



QT interval prolongation in children receiving moxifloxacin and clofazimine for rifampicin-resistant tuberculosis treatment in South Africa, India and the Philippines

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Introduction

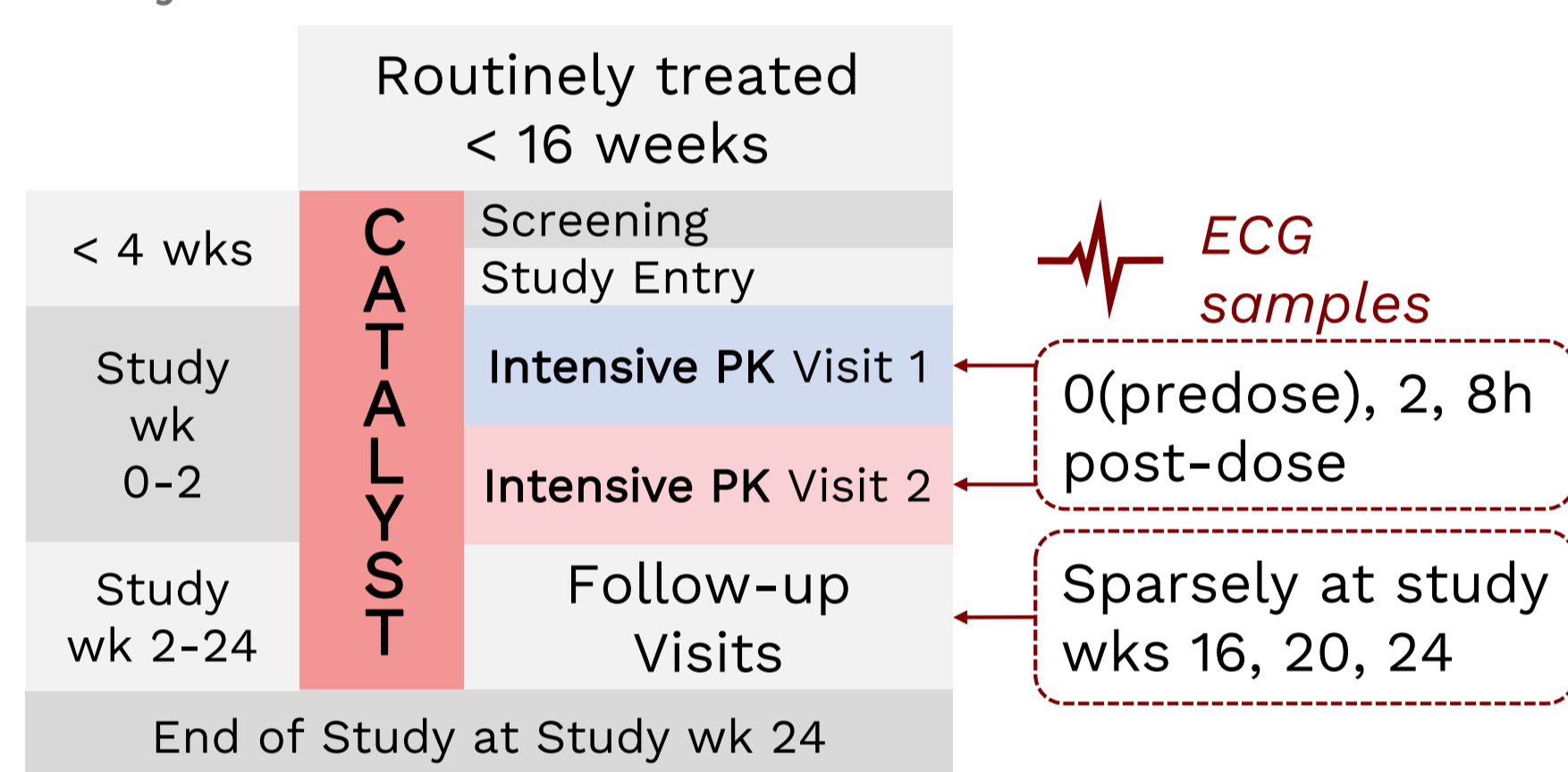
Clofazimine (CFZ) and moxifloxacin (MFX) are commonly used for the treatment of rifampicin-resistant tuberculosis (RR-TB).¹ Both drugs can prolong the QT interval.

AIM: To characterise the associations between their pharmacokinetics (PK) and Fridericia-corrected QT interval (QTcF) in children treated for RR-TB.

Methods

CATALYST Study

A multisite open-label trial for PK, safety and acceptability of MFX and CFZ in children <15 years treated for RR-TB.

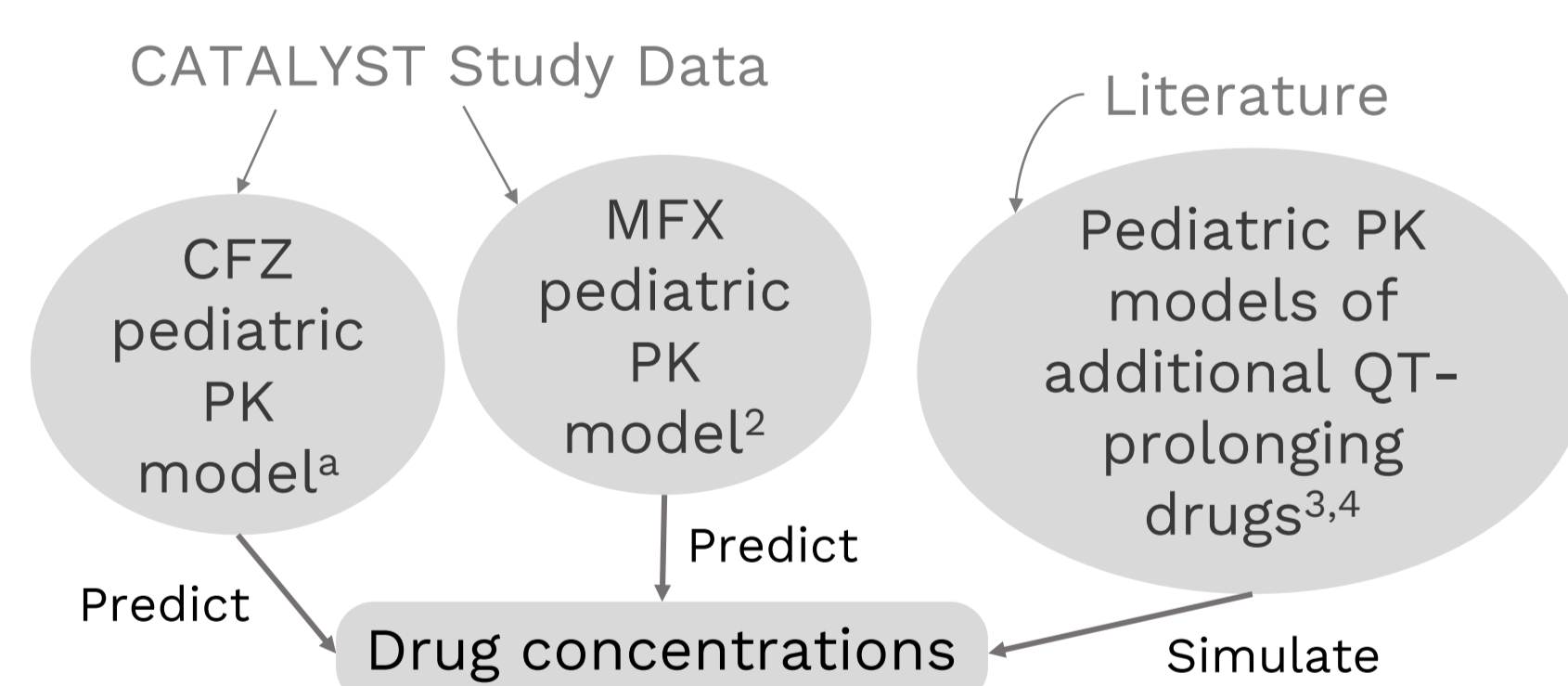


PK-QTcF Model

Structural components below were assessed and tested for statistical significance:

$$QTcF = BASE + DRUG + TIME + CIRC + COV + ERR$$

BASE: Baseline QTcF at start of treatment.
DRUG: Exposure-response relationship.



a. Unpublished

With exposures obtained from above, a competitive PKPD interaction model was then used to describe the QT-prolongation contributed by multiple drug concentrations.⁵

TIME: Drug-independent QTcF changes with time after start of TB treatment (t).⁶

CIRC: Diurnal variation.⁶

COV: Covariates for age, sex, race, country.

ERR: Residual unexplained variability.

Acknowledgments

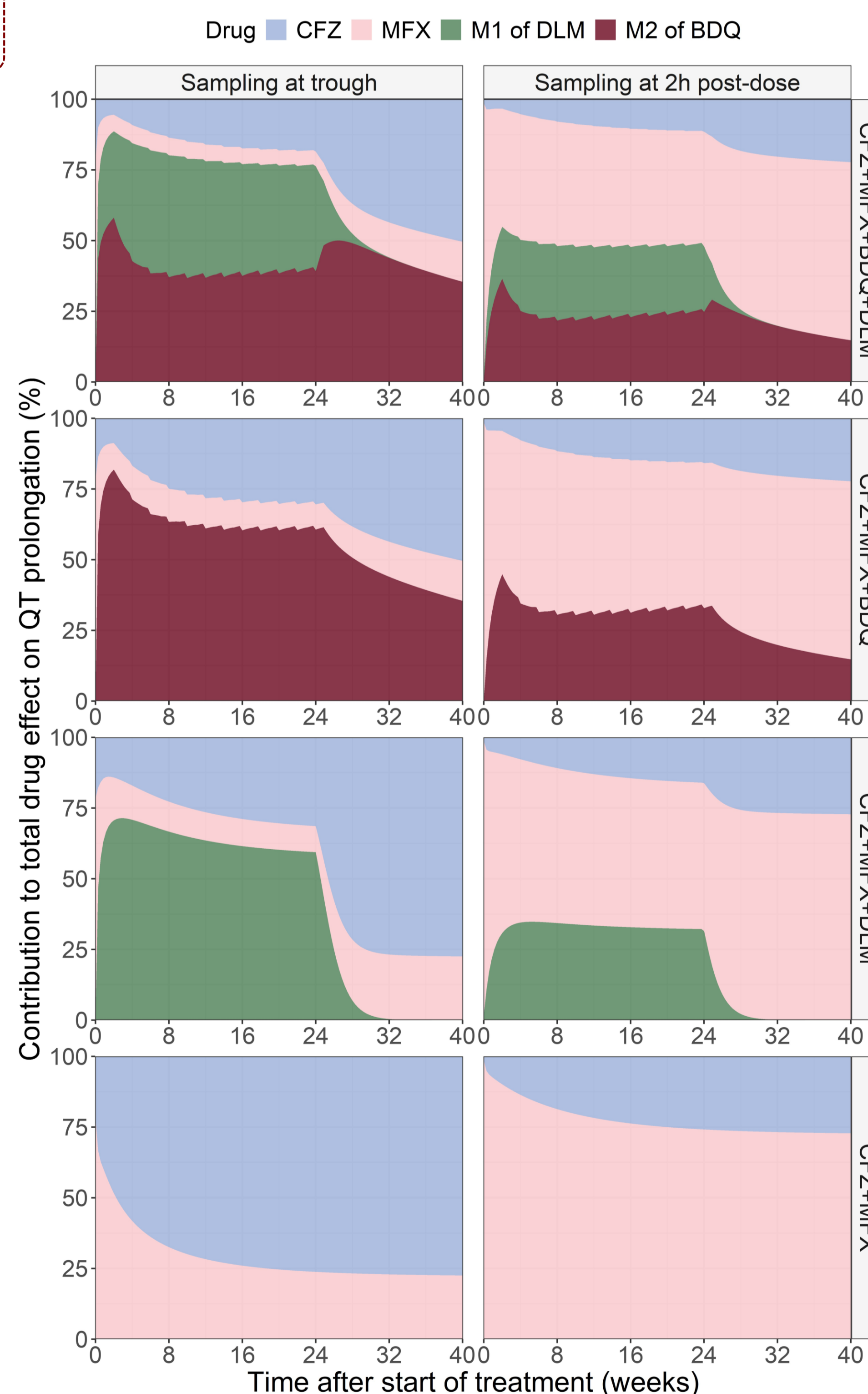
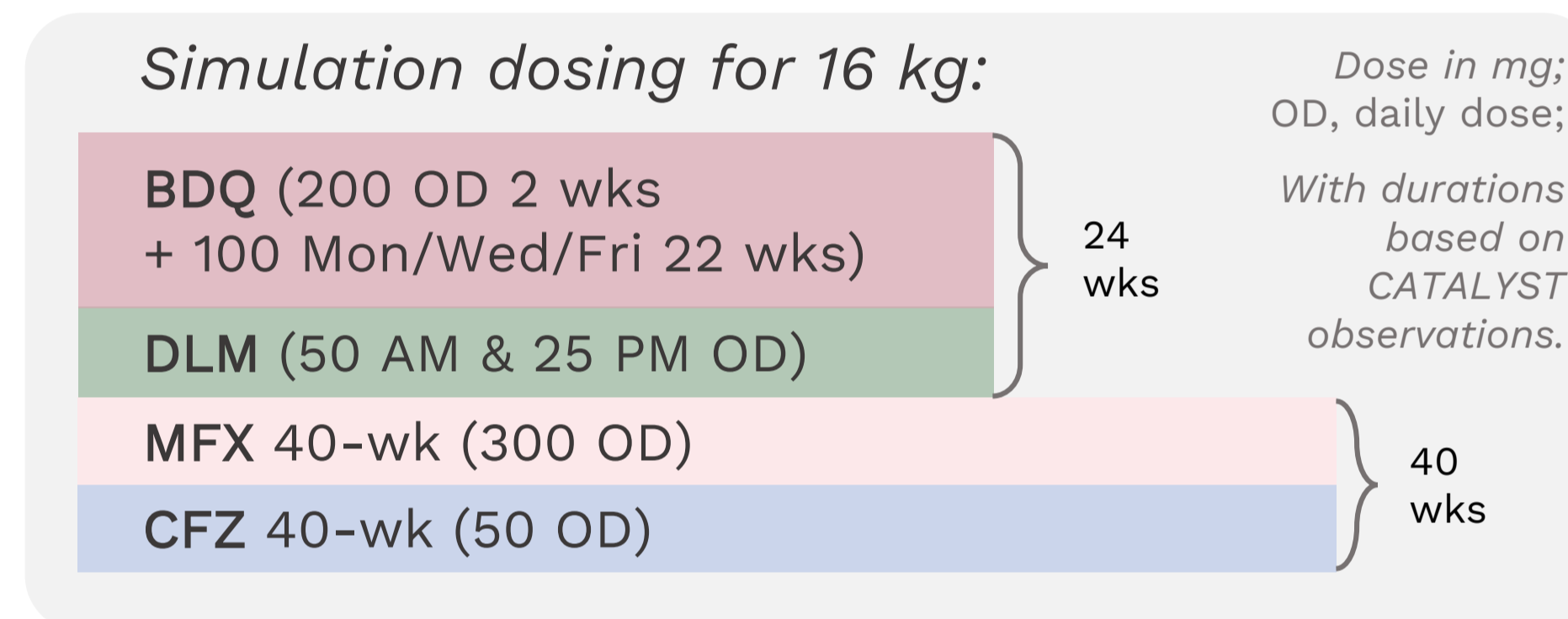
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Results

| Patient Characteristics | (n=36) |
|---|-------------------|
| Male (%) | 14 (38.9) |
| Median age [years] (IQR) | 4.8 (2.4, 8.1) |
| Median weight-for-age Z-Score (IQR) | -1.6 (-2.7, -0.5) |
| Median height-for-age Z-Score (IQR) | -0.9 (-2.3, -0.3) |
| HIV status (%) | 1 (2.8) |
| Time on RR-TB treatment at enrolment [days] (IQR) | 37 (23, 64) |
| Time on CFZ at enrolment [days] (IQR) | 37 (23, 64) |
| Time on MFX at enrolment [days] (IQR) | 0 (-1, 0) |
| RR-TB QT-prolonging drug regimen (%) | |
| CFZ/MFX | 12 (33.3) |
| CFZ/MFX/bedaquiline (BDQ) | 15 (41.7) |
| CFZ/MFX/delamanid (DLM) | 9 (25.0) |

Simulation of Drug %Contribution to QT prolongation based on the final model, of a typical (median) CATALYST patient receiving WHO doses of CFZ, MFX, and/or BDQ, and/or DLM.¹



| PK-QTcF Model Parameter | Estimate (RSE%) |
|---|---------------------------|
| QTcF Base (ms) | 416 (1) |
| IIV-Base (CV%) | 3.2 (16) |
| AGE model (referring to 15-year-old) | |
| E _{max,age} (ms) | -43.9 (14) |
| EA50 (years) | 4.86 (22) |
| Hill | 8.66 (27) |
| DRUG ^a (4-drug interaction model ⁵) | |
| E _{max} (ms) ^b | 25.9 (fixed) ⁶ |
| EC _{50,CFZ} (mg/L) | 2.12 (93) |
| EC _{50,MFX} (mg/L) | 4.70 (67) |
| EC _{50,M2} of BDQ (ng/mL) | 695 (fixed) ⁶ |
| EC _{50,M1} of DLM (ng/mL) | 205 (fixed) ⁶ |
| TIME (change over time) | |
| QT _{max_shift} (ms) | 7.05 (fixed) ⁶ |
| Half-life, or HL (weeks) | 7.52 (fixed) ⁶ |
| Additive error (ms) | 17.1 (4.9) |

a. BDQ and DLM were two additional QT-prolonging drugs in CATALYST; they prolong via metabolites M2 and M1, respectively.
b. E_{max} is shared among CFZ, MFX, M2 of BDQ, M1 of DLM, given their common mechanism of action for QT prolongation.

$$AGE Model = \frac{E_{max} \times (15 - AGE)^{Hill}}{EA50^{Hill} + (15 - AGE)^{Hill}}$$

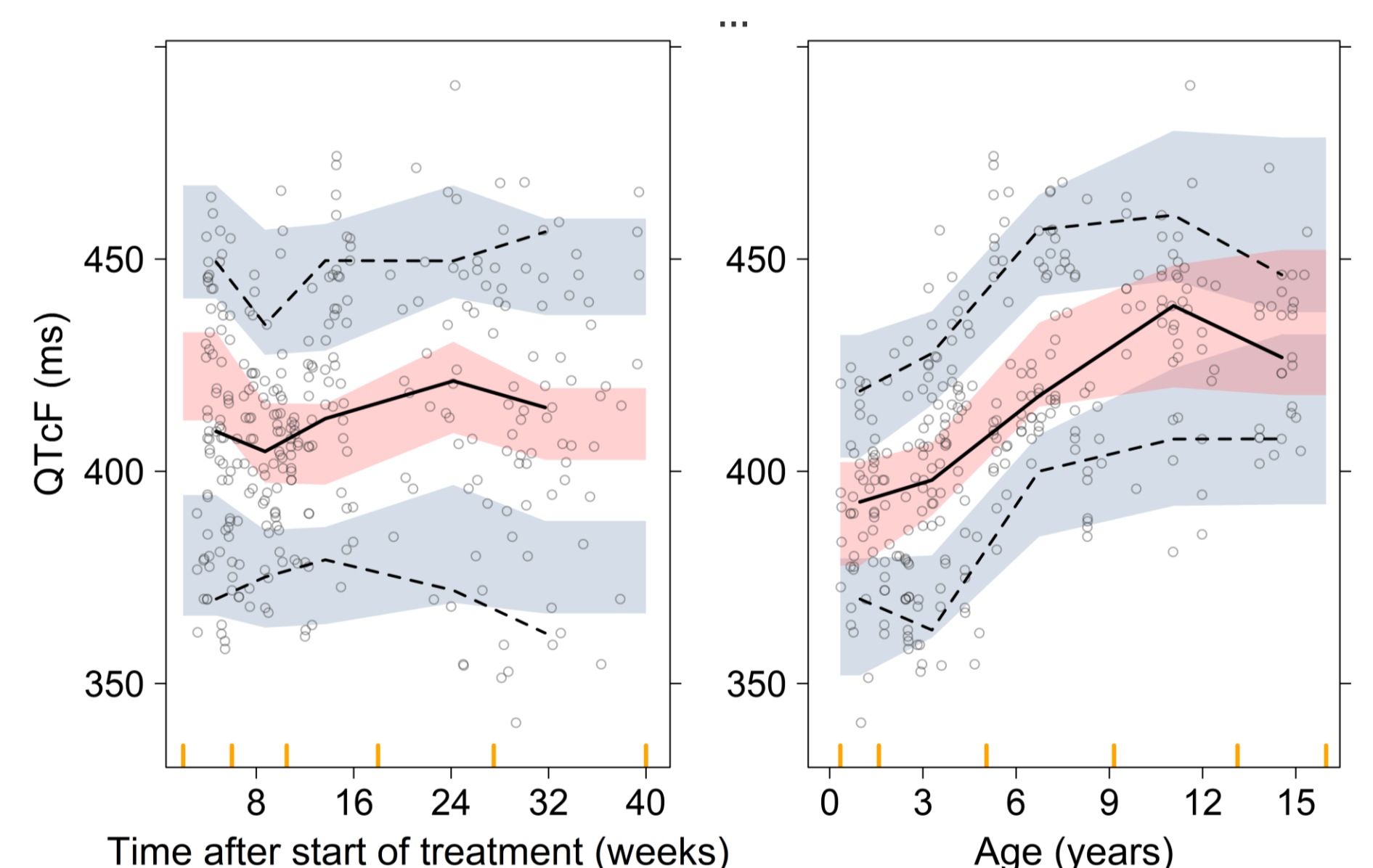
$$TIME Model = QT_{max} \times (1 - e^{-(HL) \times t})$$

t: time after start of TB treatment

$$DRUG Model = EECFZ + EEMFX + EEM2 + EEM1$$

$$EECFZ = \frac{E_{max} \times CFZPK}{EC_{50,CFZ} \times \left(1 + \frac{MFXPK}{EC_{50,MFX}}\right) \times (\dots) + CFZPK}$$

$$EEMFX = \frac{E_{max} \times MFXPK}{EC_{50,MFX} \times \left(1 + \frac{CFZPK}{EC_{50,CFZ}}\right) \times (\dots) + MFXPK}$$



Conclusions

- Younger children had lower QTcF before and during RR-TB treatment.
- MFX had an immediate post-dose effect and was the primary contributor at its peak concentration.
- CFZ and metabolites of BDQ/DLM drove long-term QTcF prolongation due to their accumulating PK characteristics. However, CFZ EC₅₀ for drug effect was estimated with large uncertainty.

References

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