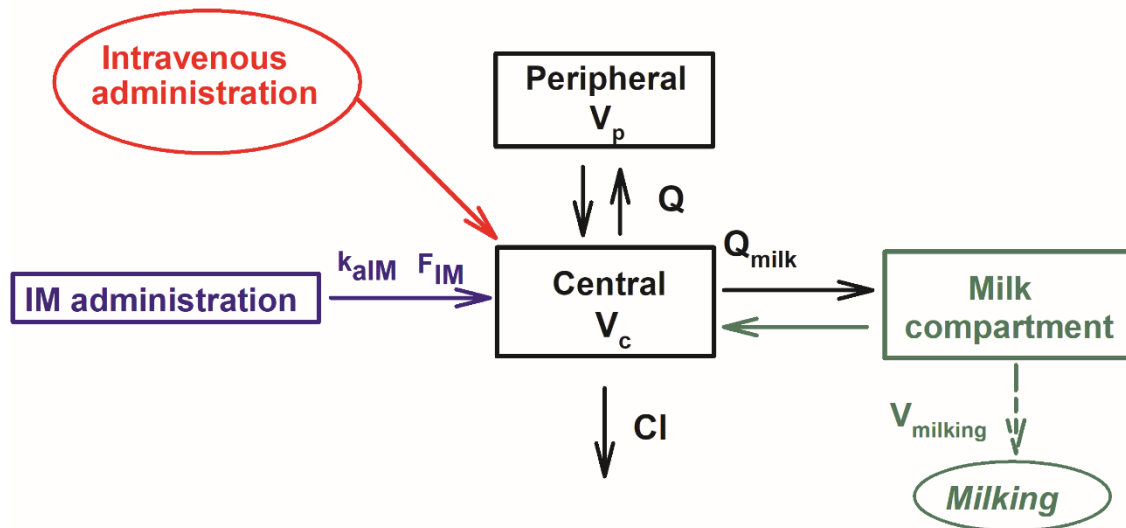


Pharmacokinetic/pharmacodynamic modelling in plasma and milk and Monte Carlo simulations of marbofloxacin against *Staphylococcus aureus* and *Mycoplasma agalactiae* in lactating sheep.

SUPPLEMENTARY MATERIAL

Non linear mixed effect model, equations and MLXTRAN code model.



$$\frac{dA_0}{dt} = -K_a \cdot A_0 \quad (1)$$

$$\frac{dA_1}{dt} = K_a \cdot A_0 - \frac{Cl}{V_c} \cdot A_1 - \frac{Q_{milk}}{V_c} \cdot A_1 + \frac{Q_{milk}}{V_{milking}} \cdot A_2 - \frac{Q}{V_c} \cdot A_1 + \frac{Q}{V_p} \cdot A_3 \quad (2)$$

$$\frac{dA_2}{dt} = \frac{Q_{milk}}{V_c} \cdot A_1 - \frac{Q_{milk}}{V_{milking}} \cdot A_2 \quad (3)$$

$$\frac{dA_3}{dt} = \frac{Q}{V_c} \cdot A_1 - \frac{Q}{V_p} \cdot A_3 \quad (4)$$

$$C_1 = A_1/V_c, C_2 = A_2/V_{milking} \text{ and } C_3 = A_3/V_p.$$

MLXTRAM CODE FOR MONOLIX MODEL

DESCRIPTION: TRICOMPARTMENTAL MODEL FOR PLASMA AND MILK
PARAMETRIZED BY CL AND Q WITH AUC AND CMAX VALUES, Vmilking FIXED

[LONGITUDINAL]

input = {F, ka, Cl, Vc, Q, Vp, Qmilk}

PK:

depot(adm=1, target=A1); IV administration

depot(adm=2, target=A0, p=F); IM administration

empty(adm=3, target=A2); ; Milk empty

EQUATION:

odeType = stiff

t_0=0

A0_0=0 ; IM administration

A1_0=0 ; IV central compartment

A2_0=0 ; Milk compartment

A3_0=0 ; Peripheral compartment

Vmilking = 0.12 ; volume of milking fixed

ddt_A0 = - ka*A0

ddt_A1 = ka*A0 - Cl/Vc *A1 - Qmilk/Vc *A1 + Qmilk/Vmilking *A2 - Q/Vc *A1 + Q/Vp
*A3

ddt_A2 = Qmilk/Vc *A1 - Qmilk/Vmilking *A2

ddt_A3 = Q/Vc *A1 - Q/Vp *A3

C1 = A1/Vc ; Plasma concentrations at central compartment

C2 = A2/Vmilking ; Milk concentrations at milk compartment

C3 = A3/Vp ; Peripheral concentrations

$AUC_0 = 0$

$ddt_AUC = C1$

$AUC24_0 = 0$

if($t < 24$)

$dAUC24 = 1/V_c * A1$

else

$dAUC24 = 0$

end

$ddt_AUC24 = dAUC24$

$AUCmilk_0 = 0$

$ddt_AUCmilk = C2$

$AUCmilk24_0 = 0$

if($t < 24$)

$dAUCmilk24 = 1/V_{milking} * A2$

else

$dAUCmilk24 = 0$

end

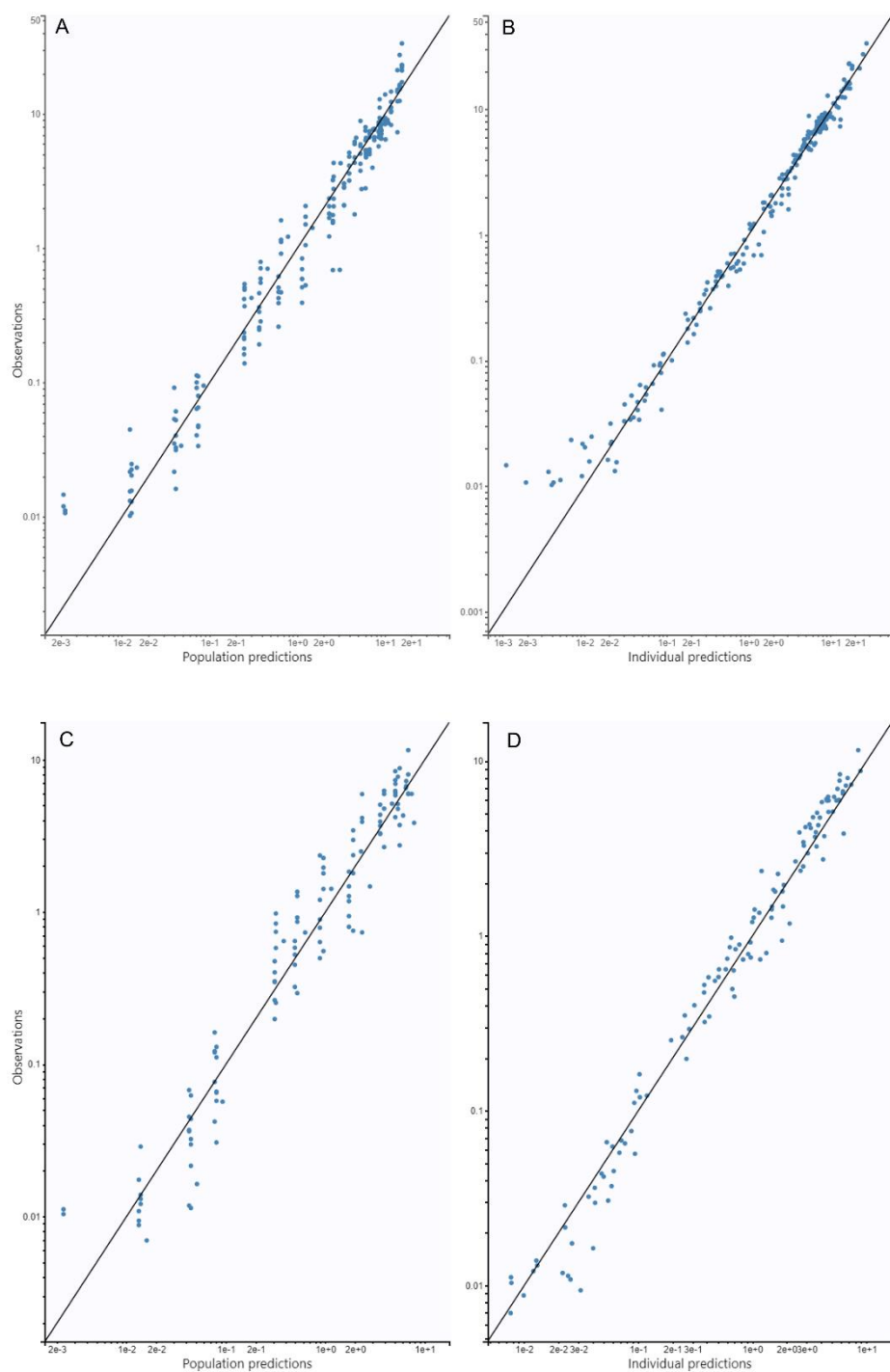
$ddt_AUCmilk24 = dAUCmilk24$

OUTPUT:

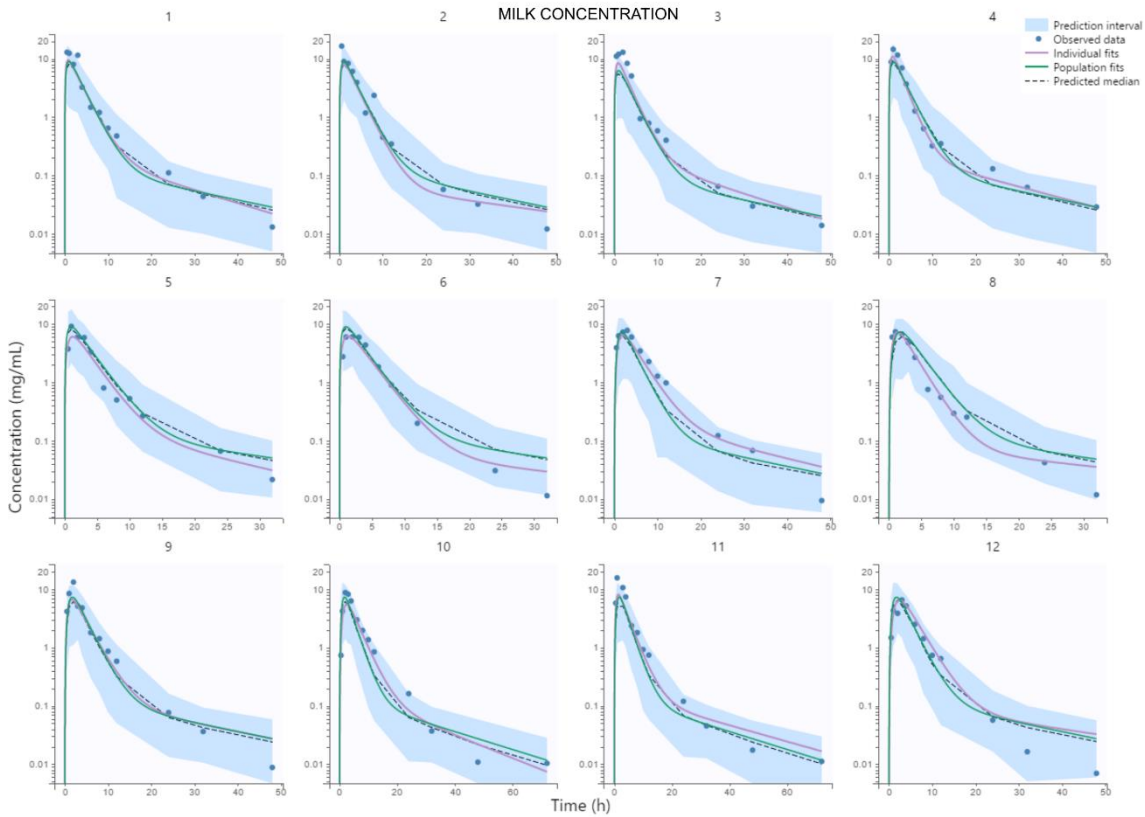
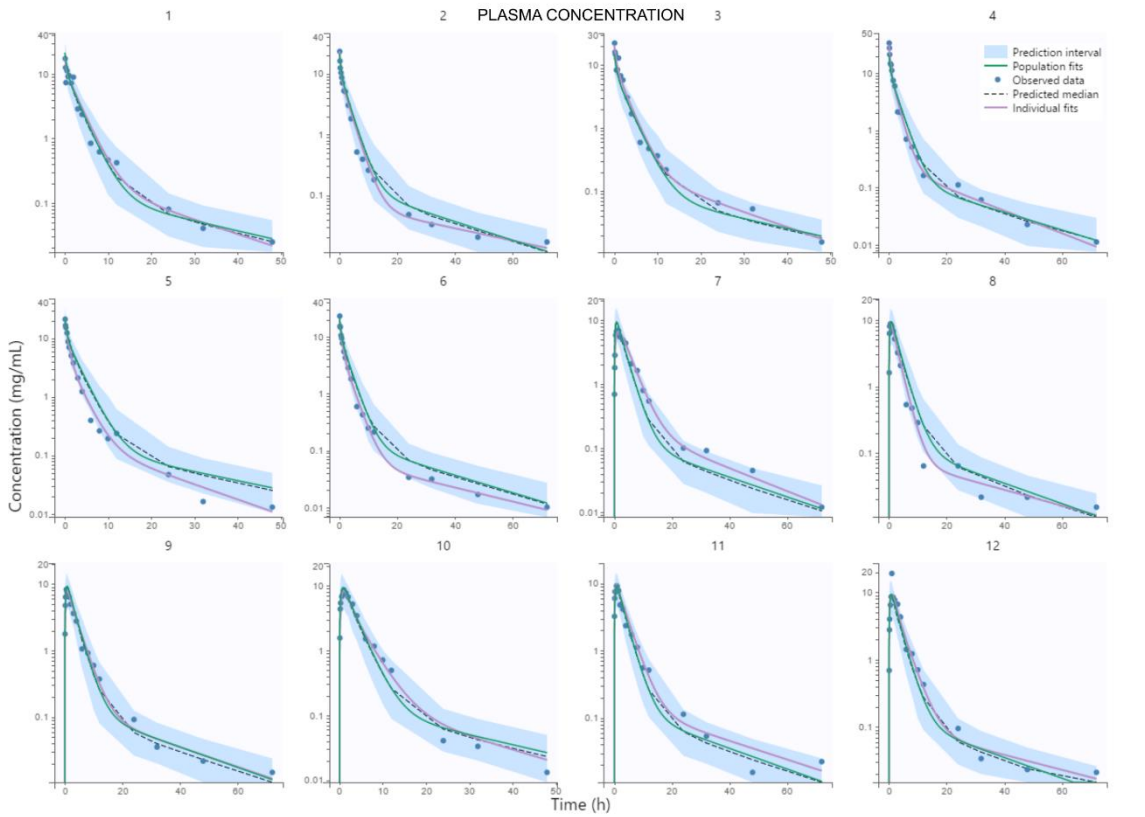
output = {C1, C2}

table = {AUC, AUCmilk, AUC24, AUCmilk24}

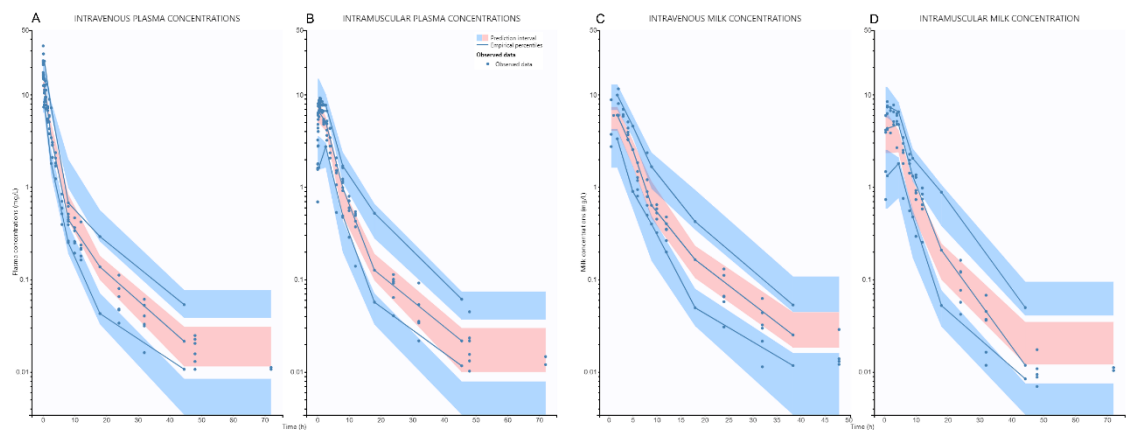
Observed versus prediction plots (A: IV plasma concentrations; B: IM plasma concentrations; C: IV milk concentrations; D: IM milk concentrations;)



Individuals prediction plots



Visual predictive check plots:



	Without covariates	Effect of V_{milk} on V_c	Effect of V_{milk} on Q_{milk}
-2 x log-likelihood (OFV)	-109.87	-108.21	-107.64
Akaike Information Criteria (AIC)	-72.21	-72.21	-69.64
Bayesian Information Criteria (BIC)	-63.48	-62.66	-60.42
Corrected BIC (BICc)	-30.4	-29.58	-27.34

Comparison of continuous covariates evaluated with the final pk model for plasma and milk concentrations.

Residuals plots versus time, individual and population predictions

