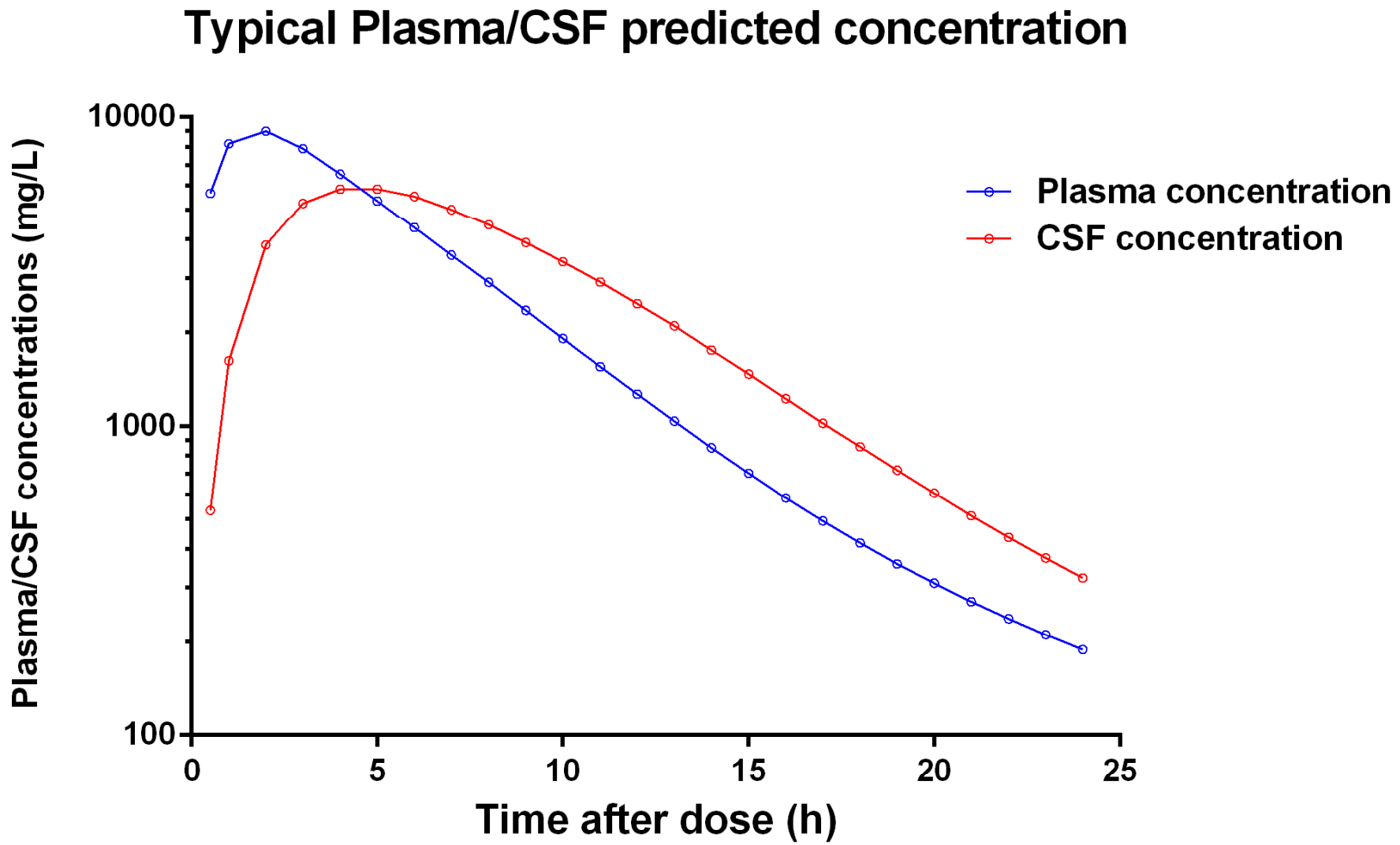
Plasma



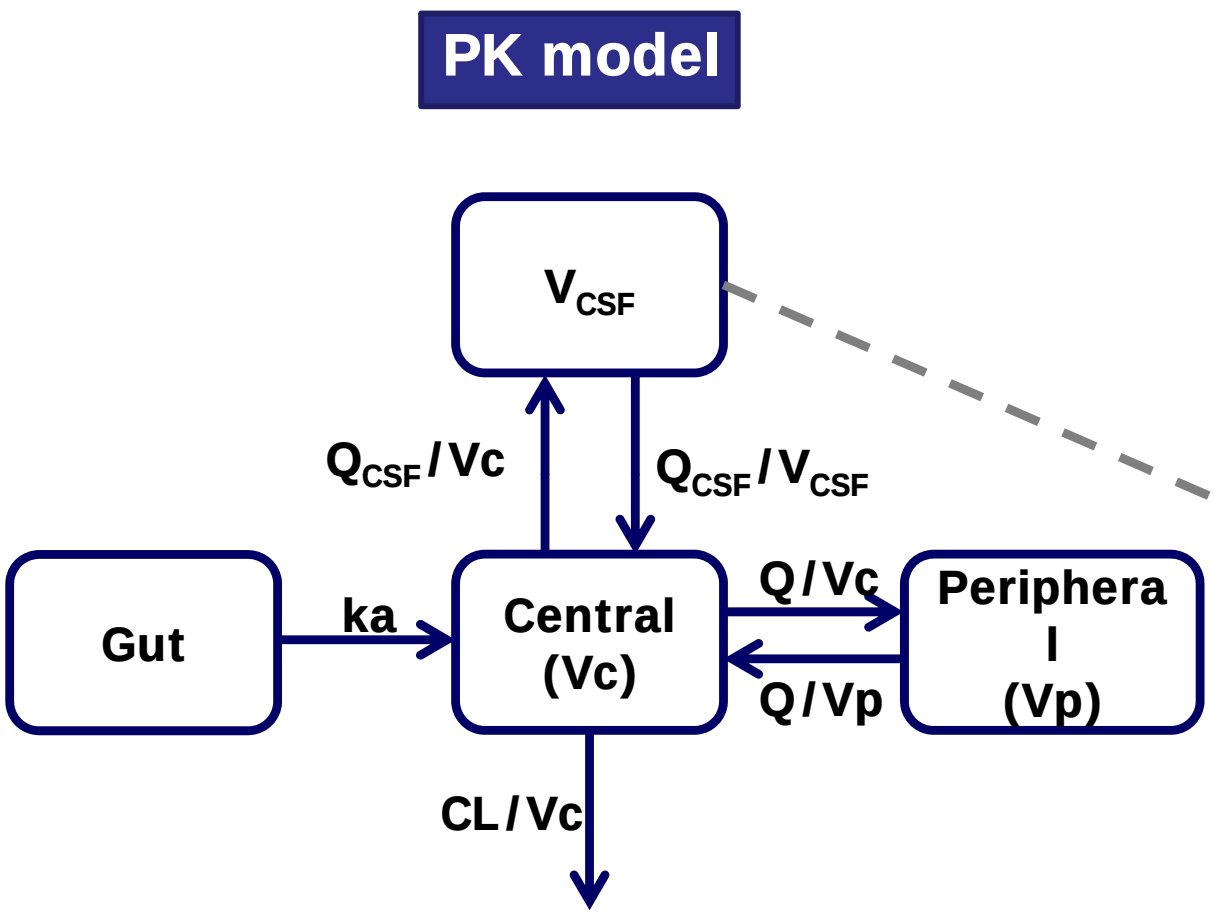
CSF

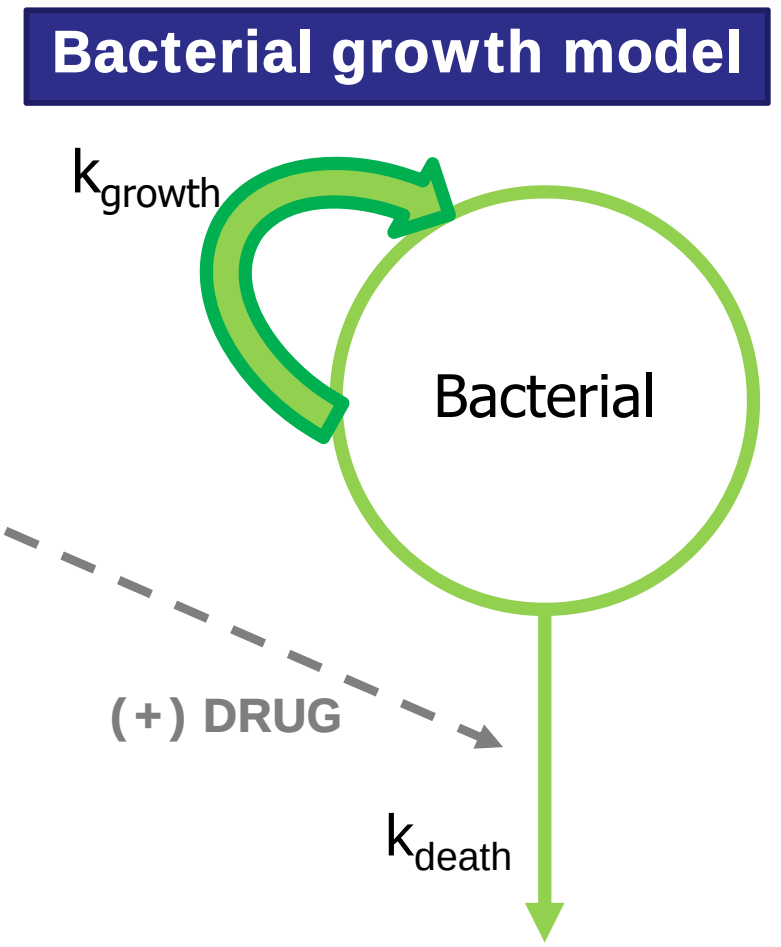
Prediction-corrected visual predictive check of the final model of isoniazid

Pharmacokinetics of Isoniazid



Planning for further study





Information from literatures

Conclusions

- Pharmacokinetics of isoniazid in children with TBM successfully described by
  - 2-compartment distribution model for plasma
  - 1-compartment distribution model for CSF
- Allometric function of body weight was used to describe the pharmacokinetic parameter.
- The increase of isoniazid clearance over time may be partly explained by improvement of organ function.
- Maturation of *NAT2* enzyme was completed during the early stage of life.
- The link between pharmacokinetics model of isoniazid and bacterial growth model is a worth investigation.

Acknowledgement

Thank you for your kind attention

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Thanks for all children and their families who participate in this study

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