Title: On our way to personalized therapy: Using therapeutic drug monitoring data of moxifloxacin for an external pharmacokinetic model evaluation

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Objectives:
Personalization of drug therapy can be realized using model-informed precision dosing (MIPD), which can enhance the therapeutic drug monitoring process. A personalized dose for an individual can be calculated using Bayesian forecasting.
Moxifloxacin (Mfx) is a fluoroquinolone and was recommended by the WHO in 2022 as part of the BPaLM regimen (bedaquiline, pretomanid, linezolid and Mfx) in treatment of multidrug- or rifampicin-resistant tuberculosis as a 6-month regimen or to be included in longer regimens [1]. Moreover, Mfx is part of treatment regimens in the DECISION and PARADIGM4TB studies within the UNITE4TB clinical trial phase 2B/C program [2].
The aim of this study was the application and evaluation of available population PK models of Mfx for the use in a MIPD workflow.

Methods:

A literature search was conducted with the keywords 'pharmacokinetics', 'moxifloxacin', 'population model' and 'tuberculosis' using PubMed. The PK models were processed in NONMEM® 7.5.6

The clinical data used in this model evaluation was provided from Research Center Borstel, Germany, and included 16 patients with multi-drug resistant tuberculosis contributing 2996 samples in total. Dataset processing was conducted using R (version 4.2.1) [3]. The Bayesian forecasting was performed iteratively such that the previous occasion would inform the forecast of the following occasion stepwise starting from the first occasion and stopping at the seventh occasion. Median prediction error (MPE) and median absolute prediction error (MAPE) were used as metrics to evaluate the model performance.

Results:

Six population PK models were recoded from the original publications (Al-Shaer et al. (2019) [4], Chang et al. (2017) [5], Chirehwa et al. (2023) [6], Yun et al. (2022) [7], Zvada et al. (2012) [8], Zvada et al. (2014) [9]). Six patients receiving 400 mg moxifloxacin once daily with a total of 161 observations included in the evaluation of the Bayesian forecasting and the *a priori* predictions.

A priori

In the evaluation of the *a priori* predictions MPE were between -5% (Chirehwa et al.) to 60% (Al-Shaer et al.). MAPE values ranged between 35% (Chirehwa et al.) and 61% (Al- Shaer et al.).

Bayesian forecasting

MPE resulting from the models of Al-Shaer et al., Chang et al., Chirehwa et al., Yun et al., Zvada et al. (2012) and Zvada et al. (2014) were 7%, 8%, 2%, -1%, 30 and 26% and the calculation of MAPE led to values of 27%, 34%, 20%, 26%, 31% and 30%, respectively.

Conclusions:

Overall, the *a priori* predictions led to higher values of the chosen metrics in comparison to Bayesian forecasting. The model from Chirehwa et al. performed best - followed by the models from Yun et al. and Al-Shaer et al. - and the model from Chang et al. showed the least favorable predictive performance guided by MAPE. Limitations of our study are the very small number of patients and observations in the investigated dataset on the one hand and the different composition of the observed occasions on the other hand.

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