

Model-based assessment of early bactericidal activity of rifampicin in combination with meropenem plus amoxicillin/clavulanate among adults with rifampicin-resistant pulmonary tuberculosis

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Introduction

Meropenem and rifampicin have been reported to have synergistic activity *in vitro* in both rifampicin-susceptible and rifampicin-resistant (RR) *Mycobacterium tuberculosis* strains¹. Rifampicin minimal inhibitory concentrations were reduced significantly enough in the presence of meropenem to suggest a restoration of rifampicin activity against RR strains, suggesting that this combination could be used in patients with RR tuberculosis (RR-TB).

The aim of this work was to evaluate the 14-day early bactericidal activity (EBA) of meropenem with and without rifampicin in patients with RR-TB using a standardized pharmacometric model-based EBA analysis approach.

Methods

Participants with smear-positive RR-TB from the COMRADE² trial were included in this analysis, and received one of the two treatments (Fig 1).

Arm A	Meropenem 2 g 0.53 hours intravenous infusion thrice daily	Amoxicillin/ clavulanic acid 500 mg/125 mg orally thrice daily	Rifampicin 20 mg/kg orally once daily
Arm B	Meropenem 2 g 0.53 hours intravenous infusion thrice daily	Amoxicillin/ clavulanic acid 500 mg/125 mg orally thrice daily	

Fig 1. Treatment and dosing information

Sputum samples were collected at baseline and on days 1, 2, 3, 4, 6, 8, 10, 12 and 14 of treatment to determine colony forming units (CFU) and time-to-positivity (TTP). CFU data was available for 47 participants (29 in arm A and 18 in arm B), and TTP data for 50 participants (31 in arm A and 19 in arm B).

CFU and TTP data analysis was performed following a standardized pharmacometric model-based EBA analysis approach³.

Acknowledgements

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References

- 1 Kaushik et al. 2015 Antimicrob Agents Chemother.
- 2 ClinicalTrials.gov Identifier: NCT03174184
- 3 Mockeliunas et al. 2023 Front Pharmacol.

Results

The final CFU model consisted of a mono-exponential function with inter-individual variability in baseline and CFU slope (Fig 2). CFU baseline was identified as a covariate on CFU slope (41% increase in CFU slope per 1 unit increase in baseline log₁₀CFU/mL).

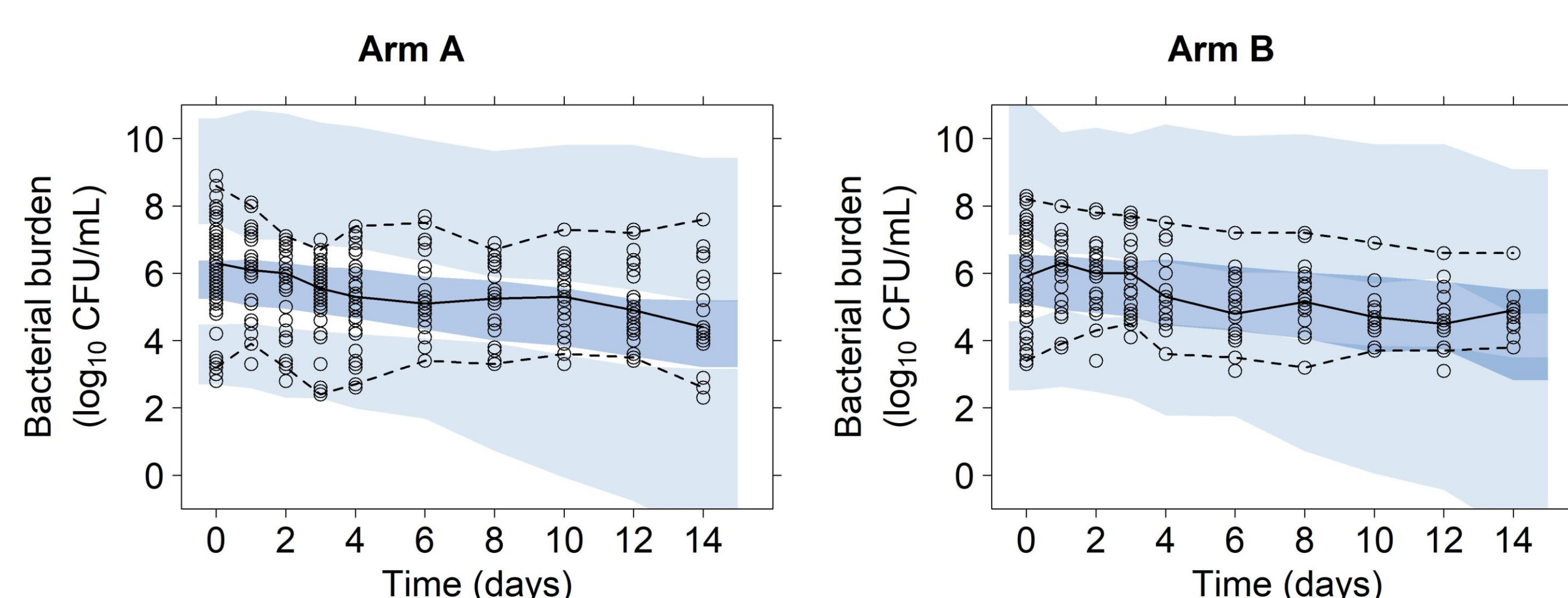


Fig 2. Visual predictive check of the final CFU model.

The final TTP model consisted of a mono-exponential function, and inter-individual variability was included in both baseline and TTP slope (Fig 3). Participants with single or multiple cavities of diameter ≥ 4 cm in aggregate were found to have 52% lower TTP baseline compared to participants with no cavities or with the presence of single or multiple cavities with diameter < 4cm in aggregate.

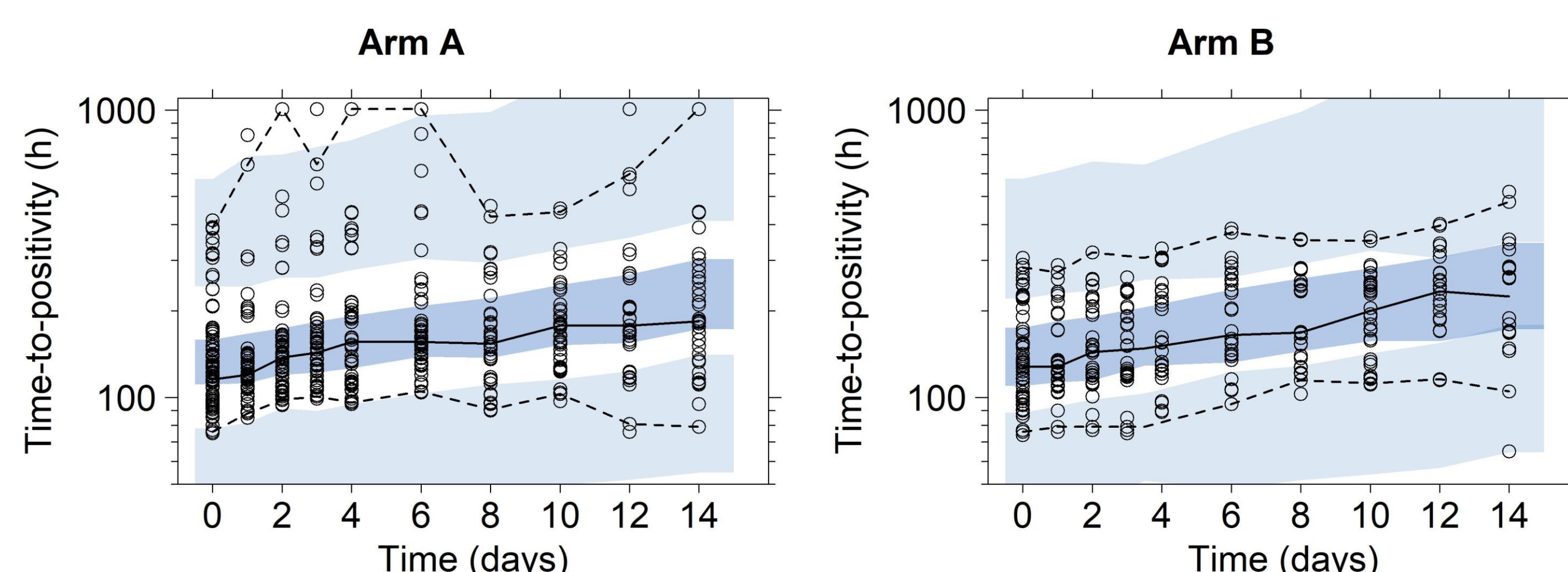


Fig 3. Visual predictive check of the final TTP model.

Both treatment arms showed statistically significant EBA in both CFU and TTP but no statistically significant difference was identified between the treatment arms (Fig 4).

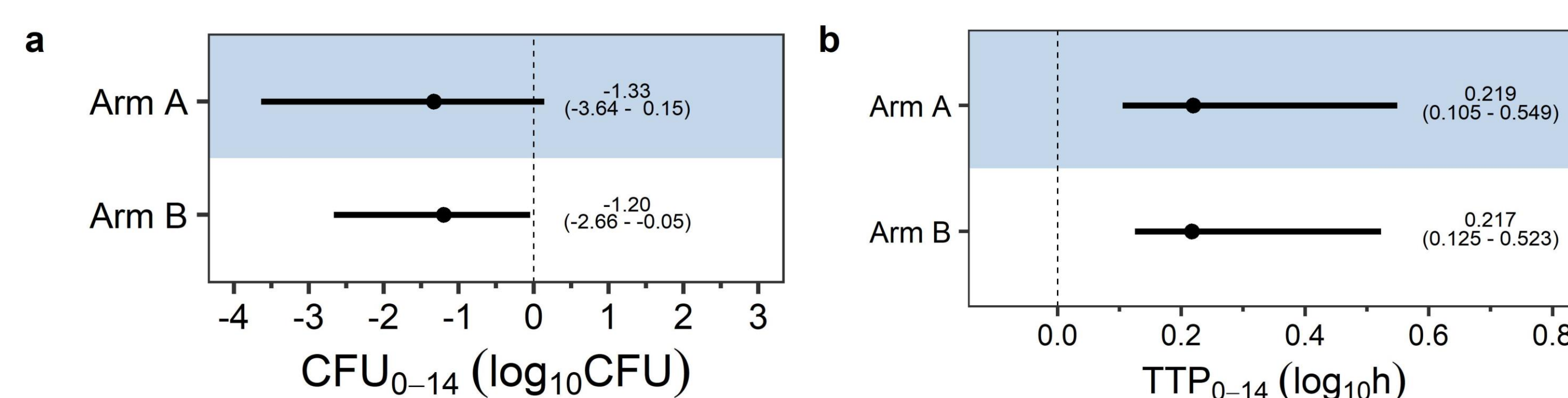


Fig 4. Model-predicted 14-day bactericidal activity based on a) CFU and b) TTP.

Conclusion

Previously developed standardized EBA analysis approach was successfully applied to analyse Phase 2a trial data from the COMRADE trial. Meropenem with amoxicillin/clavulanate does not appear to restore rifampicin susceptibility for participants with RR-TB based on Phase 2a data.



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