



A Population WB-PBPK Model of Colistin and its Prodrug CMS in Pigs and extrapolation to humans

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CONTENT

- Introduction
- Experimental part
 1. Animal PBPK model development
 2. Extrapolations :
 - Towards piglets
 - Towards adult humans
 - Towards children
- Conclusion/Perspectives

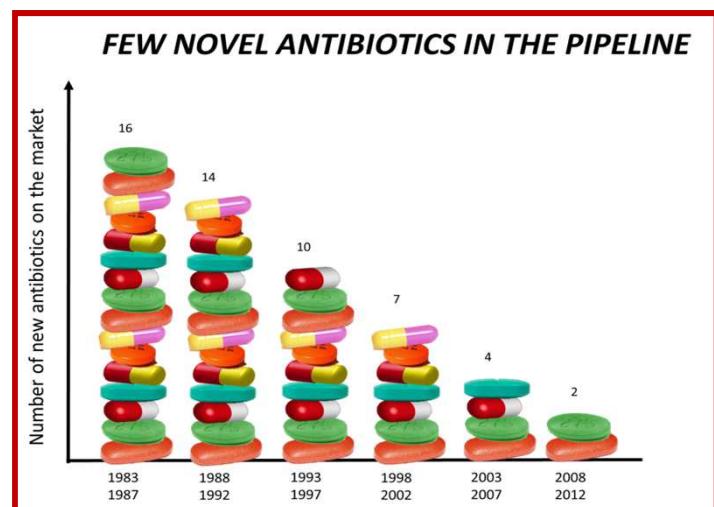
Context

Human medicine:

- antimicrobial resistance
- new antimicrobial molecules

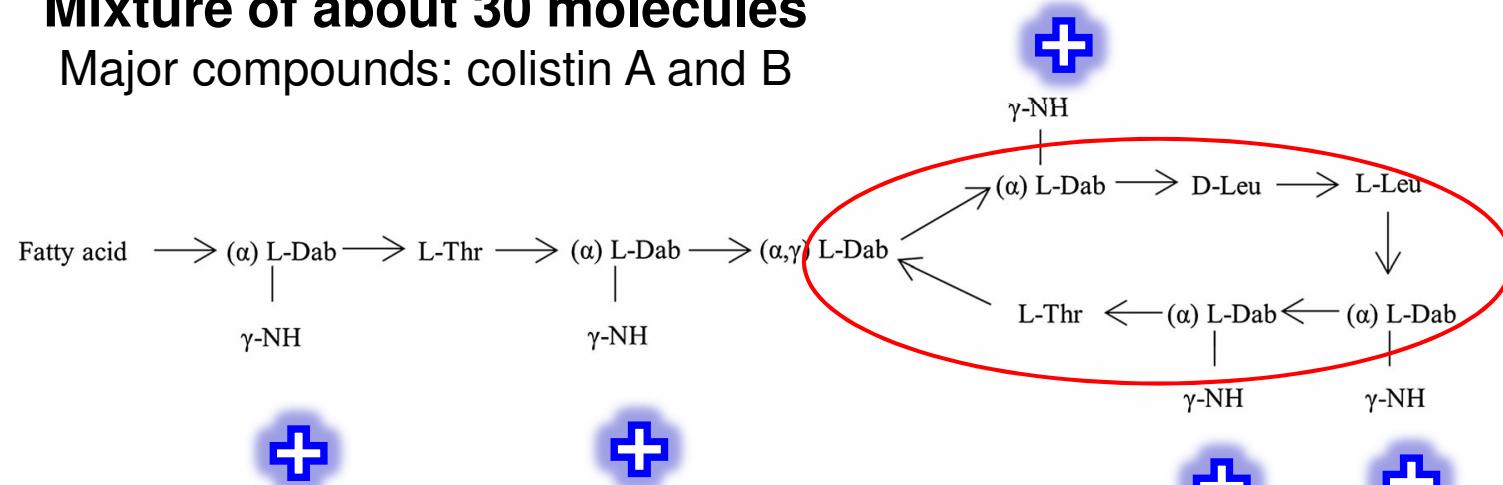
→ Renewed interest for old antibiotic compounds,
e.g. **colistin**

- ❖ For critically ill patients, against multi-drug resistant bacteria
- ❖ Through inhalation (cystic fibrosis) or intravenous-administration



Structure

Mixture of about 30 molecules
 Major compounds: colistin A and B



Properties :

- Peptide
- Hydrophilic
- Polycation (physiological pH value)
- **Binding properties (lab materials/tissues)**

} **Weak passage across cell membranes**

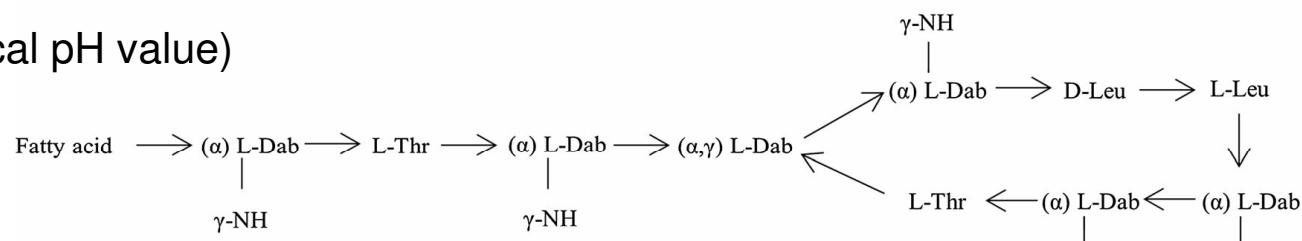
Systemic use

Properties :

- Hydrophilic
- Polyanion (physiological pH value)

{

**Weak
passage
across cell
membranes**

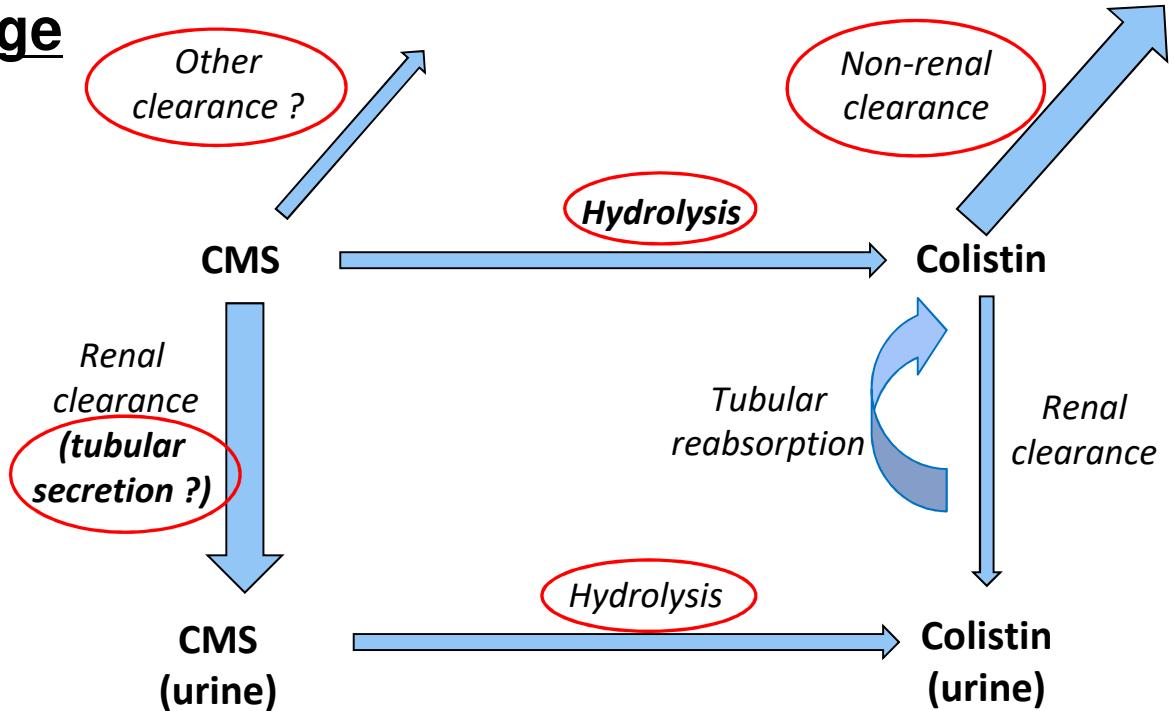


Pro-drug:
**colistin methanesulfonate
(CMS)**

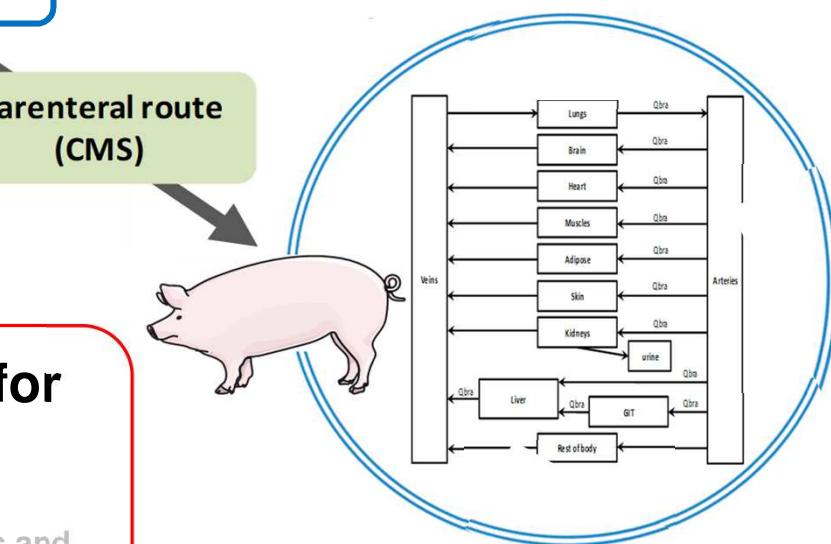
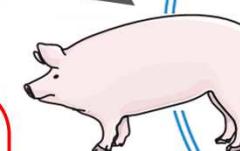
hydrolysis → **Colistin**
Mixture of methanesulfonated derivatives

Pharmacokinetic knowledge

- Underlying mechanisms mostly unknown
→ no major organ involved in metabolism (liver)
- Narrow therapeutic index (nephrotoxicity)



Nation, R. L. et al. (2014). Clinical Infectious Diseases, 59(1), 88-94.

ColistinParenteral route
(CMS)**1 → Development of a PBPK model for CMS and colistin in adult pigs****2 → Study of the influence of age – extrapolation to adults and children (human medicine)****PBPK model**

Objectives

➤ Development of a PBPK model to:

- To improve the PK knowledge about CMS and colistin, especially for the renal disposition (nephrotoxicity concern)
- (*To estimate withdrawal period in veterinary medicine*)

RESEARCH PAPER

A Population WB-PBPK Model of Colistin and its Prodrug CMS in Pigs: Focus on the Renal Distribution and Excretion

Viel, A et al. Pharm Res (2018) 35: 92.

Alexis Viel^{1,2,3} • Jérôme Henri² • Salim Bouchène⁴ • Julian Laroche^{1,5} • Jean-Guy Rolland² • Jacqueline Manceau² • Michel Laurentie² • William Couet^{1,3,5} • Nicolas Grégoire^{1,3} 

➤ Use of pigs for model development

- Physiological proximity with human → for future extrapolations
- (*Veterinary purpose*)

Gasthuys, Elke, et al. Current pharmaceutical design (2016), 22(26), 4069-4085



PBPK model

Flow-limited model

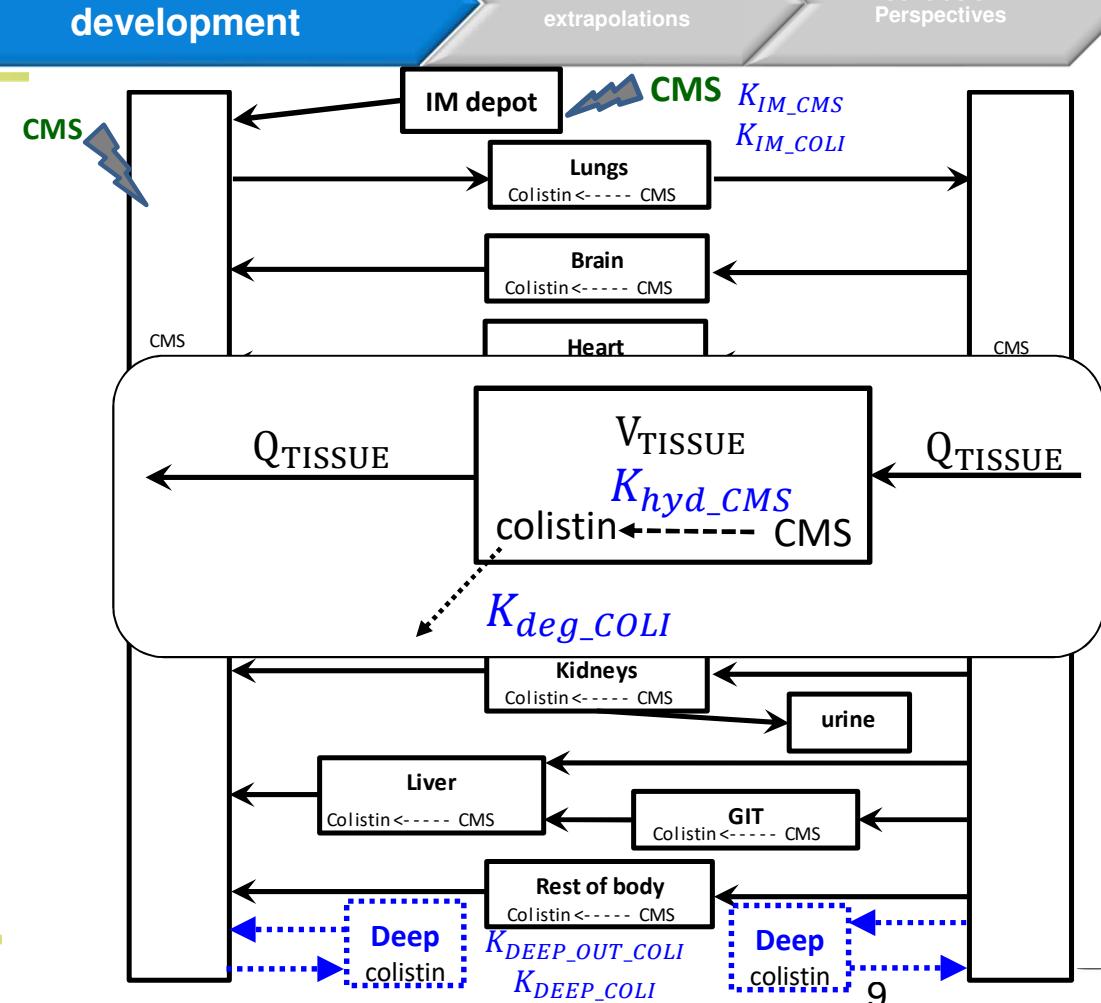
Fixed parameters (*literature*)

- Flows (blood, urine) and organs volumes
- Unbound fraction colistin

Fixed parameters (*experimentally determined*)

- Partition coefficient(K_p) (*in vivo*)
- Unbound fraction CMS (*in vitro*)

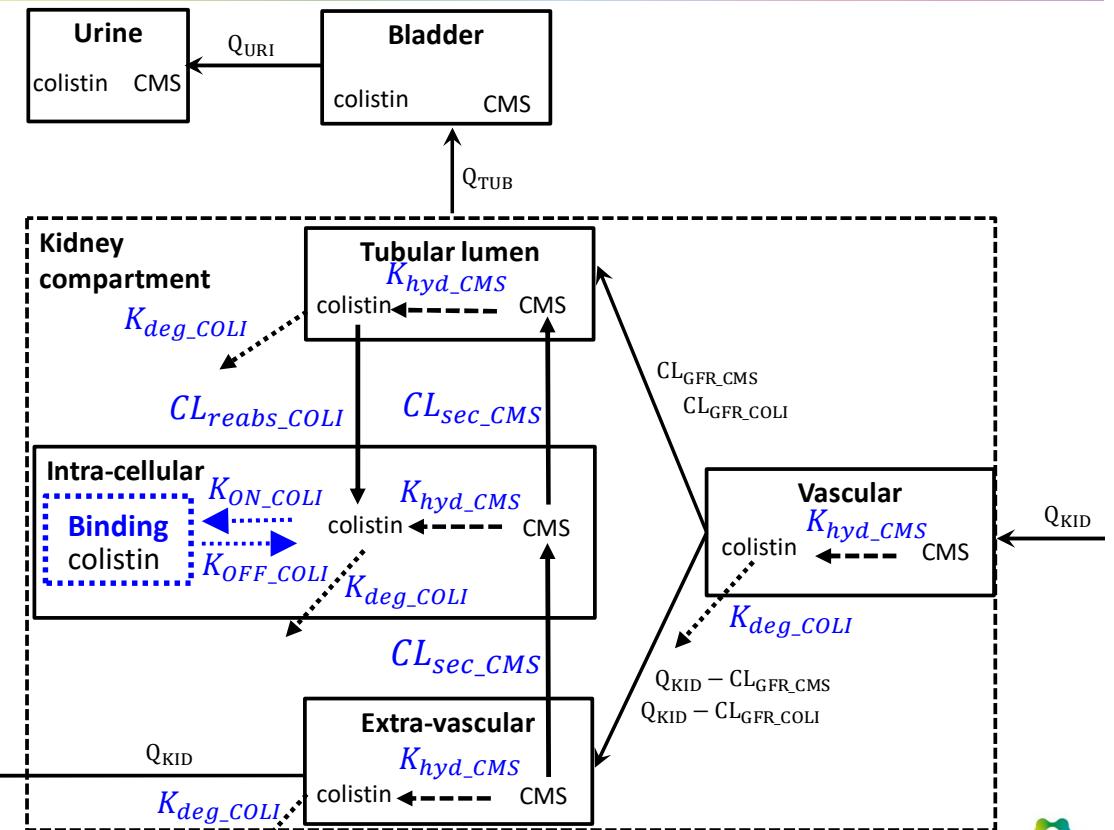
Estimated parameters



Renal sub-model

Permeability-limited model

- ❖ Colistin tubular reabsorption
Li J et al., 2003. Antimicrob. Agents Chemother. 47:1766-1770.
Ma Z et al., 2009. Antimicrob. Agents Chemother. 53:2857-2864
- ❖ CMS tubular secretion
Li J, et al. 2004. J. Antimicrob. Chemother. 53:837-840.
- ❖ Intracellular-binding of colistin

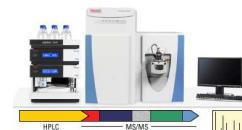




Experimental data for calibration

IV and IM unique injection

- *plasma/urinary/renal data*



Repeated IM injection

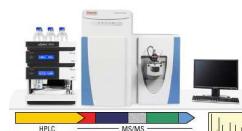
- *renal/plasma data*



Infusion

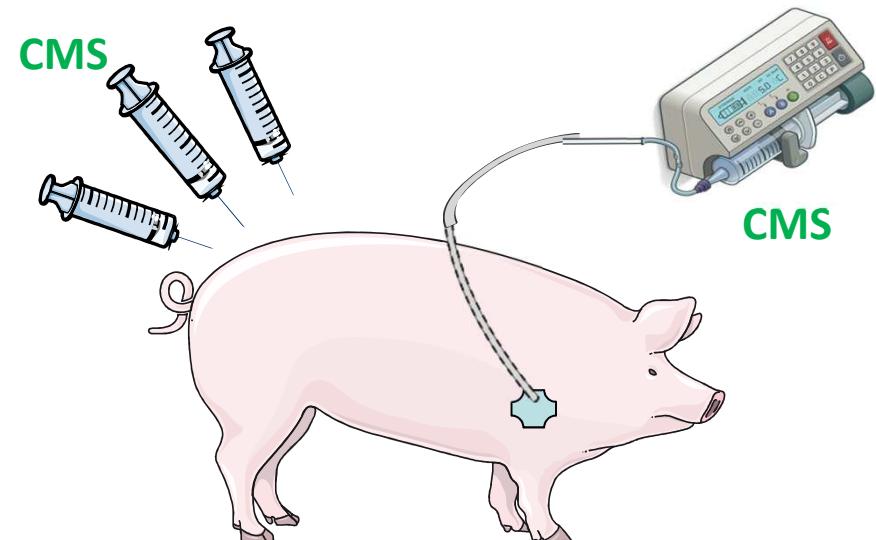
- *organ data for Kp calculation*

$$K_p = \frac{C_{SS_TISSUE}}{C_{SS_PLASMA}}$$



Data for model calibration

→ **unknown parameters estimation : NONMEM® v7.4, NLME approach**

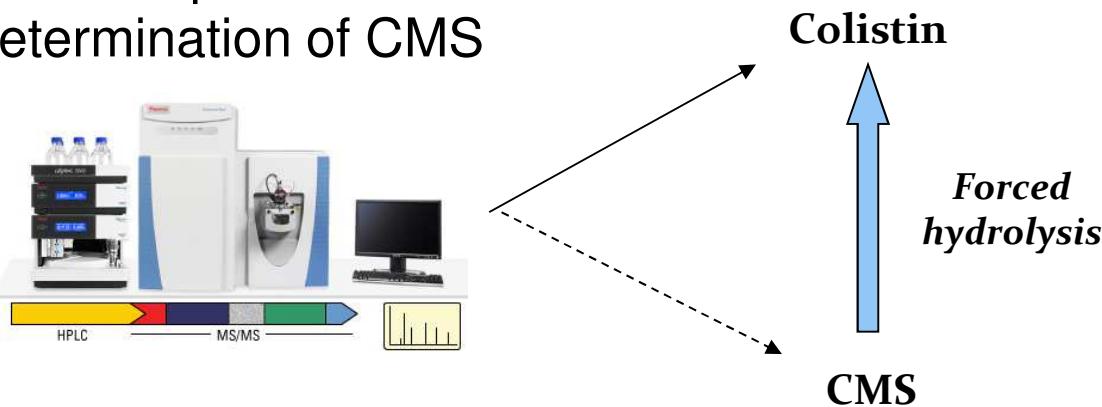


10 adult pigs (~)
15 adult pigs (~)
6 adult pigs (~)



Data and model adjustment

- Fit of the pooled CMS and colistin renal concentrations → due to indirect determination of CMS



Gobin, P., et al. (2010). *Antimicrobial agents and chemotherapy*, 54(5), 1941-1948.

- Many tissue data < LOQ for CMS → estimation of CMS Kp (M3 method)



| Parameters (unit) | Value [CI 95%] | IIV (%CV) [CI 95%] |
|------------------------------------|-------------------------------|---------------------------------------|
| Colistin | | |
| K_{deg_COLI} (h^{-1}) | 0.389 [0.334-0.456] | 0.0737 (26.6 %) [0.0437-0.139] |
| K_{IM_COLI} (h^{-1}) | 5.99 [3.09-13.77] | - |
| K_{DEEP_COLI} (h^{-1}) | 0.187 [0.135-0.295] | - |
| $K_{DEEP_OUT_COLI}$ (h^{-1}) | 0.104 [0.0670-0.149] | - |
| K_{ON_COLI} (h^{-1}) | 0.0910 [0.0524-0.157] | - |
| K_{OFF_COLI} (h^{-1}) | 0.0145 [0.0051-0.0230] | - |
| CL_{reabs_COLI} ($L.h^{-1}$) | 106 (fixed) | - |
| CMS | | |
| K_{hyd_CMS} (h^{-1}) | 0.262 [0.238-0.290] | - |
| K_{IM_CMS} (h^{-1}) | 1.78 [1.39-2.35] | - |
| $K_{p_{mix_CMS}}$ (unitless) | 0.217 [0.189-0.242] | - |
| CL_{sec_CMS} ($L.h^{-1}$) | 8.39 [6.53-10.94] | 0.193 (43.5 %) [0.0840-0.403] |

| Parameters (unit) | Value [CI 95%] |
|--|---------------------------------------|
| Residual errors (proportional) | |
| RV_{plas_CMS} | 0.171 (41 %) [0.136-0.225] |
| RV_{plas_COLI} | 0.166 (41 %) [0.136-0.205] |
| Common RV term of CMS and colistin in plasma | 0.0824 [0.0541-0.116] |
| RV_{tissue_CMS} | 0.111 (33 %) [0.0644-0.192] |
| RV_{KID} | 0.331 (57 %) [0.193-0.574] |
| RV_{URINE} | 0.258 (51 %) [0.171-0.402] |

Results of model calibration (plasma data)

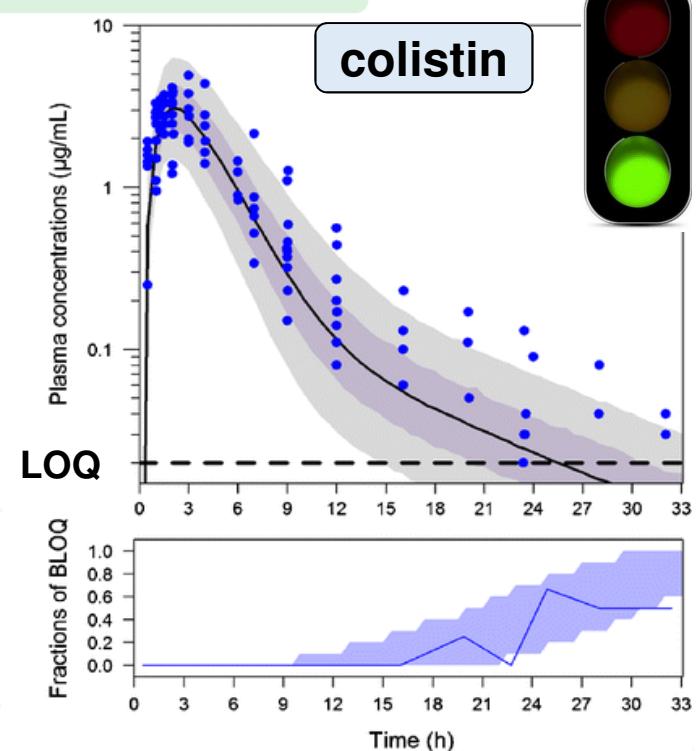
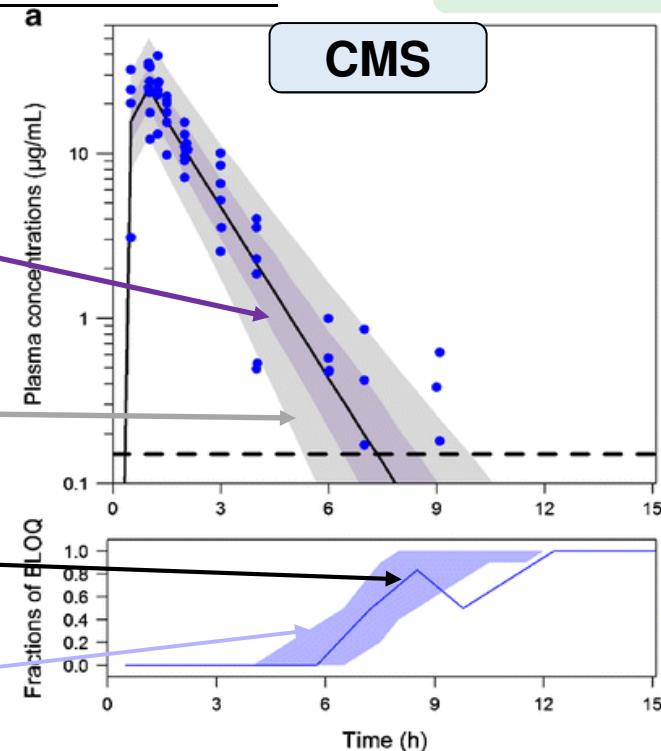
After IV injection of CMS

95% CI around the median prediction

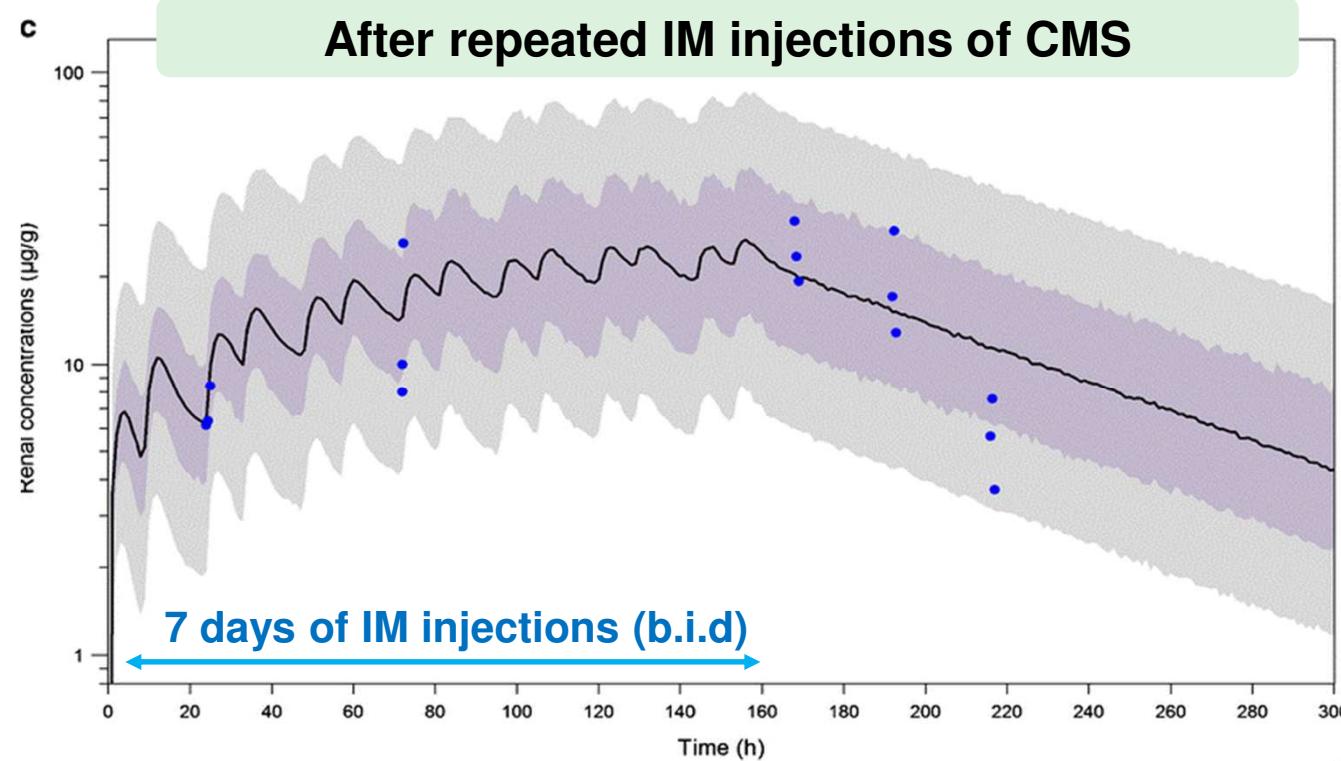
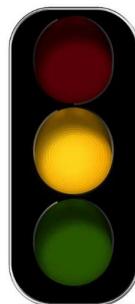
90% PI

Actual fraction of data BLOQ

95% CI



Results of model calibration (renal data)



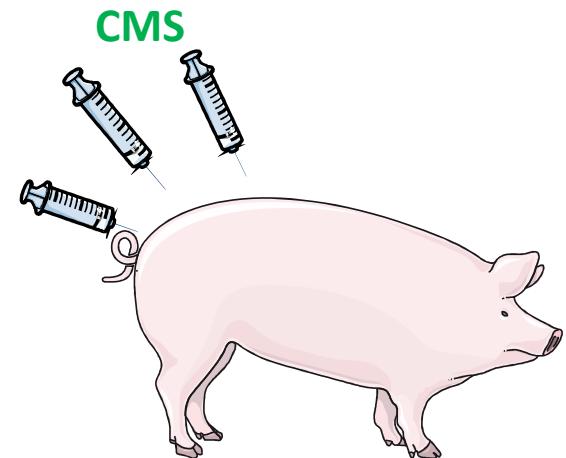


Experimental data for external validation

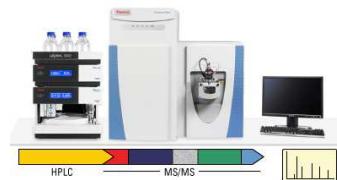
→ ***Model predictions versus NEW experimental data***

Repeated IM injection

- *Plasma data and tissue data : kidney, skin, muscles, liver, fat → 5 sampling times after last injection*

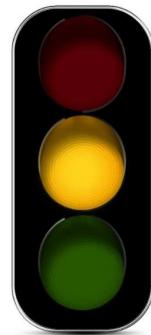


20 adult pigs (~50kg)



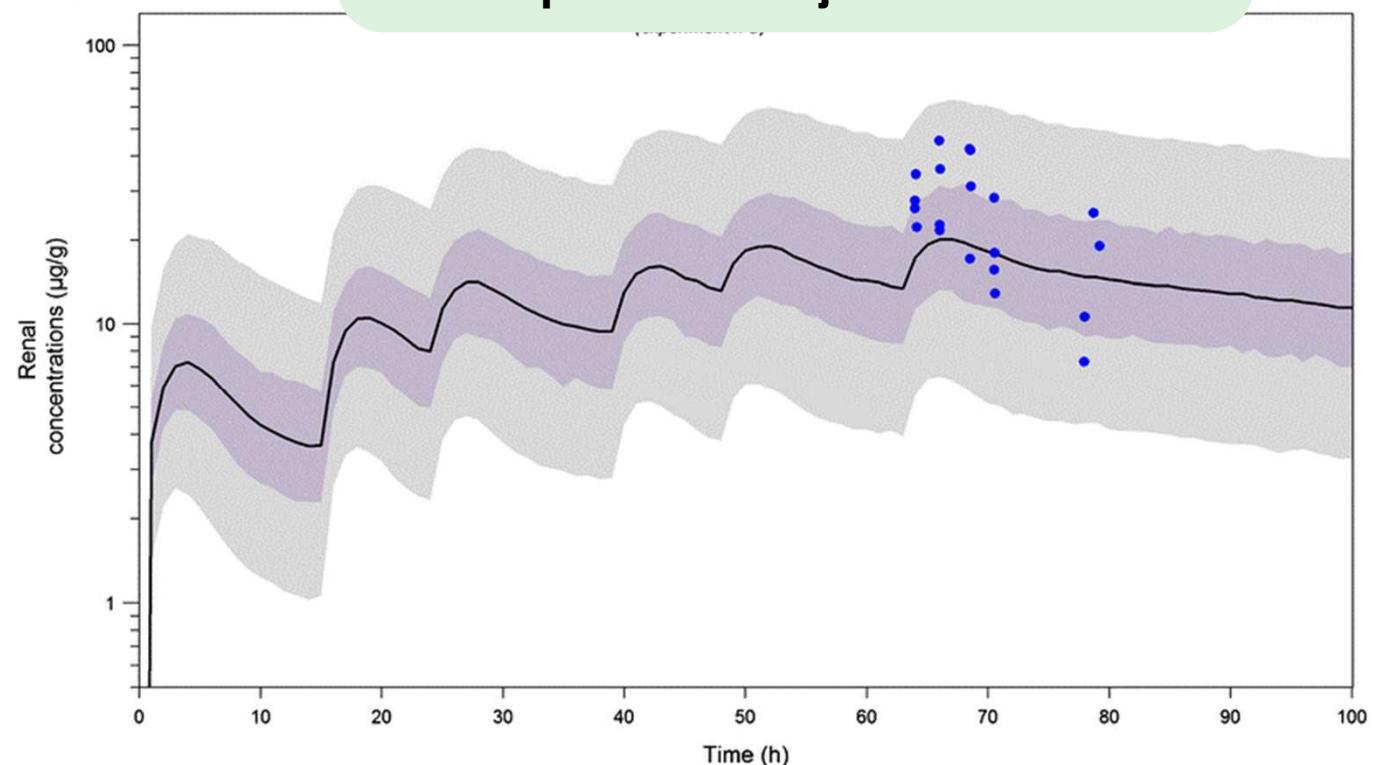
Results of model external validation

Plasma data



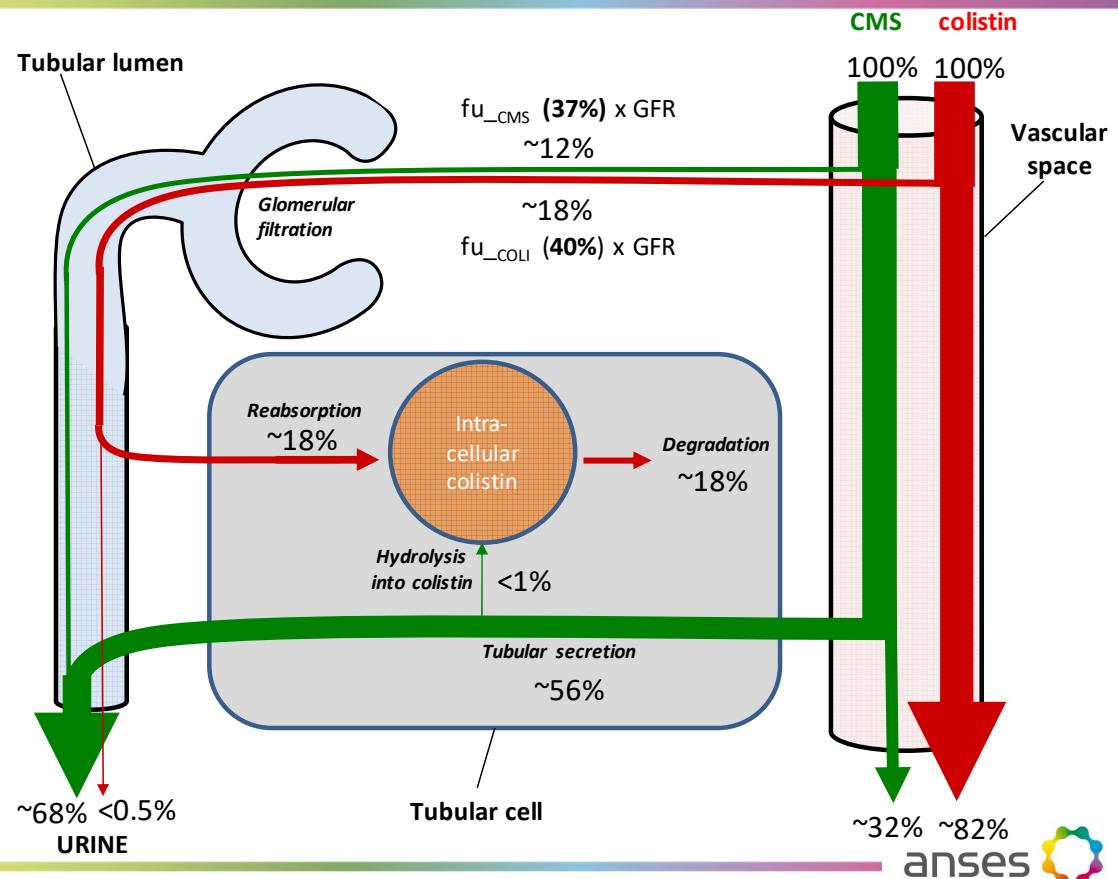
*Renal data
(for other tissues, CMS and colistin quickly eliminated)*

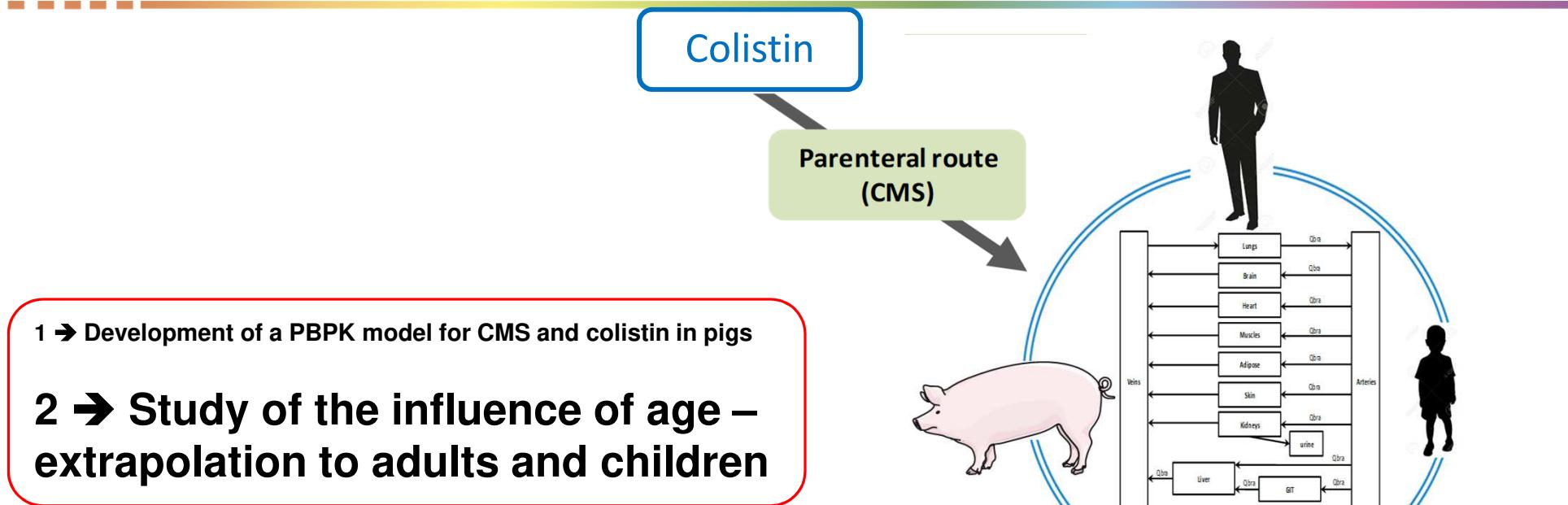
After repeated IM injections of CMS



Overview of the Renal disposition

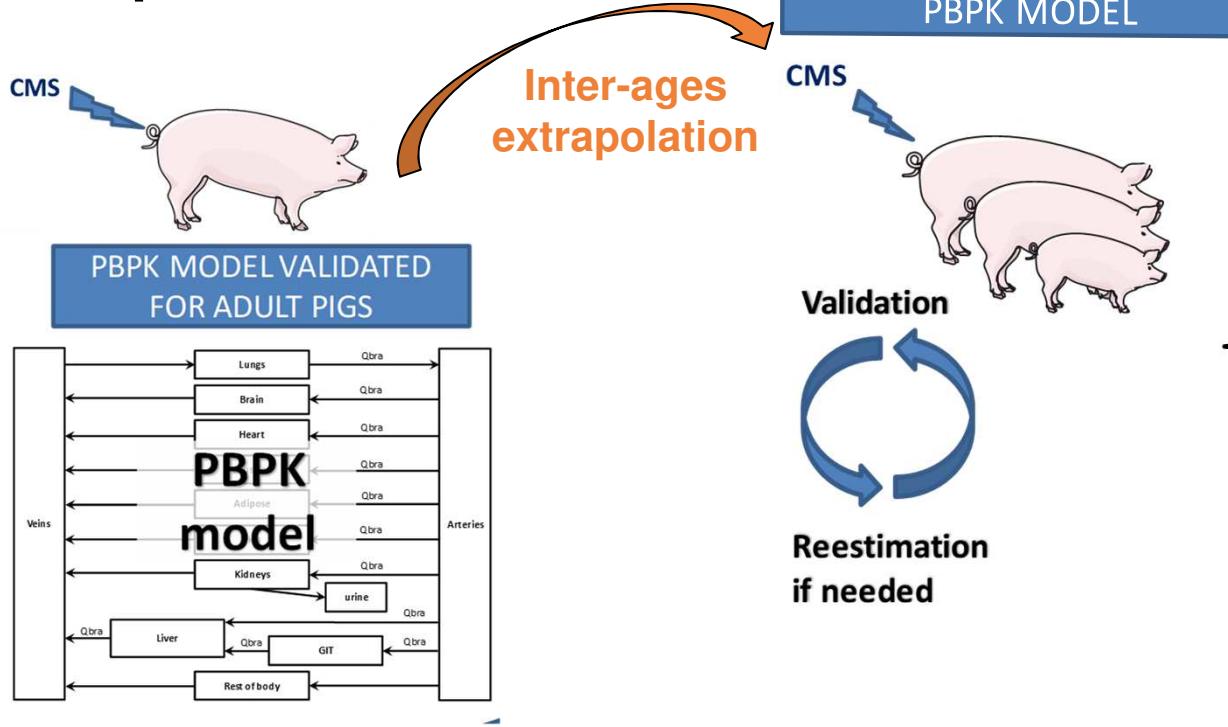
- Renal accumulation with slow depletion of colistin
- Important intra-renal metabolism of colistin
- Tubular secretion of CMS: major elimination mechanism





PRELIMINARY RESULTS

Extrapolation method



3 groups of different ages:

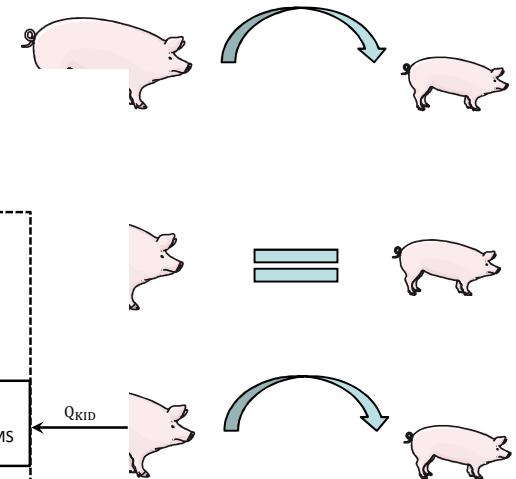
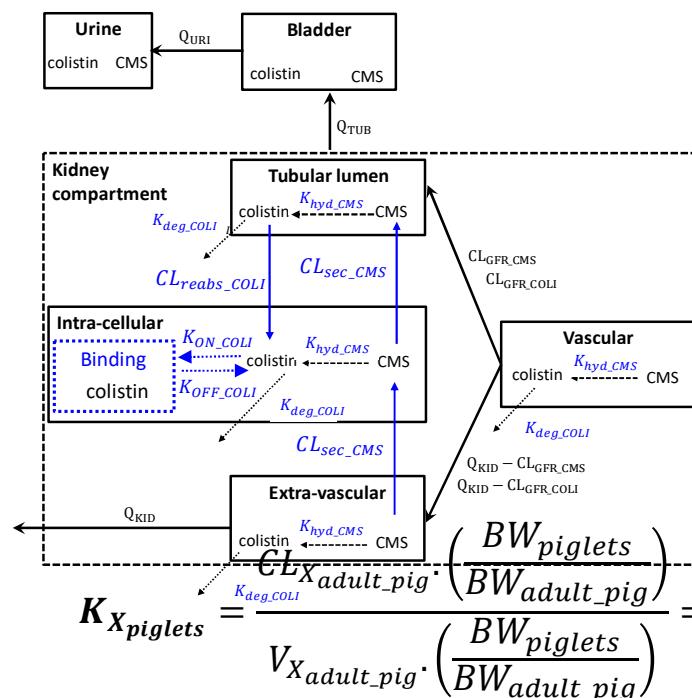
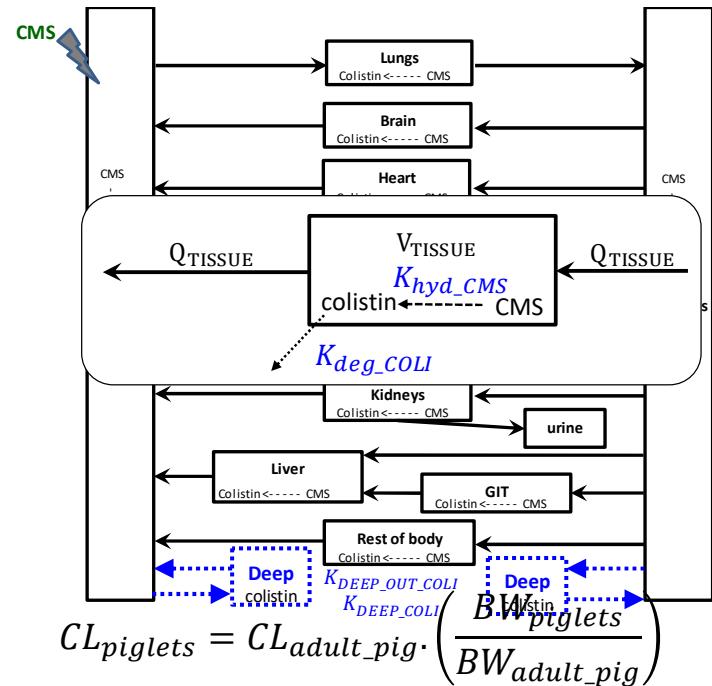
4 week-old (7,5 kg)
9 week-old (15 kg)
11 week-old (30 kg)

Treatment:
One IV injection of CMS
Then CMS infusion

Data:
Plasma and urinary data over 24h
 K_p (tissues)

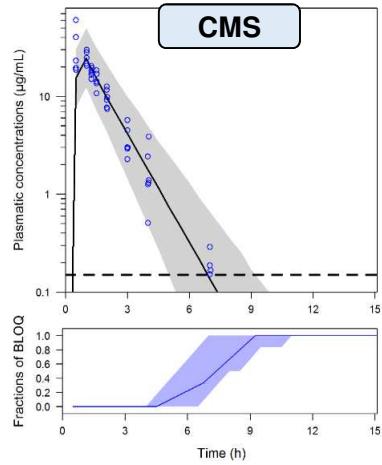


Juvenile porcine PBPK model

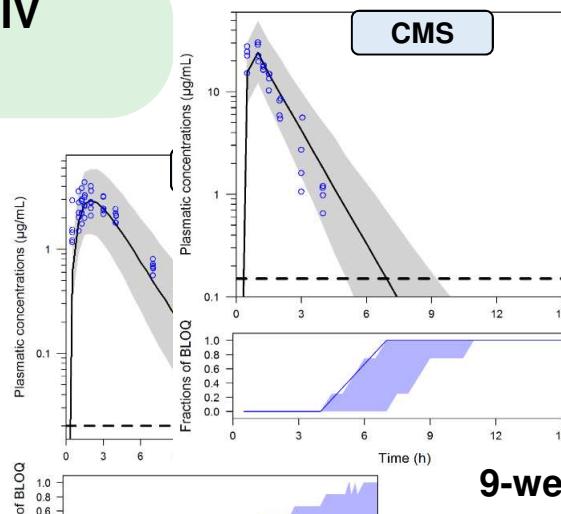


Model prediction vs observed data

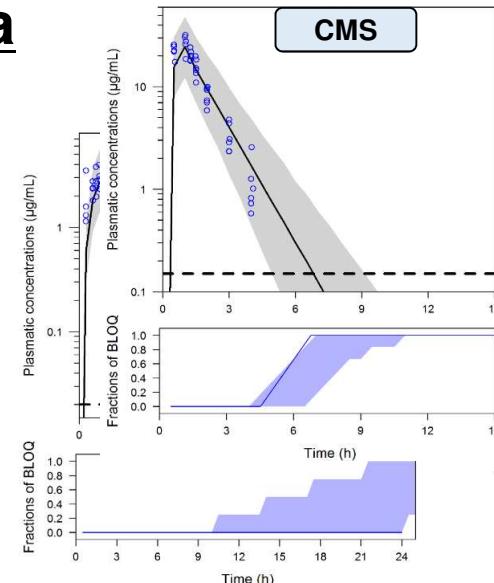
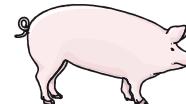
Plasma data after IV injection of CMS



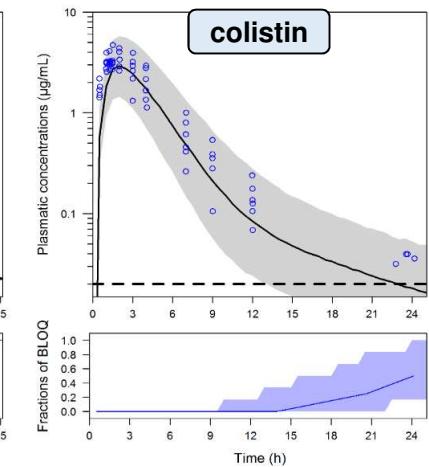
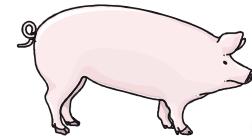
4-week old (7,5 kg)



9-week old (15 kg)

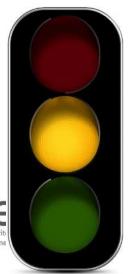
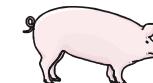
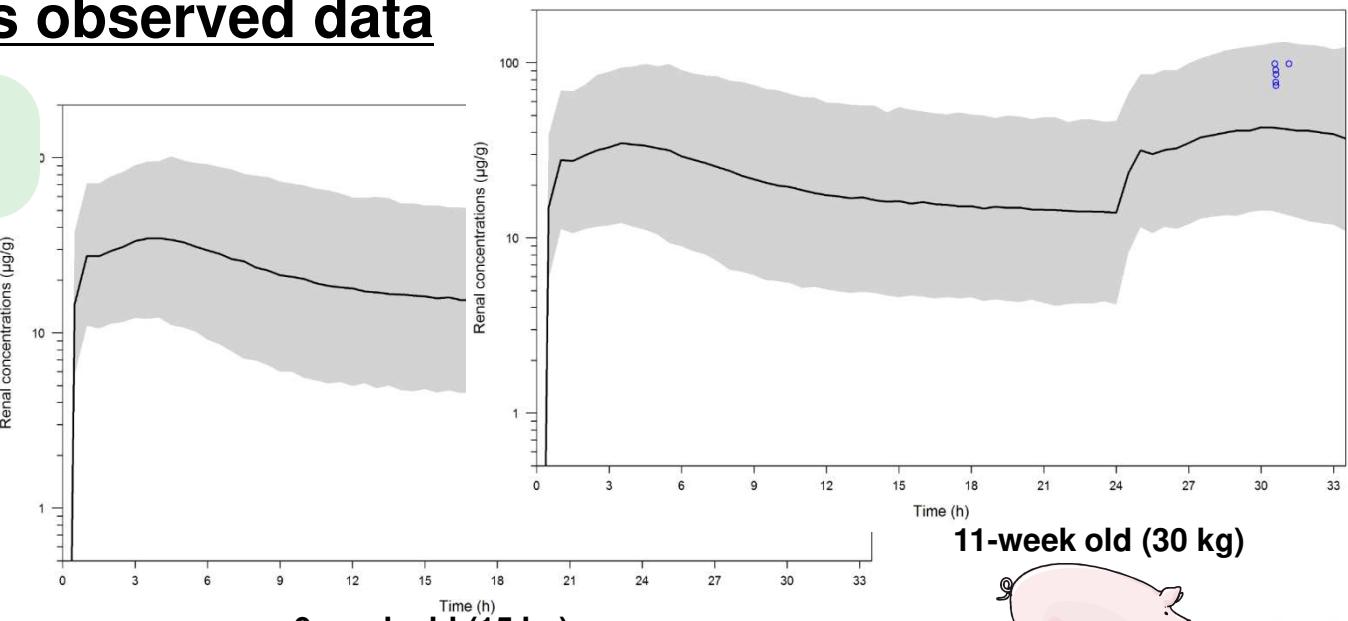
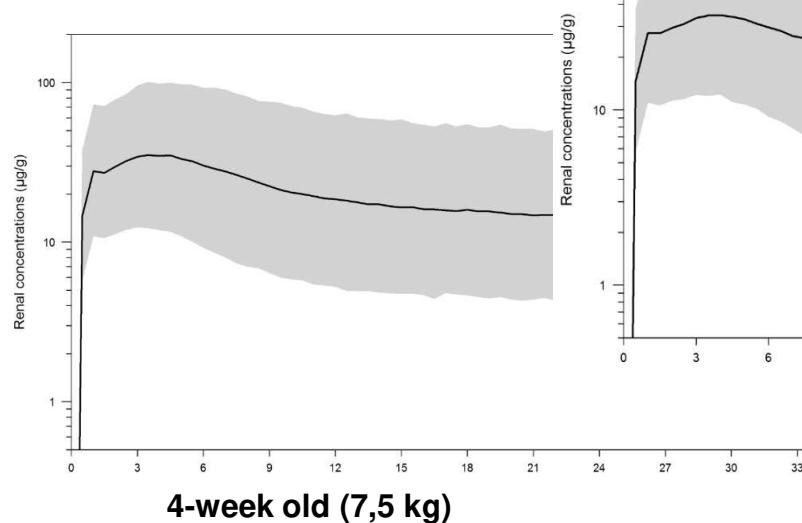


11-week old (30 kg)



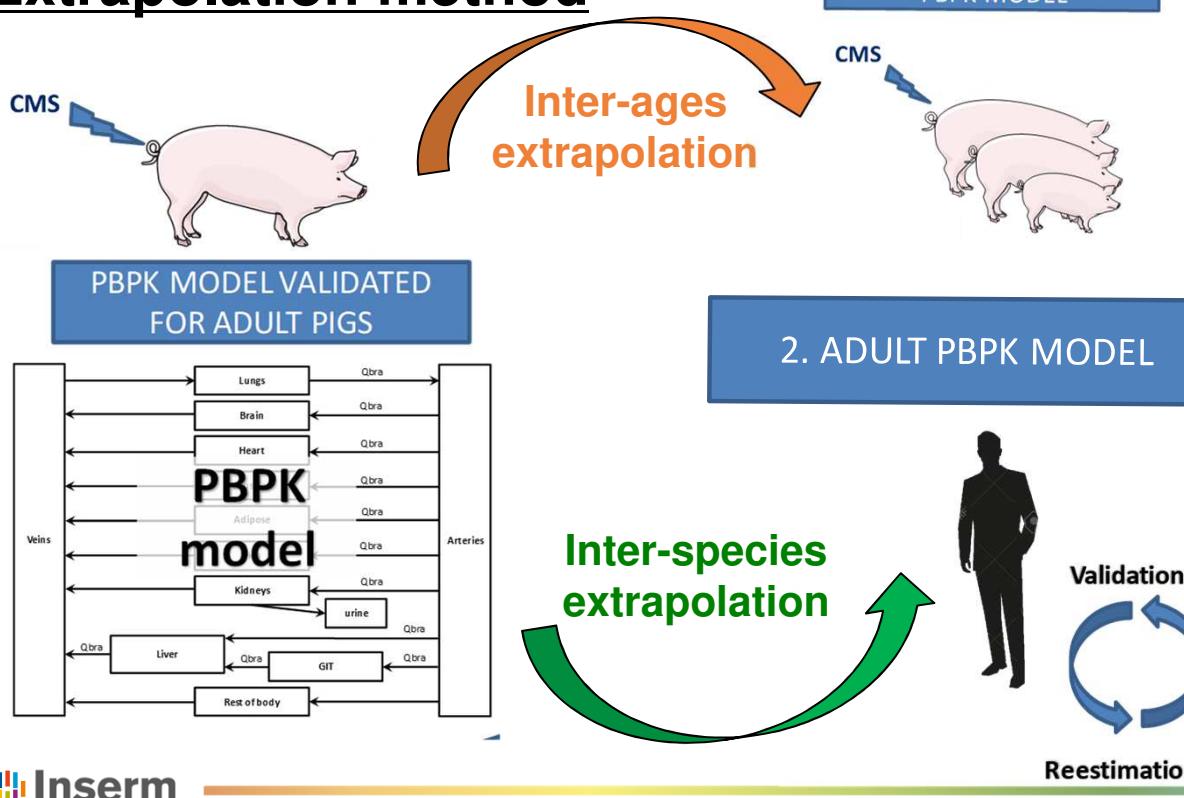
Model prediction vs observed data

Renal data after one IV then one infusion of CMS





Extrapolation method



Healthy volunteers

Data used:

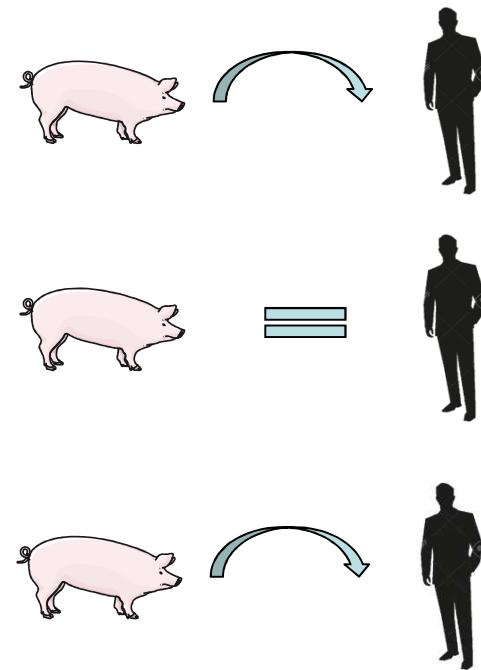
Plasma and urinary data over 16h after one IV injection of CMS

Couet et al., 2011; Clin Pharmacol Ther, 89(6), 875-879



Adult PBPK model

- Physiological parameters (fixed) from litterature (IRCP)
- K_p fixed to *in vivo* K_p values of adult pigs
- Estimated parameters (from adult pig) → proportionally adapted to the bodyweight of men

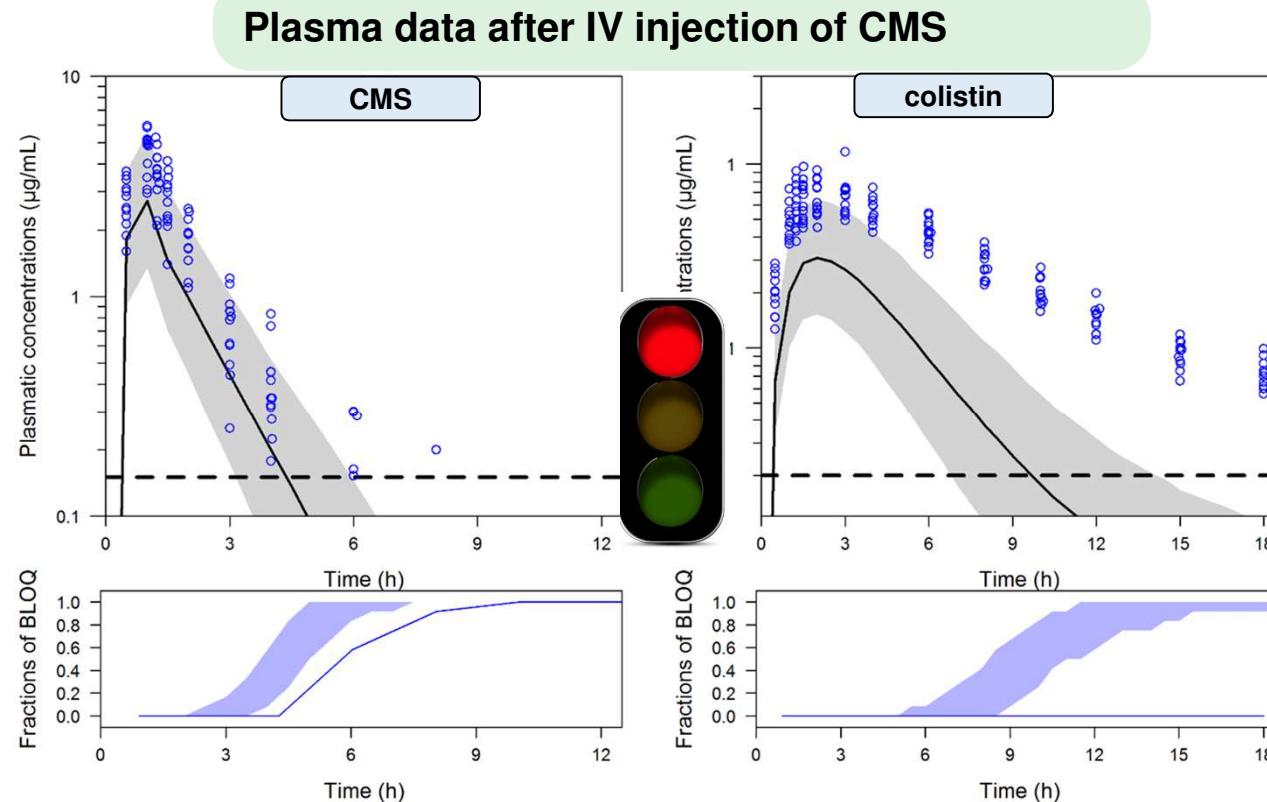


Results

Unsatisfying

- Different elimination mechanisms between species ?

➤ **Reestimation of parameters except the renal ones**
 (calibration with 75% of individuals)



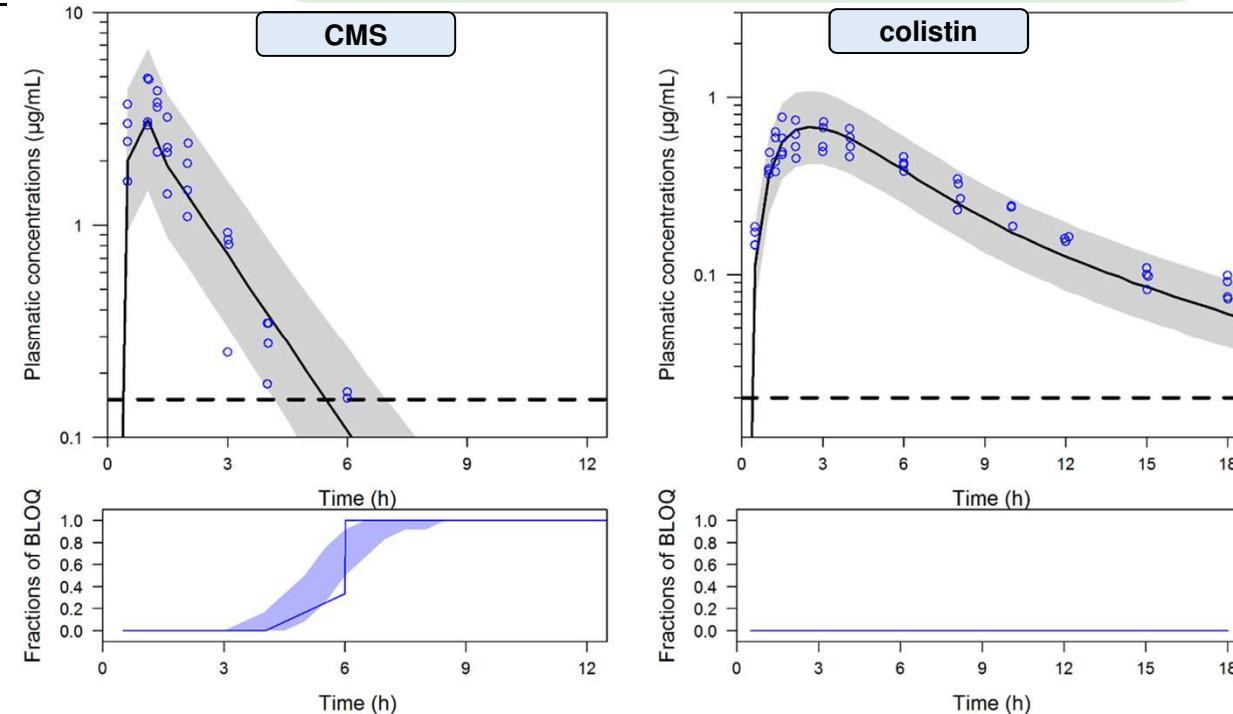
Comparison of parameters estimates (pigs vs humans)

|  |  | |
|---|---|-------------------------|
| Parameters (unit) | Value In adult pig | Value in adult human |
| CMS | | |
| K_{hyd_CMS} (h^{-1}) | 0.262 | 0.414 / IIV : 14% |
| CL_{sec_CMS} ($L.h^{-1}$) | 8.39 | 2.07 |
| Colistin | | |
| K_{deg_COLI} (h^{-1}) | 0.389 | 0.154 |
| K_{BIND_COLI} (h^{-1}) | 0.187 | 0.557 |
| $K_{BIND_OUT_COLI}$ (h^{-1}) | 0.104 | 0.190 |
| CL_{reabs_COLI} ($L.h^{-1}$) | 106 (fixed) | 148 (fixed) |

|  |  | |
|---|---|-------------------------|
| Parameters (unit) | Value In adult pig | Value in adult human |
| Residual errors (proportional) | | |
| RV_{plas_CMS} | 41 % | 45% |
| RV_{plas_COLI} | 41 % | 26% |
| Common RV term of CMS and colistin in plasma | 28% | 20% |
| RV_{URINE} | 51 % | 58% |

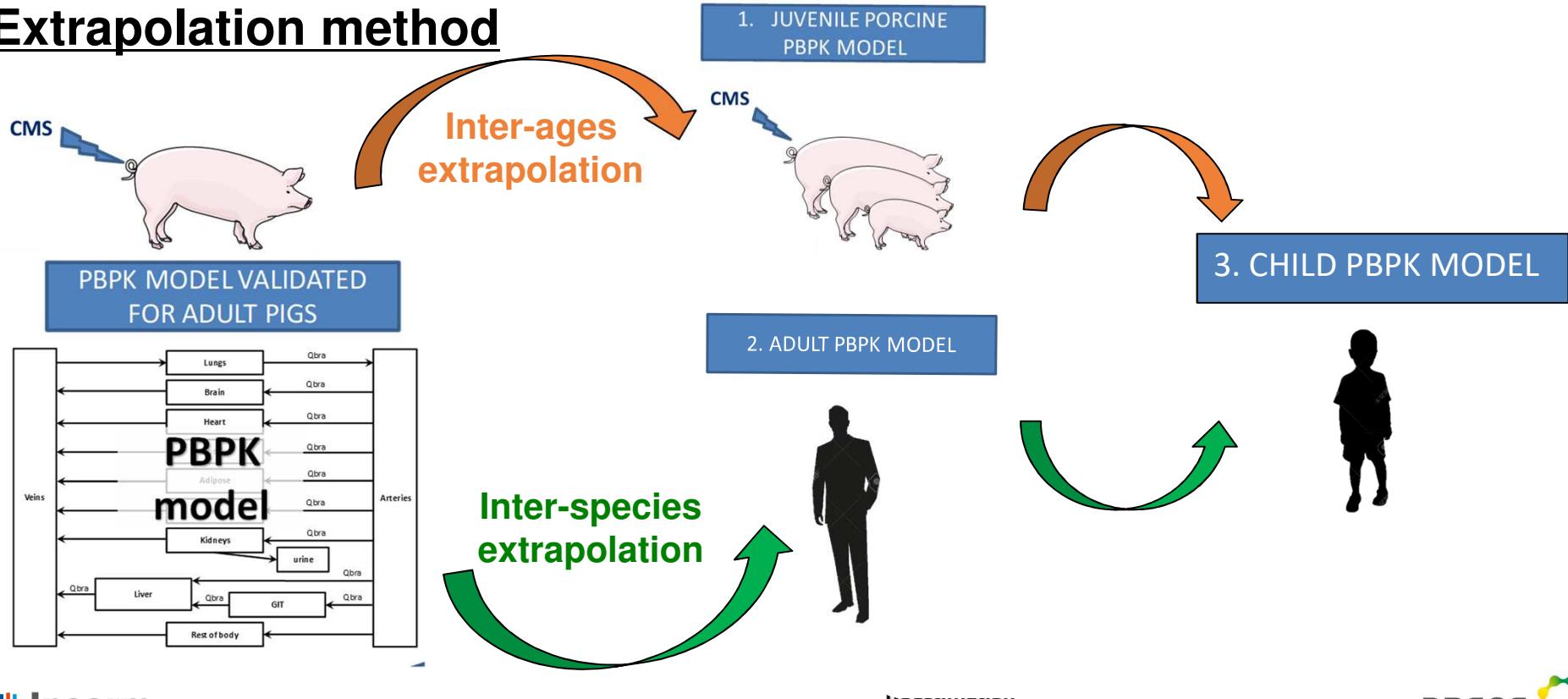
Results after re-estimation (validation)

Plasma data after IV injection of CMS (Validation with 25% of individuals)





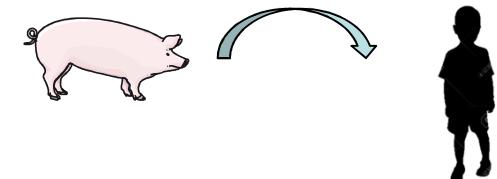
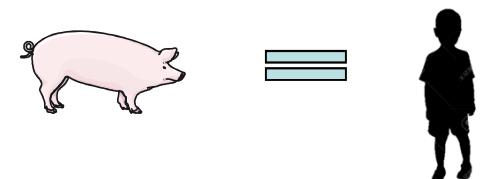
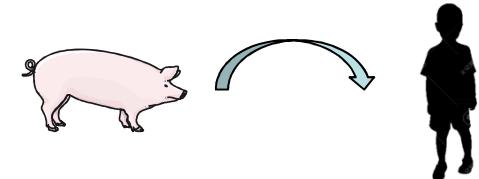
Extrapolation method





Child PBPK model

- Physiological parameters (fixed) from litterature
- K_p fixed to *in vivo* K_p values of adult pigs
- (Re)estimated parameters (from human adult) → proportionally adapted to the bodyweight of children



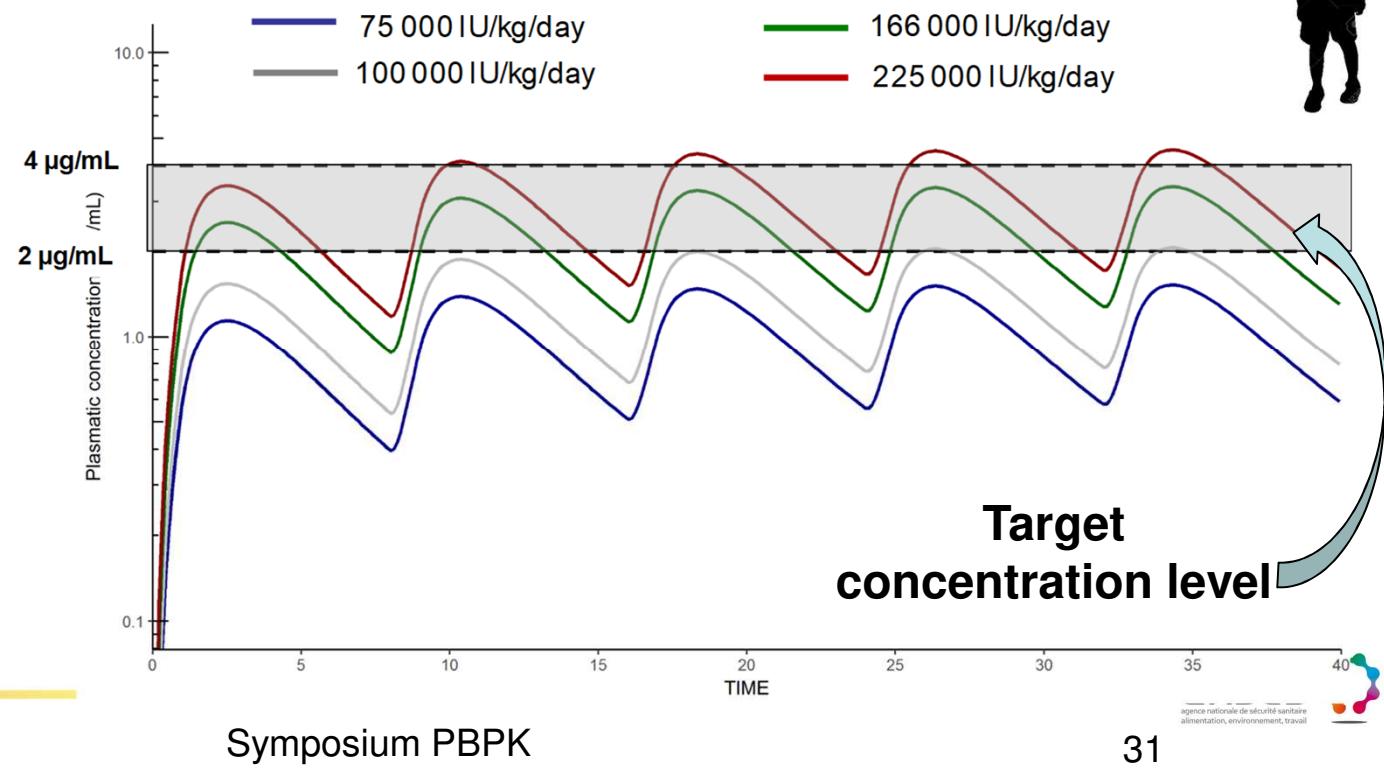
Results

Colistin plasma predictions after IV injection of CMS Typical profile for a 5-years old child – 20 kg



CMS doses:

- ❖ From litterature (blue and red)
- ❖ recommended by WHO and FDA (grey and green)





Comparison with litterature data

5-years old child (15 kg)

- Normal renal function
- Meningitis

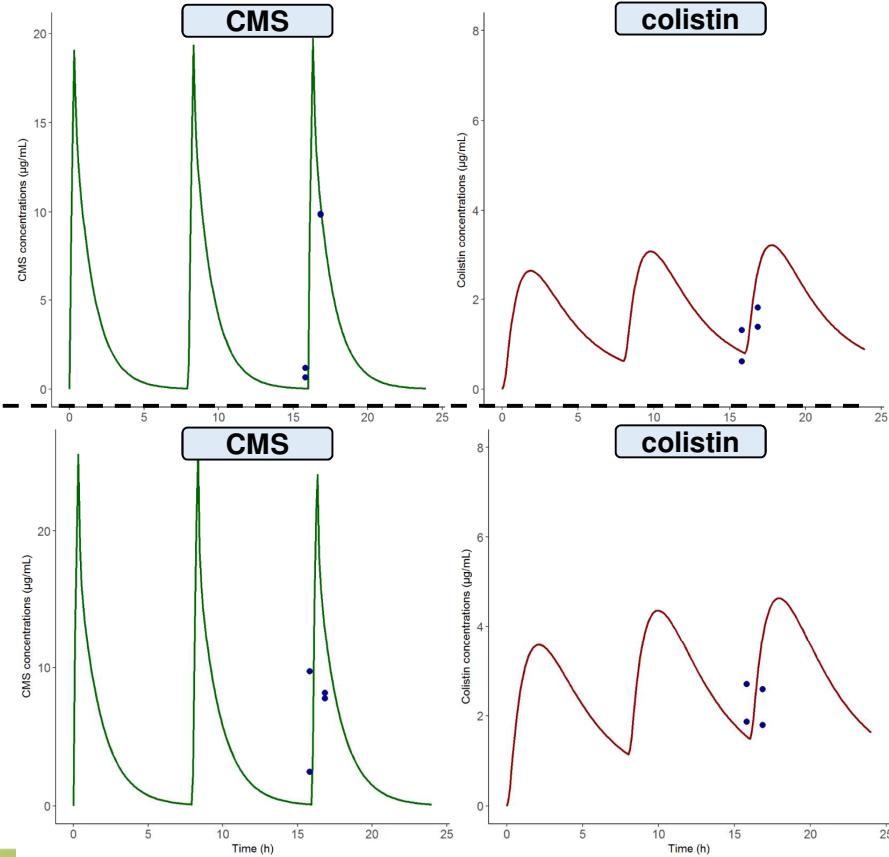
- CMS dose : 200 000 IU/kg/day

14-years old child (40 kg)

- Normal renal function
- Septicemia

- CMS dose : 225 000 IU/kg/day

Antachopoulos, et al (2010). Antimicrobial agents and chemotherapy, 54(9), 3985-3987.





Discussion

- **Inter-ages extrapolation (piglets)**
 - Validated model with parameters adaptation only to bodyweight. Still valid for more immature individuals ?
- **Inter-species extrapolation (Adults)**
 - Validated model for plasma predictions.
 - Reestimation of parameters ➔ different values that may be linked to different mechanisms (transporters, enzymes...). Need of further investigations about extrapolation methods
- **Inter-ages extrapolation (children)**
 - Preliminary results ➔ Dose adaptation to bodyweight and need of high dose of CMS
 - Need of data for model validation

Introduction

Objectives

PBPK model
development

PBPK model
extrapolations

**Conclusion
Perspectives**

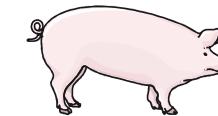
Conclusion and Perspectives





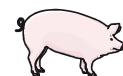
➤ **Development of a PBPK model for CMS and colistin**

- Colistin accumulation within kidneys and slow depletion.
- Mechanistic pathways: CMS tubular secretion and intra-renal degradation of colistin seem important
- « Middle-out » approach



➤ **Useful for extrapolations:**

- Weak influence of age (over the tested range) on the plasma and tissue PK of CMS and colistin in piglets
- Prediction of plasma concentrations in adults and children (healthy)





- Lack of information about mechanisms of CMS/colistin excretion/metabolism
→ need further *in vitro* investigations
- Improve the analytical method (CMS direct determination)
- Need of pediatric data for validation
- Extrapolation to other sub-populations, e.g. critically ill patients



Acknowledgments

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A. Perrin
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Inserm Poitiers' team:

N. Grégoire
W. Couet



Connaitre, évaluer, protéger



Thanks for your attention

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