

External validation of para-aminosalicylic acid population pharmacokinetics model using *ncappc* R package

Ahmed A Abulfathi (1), Piyanan Assawasuwannakit (2), Peter Donald (3), Helmuth Reuter (1), Andreas H Diacon (4,5), Elin M Svensson (2,6)

(1) Division of Clinical Pharmacology, Department of Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa, (2) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden, (3) Paediatrics and Child Health and Desmond Tutu TB Centre, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa, (4) Task Applied Science, Bellville, South Africa, (5) Department of Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa, (6) Department of Pharmacy, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, the Netherlands
E-mail-address: aaabulfathi@sun.ac.za

Introduction:

- Para-aminosalicylic acid (PAS) is one of the essential add-on Group C medicines recommended by the World Health Organisation for the treatment of multi-drug resistant tuberculosis[1].
- Compared to the salt formulations of PAS, the granular-release formulation (PASER) is expected to be better tolerated[2]. There is limited information on the pharmacokinetics (PK) of this now widely available formulation.
- De Kock *et al* developed a one-compartment disposition model with 3-transit absorption compartments in series to describe the population PK of the granular-release formulation of PAS in South African patients with multi-drug or extensively drug resistant tuberculosis[2]. Understanding the dose-exposure and exposure-response relationships of high-doses of PASER are critical for its optimisation.

Objective:

- To externally validate a previously published PAS population PK model[2] using the *ncappc* R package[3].

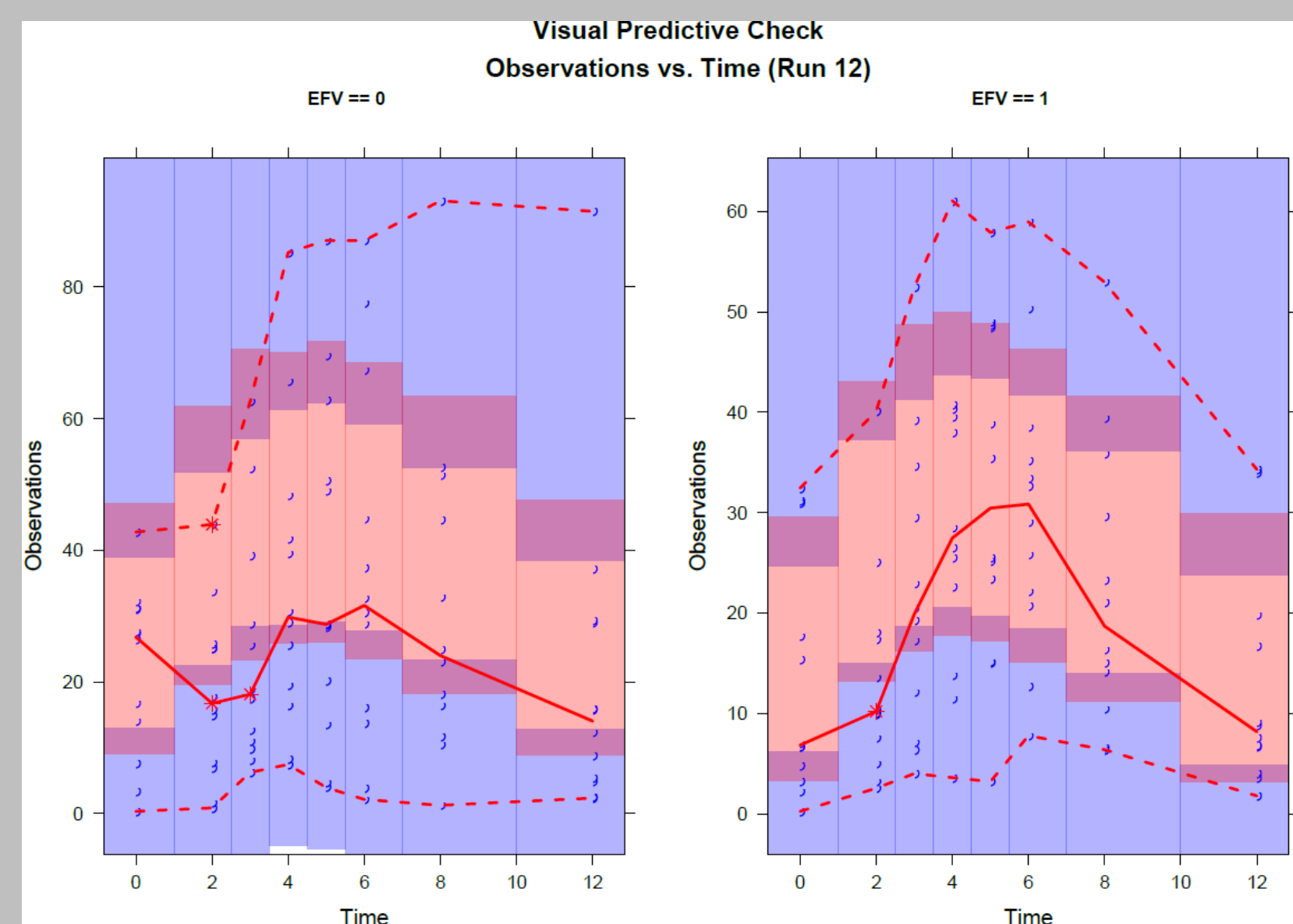
Methods:

- We used the final parameter estimates from the PAS population PK model developed by de Kock *et al*[2] and applied this model to a separate data set obtained in a similar population[4]. Nonlinear mixed effects modeling (NONMEM) software version 7.4.3 was used[5].
- R, an open-source statistical software[6] was used to implement the *ncappc* R package[3]. The de Kock *et al* model[2] was used to simulate concentration-time profiles of each individual 1000 times through Perl-Speaks-NONMEM (PsN)[7].
- Non-compartmental analysis (NCA) metrics such as peak plasma concentrations (C_{max}) and area under the concentration-time curve from time zero to the time of last measured concentration (AUC_{last}), were estimated from both observed and simulated datasets. The estimated observed and simulated NCA metrics were compared graphically.
- Additionally, PsN and Xpose[8] were used to create visual predictive checks and standard goodness-of-fit plots.

Results:

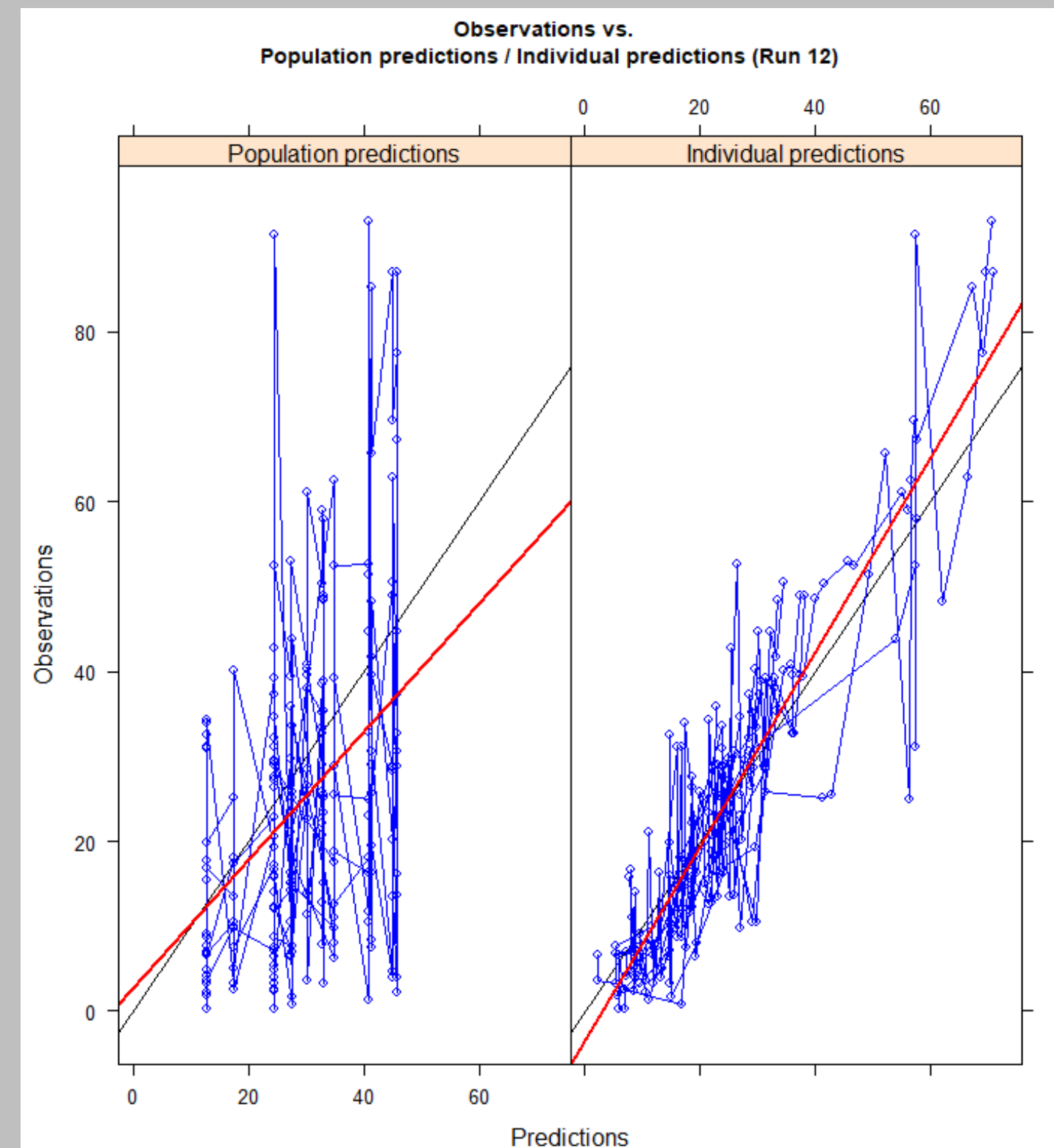
- The visual predictive checks showed that de Kock *et al* PAS population PK model[2] describes the external data[4] reasonably well (figure 1).

Figure 1: Visual predictive check



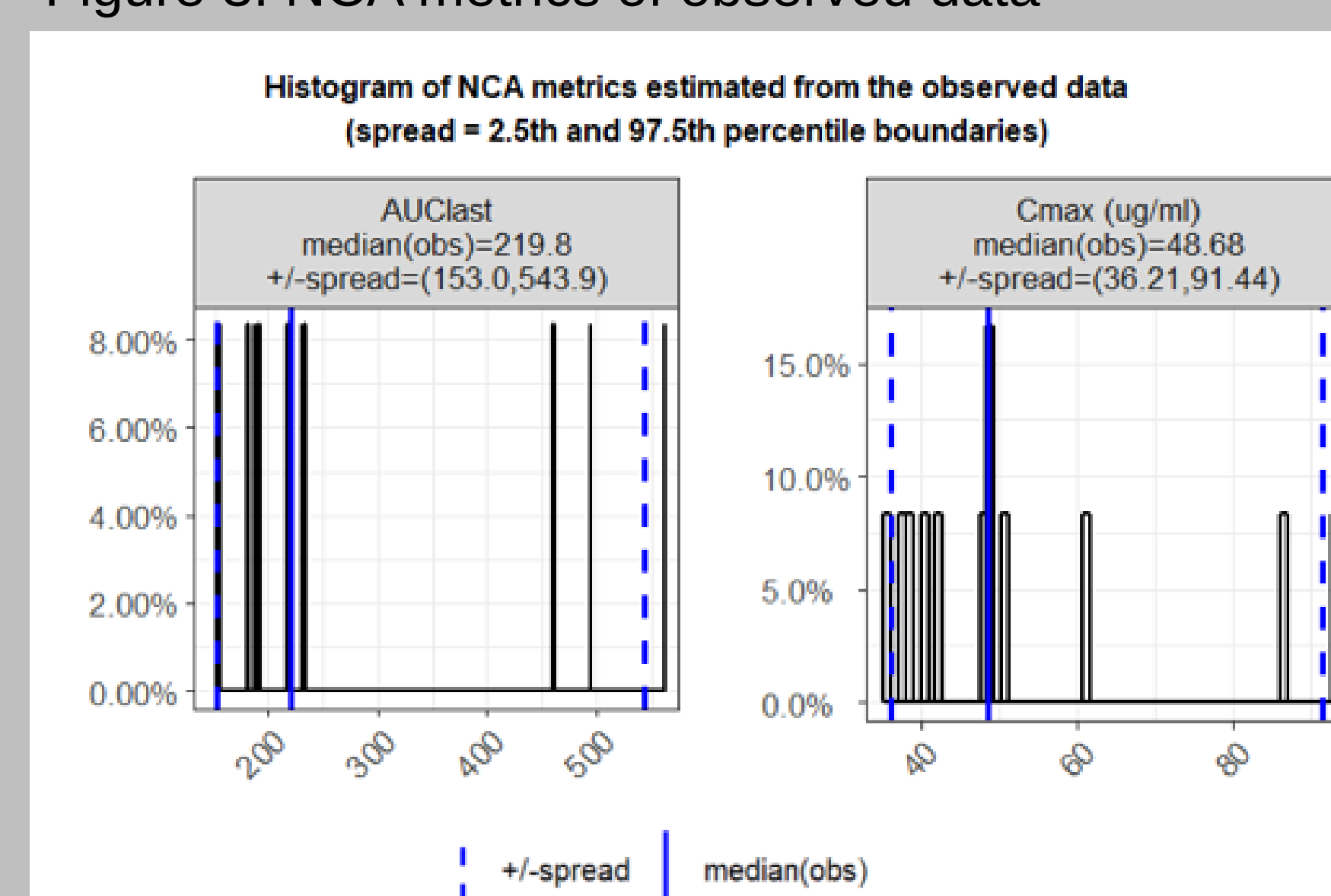
- However, the goodness-of-fit plots showed a systematic deviation between observed concentrations and population predictions. This deviation was compensated by the between-subject variability as shown in the observed versus individual prediction plot.(figure 2).

Figure 2: Basic goodness of fit plots



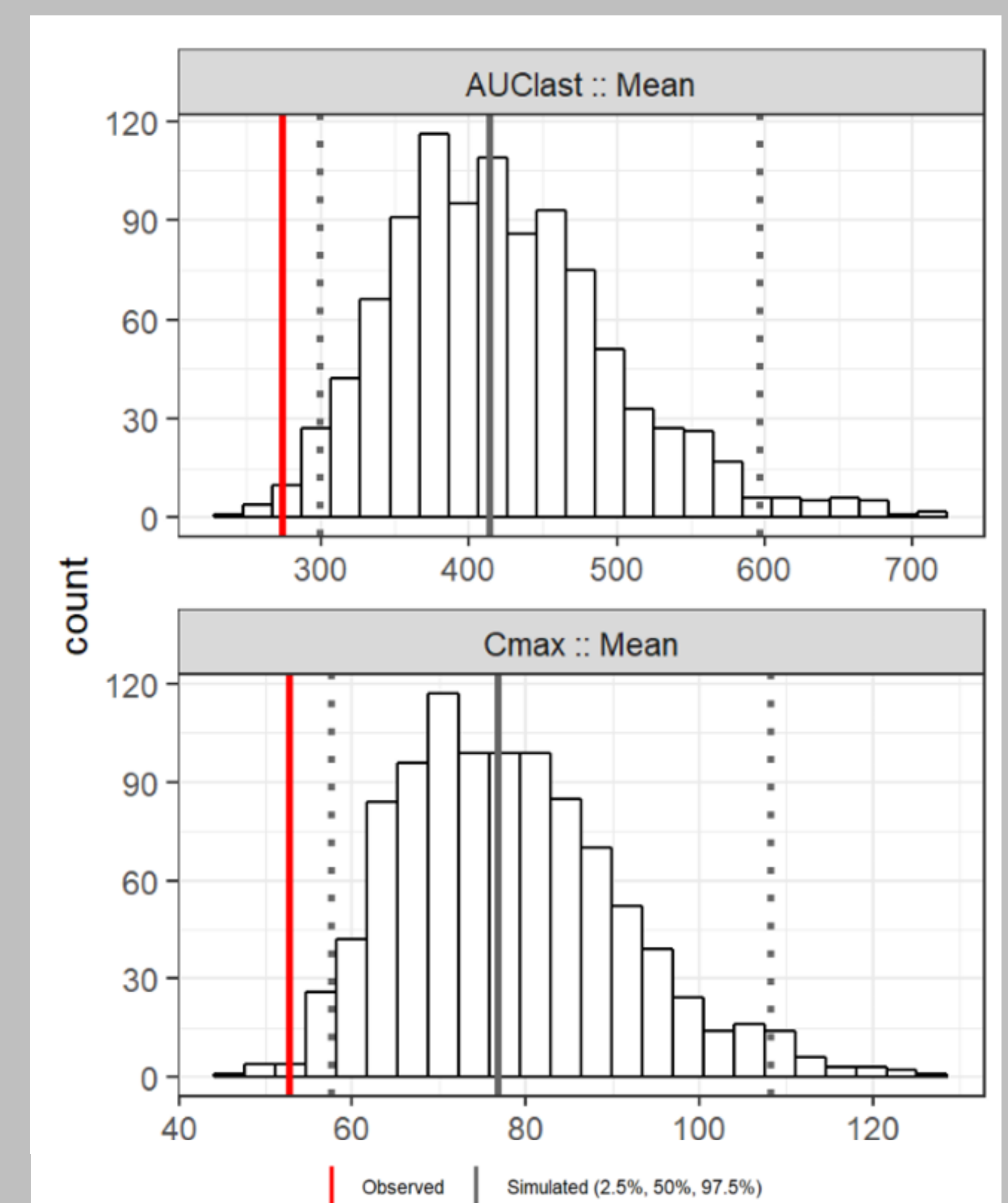
- The median C_{max} of the observed dataset fell outside the histogram of 95% non-parametric prediction interval (npi) of the simulated datasets. Similarly, the median AUC_{last} of the observed dataset fell outside the histogram of the 95% npi of the simulated datasets. (figures 3 and 4).

Figure 3: NCA metrics of observed data



- These findings suggest the model[2] needs optimisation.

Figure 4: NCA metrics of 1000 simulated datasets



Conclusion:

- Our findings suggest the inability of a PAS population PK model[2] to adequately simulate the concentration-time profile of an external dataset[4].
- On average, the model was under-predicting PAS plasma concentrations.
- There is a need for the current model to be optimised with pooled PASER datasets[2,4] before using the improved model for simulation studies evaluating target attainment with novel dosing strategies with PASER.

References:

- [1] WHO | Rapid Communication: Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). WHO. 2018.
- [2] de Kock L et al. Antimicrob Agents Chemother. 2014;58(10):6242-50.
- [3] Acharya C et al. Comput Methods Programs Biomed. 2016;127:83-93.
- [4] Liwa AC et al. J Trop Pediatr. 2013;59(2):90-94.
- [5] S. Beal et al. NONMEM | Nonlinear Mixed Effects Modelling | ICON plc.
- [6] R: The R Project for Statistical Computing.
- [7] PsN :: <https://uupharmacometrics.github.io/PsN/>.
- [8] Xpose :: Documentation :: Citation. http://xpose.sourceforge.net/docs_citation.php.

Acknowledgement: Prof B Rosenkranz, Dr S Sy, Prof S Schaaf, Dr A Liwa, Ms L de Kock and Prof Mats Karlsson.