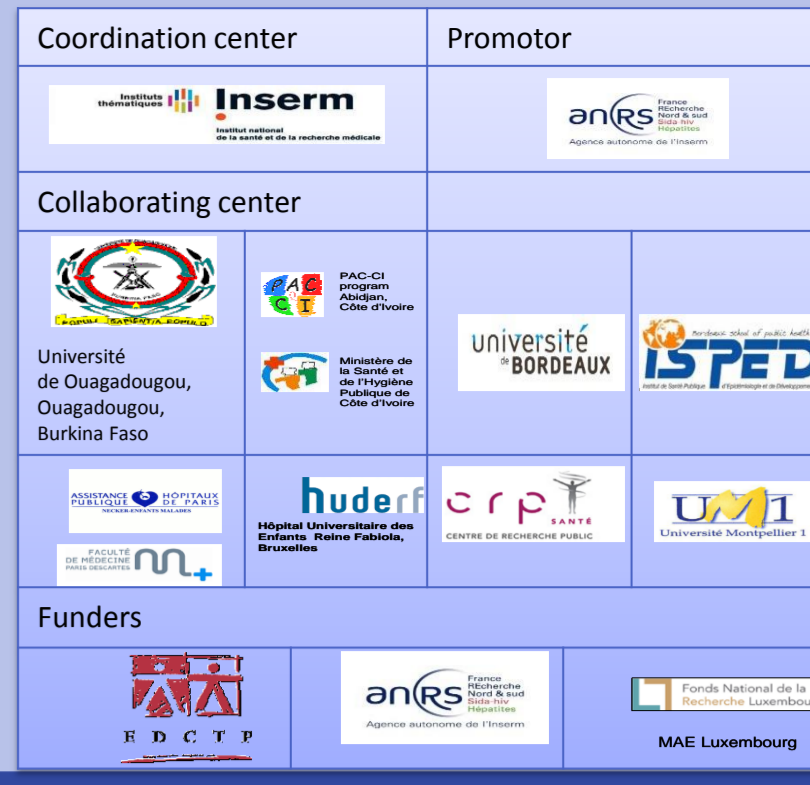




# Population pharmacokinetics of cotrimoxazole West African HIV-infected children

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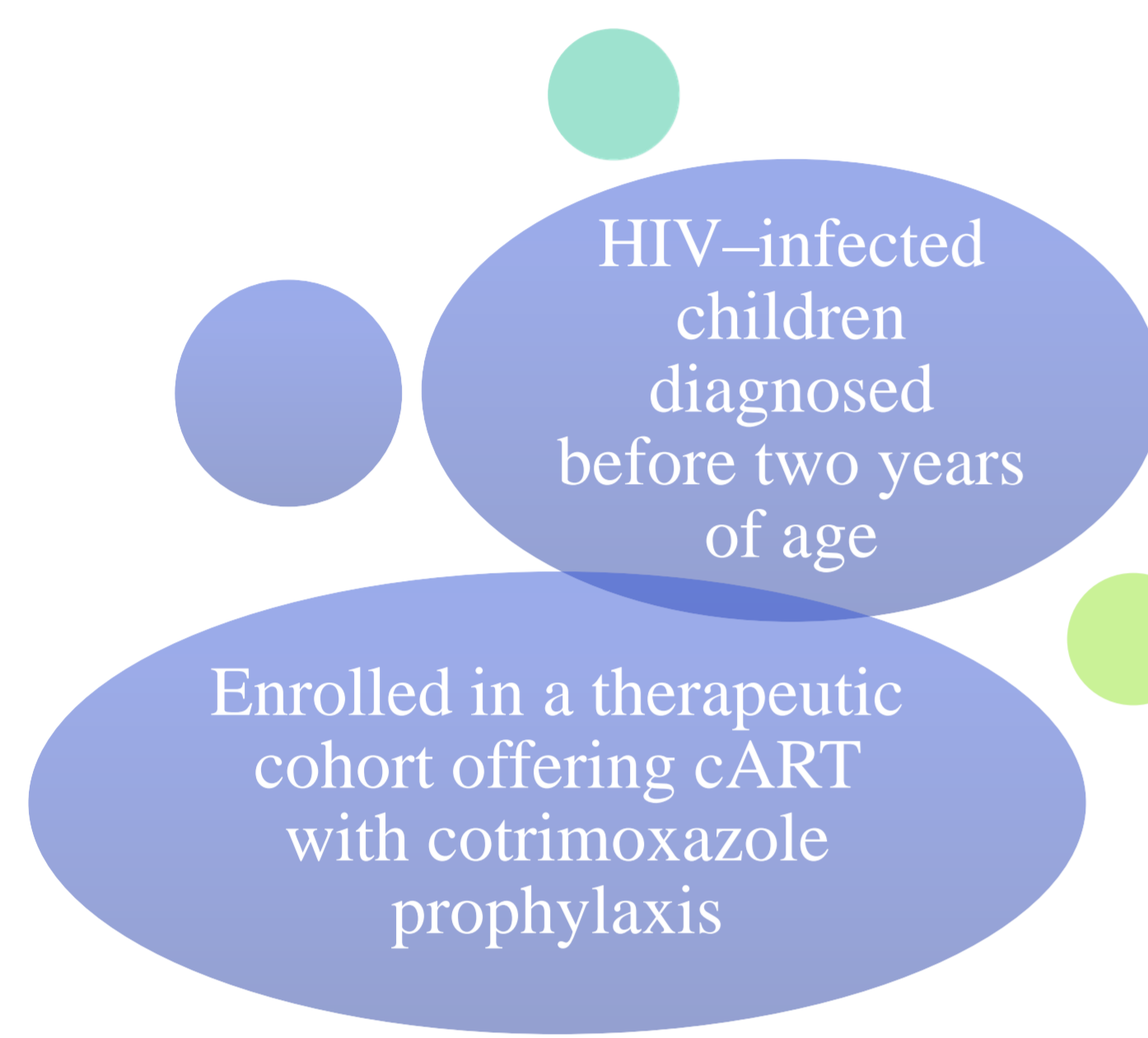
## INTRODUCTION

This project is part of the MONOD-ANRS 12206 trial designed to evaluate a simplified once-daily antiretroviral therapy in children infected with HIV in Ivory Coast and Burkina Faso. In addition to antiretroviral treatment, all children received **cotrimoxazole prophylaxis**. The drug, used to prevent opportunistic infections, is a combination of two active molecules: **trimethoprim (TMP)** and **sulfamethoxazole (SMX)**. Some pharmacokinetics (PK) data in neonates and children are available but the age group 6 months - 3 years is very poorly described. However, the few data that are available suggest that current doses should evolve according to the maturity of the child to prevent from over or under dosages of medication.

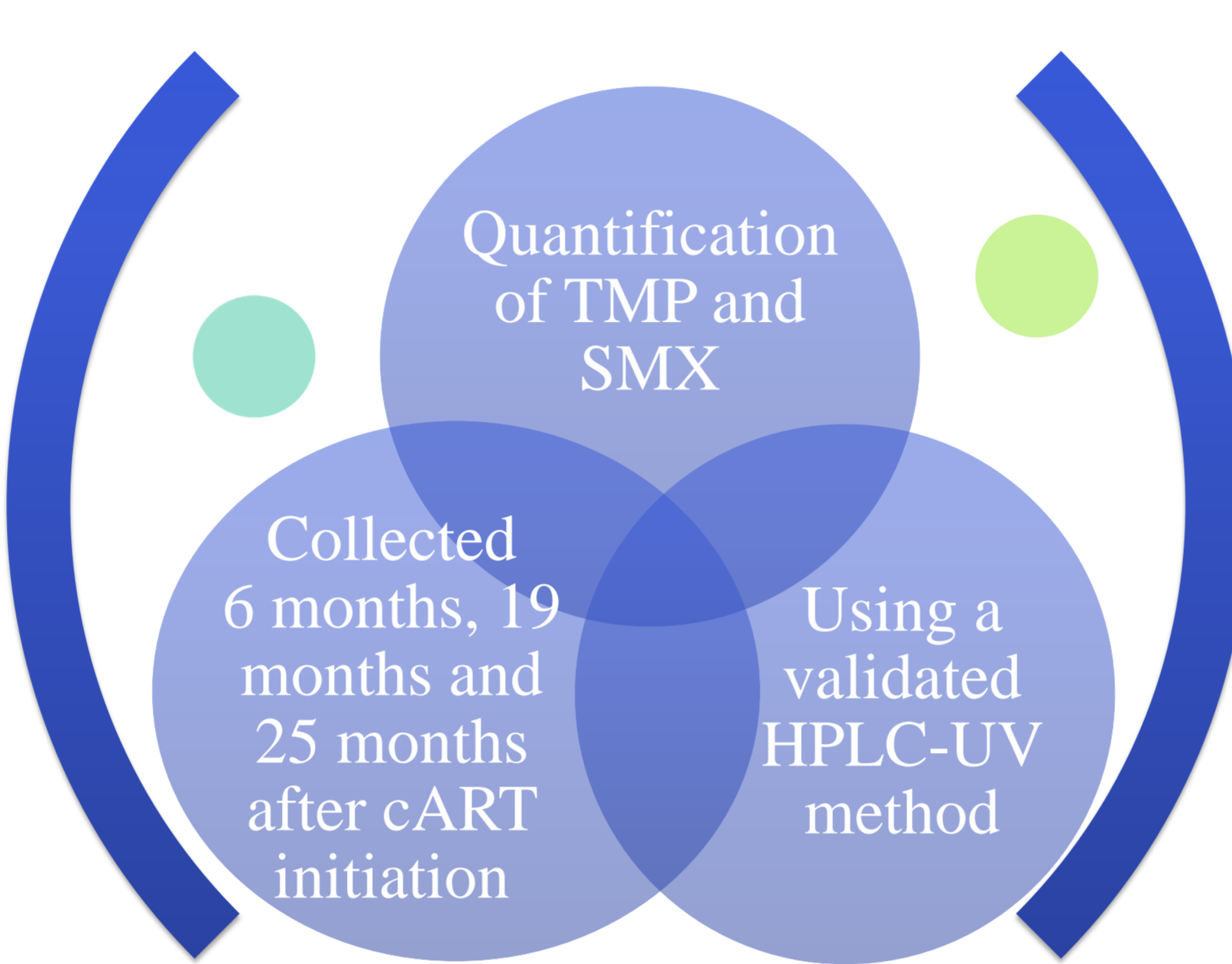
The aims of this study were to describe **the pharmacokinetics of the cotrimoxazole in a large population of children**, to identify factors influencing the pharmacokinetics of TMP and SMX, and to evaluate the doses recommended by the World Health Organization during childhood.

## METHODS

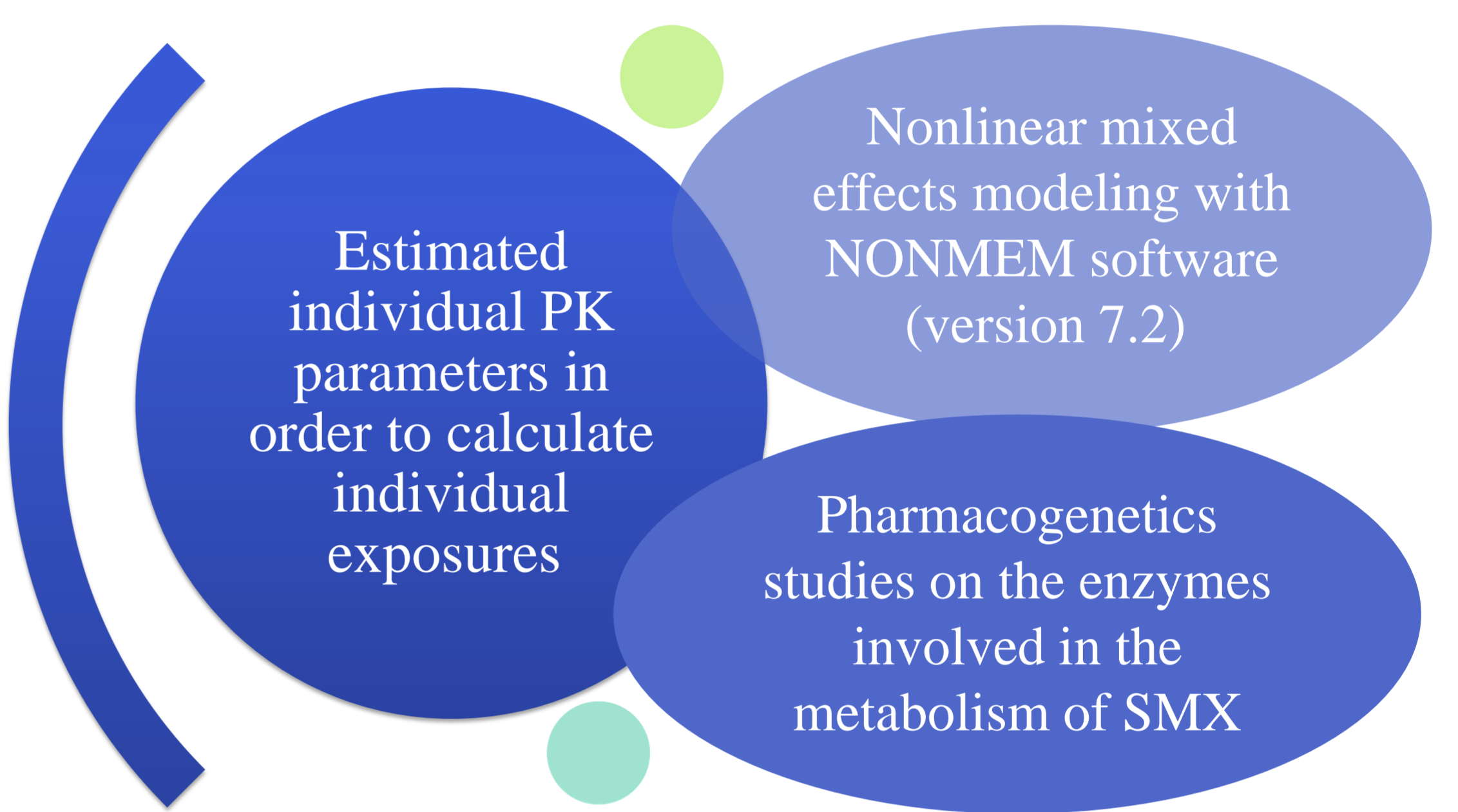
### Therapeutic cohort



### Plasma samples



### Population Pharmacokinetic Model



## RESULTS

### POPULATION STUDY

A total of **136 patients** (73 boys and 63 girls; 53.6 % and 46.3 %, respectively) ranging in age from **8 months to 4 years** (median age, 1.9 years) were available for pharmacokinetic evaluation. A total of **482 plasma concentrations** were collected (mean, 3.5 samples; range, 1 to 7 samples per child). The median values for body weight were **9.5 kg** (minimum and maximum, 6 and 16.3 kg, respectively). Cotrimoxazole was administered every 24h with a **median TMP dose administered of 40 mg** (range, 20 to 80) once daily whereas **the median SMX dose administered was 200 mg** (range, 100 to 400) once daily.

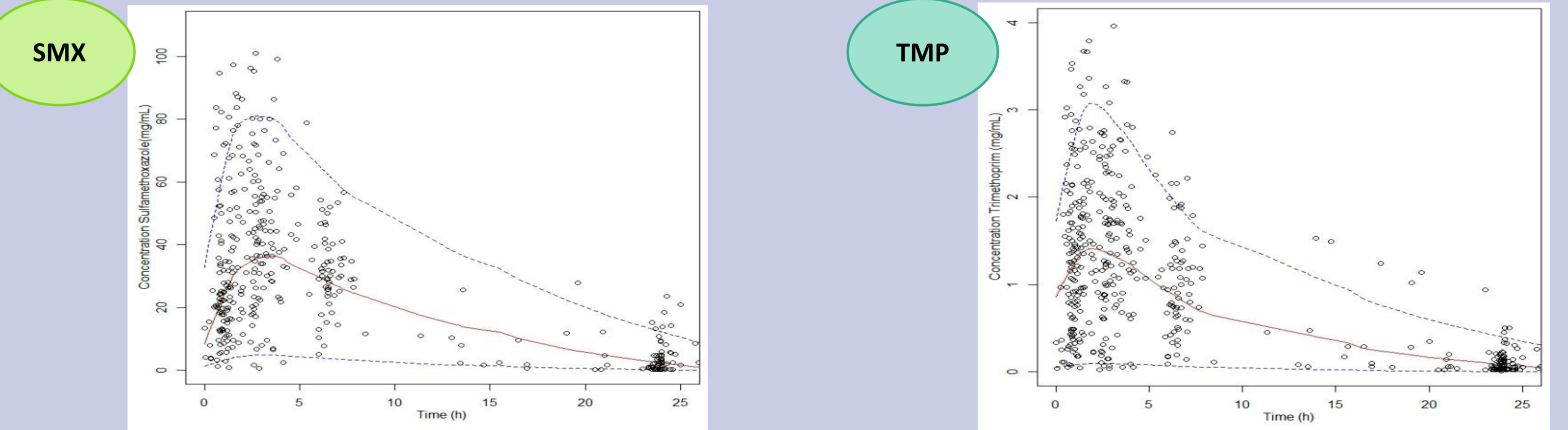
### MODEL PARAMETERS

Parameter	Estimated Value	RSE (%)
<b>SMX</b>		
<b>Structural model</b>		
Ka (h <sup>-1</sup> )	0.43	18.5
CL/F (liters/h)	0.49	4.8
V/F (liters)	2.58	11.6
NAT1/CL	0.77	10.8
<b>Statistical model</b>		
$\omega_{ka}$	0.69	31.0
$\omega_{cl/f}$	0.29	20.3
$\sigma$	0.55	18.1
<b>TMP</b>		
<b>Structural model</b>		
Ka (h <sup>-1</sup> )	1.30	20.5
CL/F (liters/h)	3.06	4.2
V/F (liters)	23.40	6.8
<b>Statistical model</b>		
$\omega_{cl/f}$	0.26	24.6
$\omega_{v/f}$	0.23	47.2
$\sigma$	0.57	8.6

Key - RSE (%) relative standard error (standard error of estimate/estimate × 100); -  $\omega$  and  $\sigma$  between-subject and residual variabilities

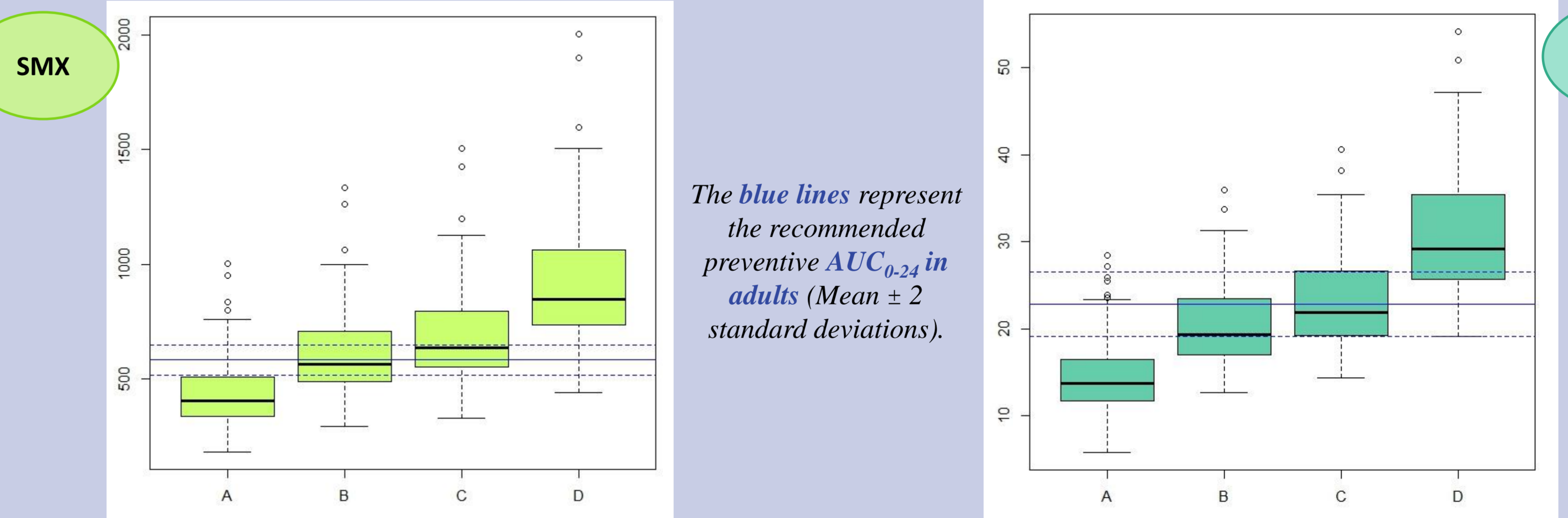
### VALIDATION OF THE MODELS

The use of the model was validated by Visual Predictive Check.



Key : Visual Predictive Check: comparison between the 5<sup>th</sup> (dashed blue line), 50<sup>th</sup> (full red line) and 95<sup>th</sup> (dashed blue line) obtained from 400 simulations and the observed data (points) for SMX (left) and TMP (right)

### DOSE SIMULATIONS



Key - AUC<sub>0-24</sub> sulfamethoxazole for different regimens: regimen currently recommended to be 200 mg per day (A), dosing schedule at 260 mg daily (B), dosing schedule at 300 mg daily (C), dosing schedule at 400 mg daily (D).

Key - AUC<sub>0-24</sub> trimethoprim for different regimens: regimen currently recommended 40 mg daily (A), dosage regimen to 52 mg per day (B), regimen at 60 mg per day (C), regimen at 80 mg daily (D).

A **increase of 30%** of the dose of **SMX** at these children should allow to obtain **an exposure comparable to that of the adult**. This increase would lead to increase by 30% the dosage of **TMP** associated.

With this dose of 52 mg daily, the exposure in TMP at the child would be slightly lower than that at the adult.

All these simulations are preliminary because the ratio risk / benefit of such a change of dose should be evaluated for each patient before considering a change in dosage.

## CONCLUSION

With the dosing regimen currently recommended for prophylaxis, exposures are much lower for the children than those found in adults. In order to maintain an exposure comparable with that in adults of this population, an increase of the dose should be considered.