

An interactive pharmacokinetic, pharmacodynamic and long-term outcome model framework to evaluate bedaquiline dose modifications in adults

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Introduction

- Bedaquiline exposure-response-long term outcome relationships have been established under the approved thrice-weekly (TIW) dosing regimen^[1-4]
- Once-daily (QD) doses enable fixed-dose combinations, which could improve adherence
- A high loading dose in the first 2 weeks is important for maximizing early bactericidal activity

Aim

- Build an interactive R Shiny simulation tool to enable evaluation of different bedaquiline dosing schedules in an integrated dose-PK-efficacy/safety-outcome model framework

Methods & Results

1

Registered dosing

400 mg QD x 2 weeks +
200 mg TIW x 22 weeks

2

ZeNix once-daily dosing

200 mg QD x 8 weeks +
100 mg QD x 16 weeks

3

High-loading-dose once-daily dosing

400 mg QD x 2 weeks +
100 mg QD x 22 weeks

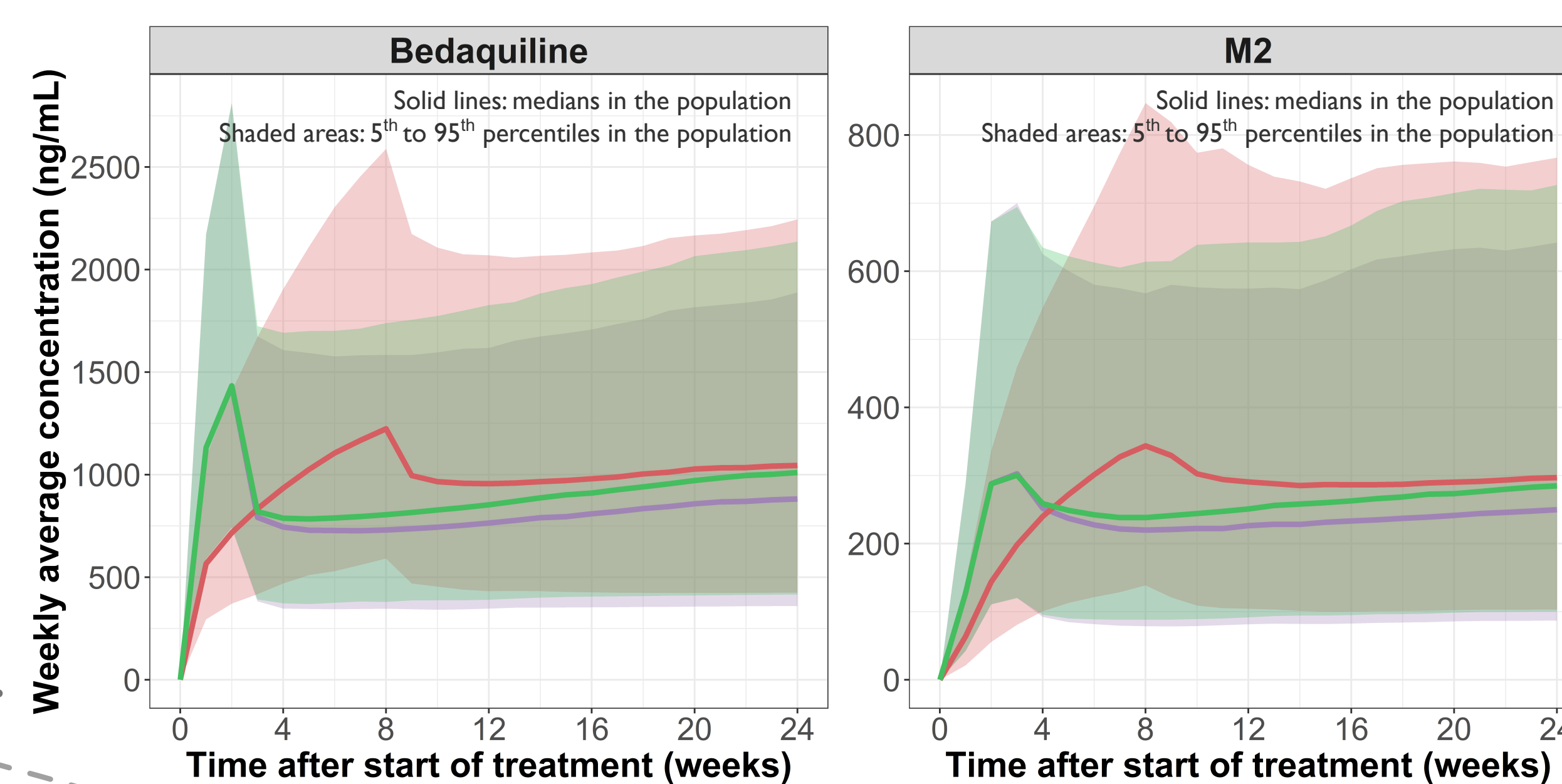
Tested in PARADIGM4TB trial (NCT06114628)



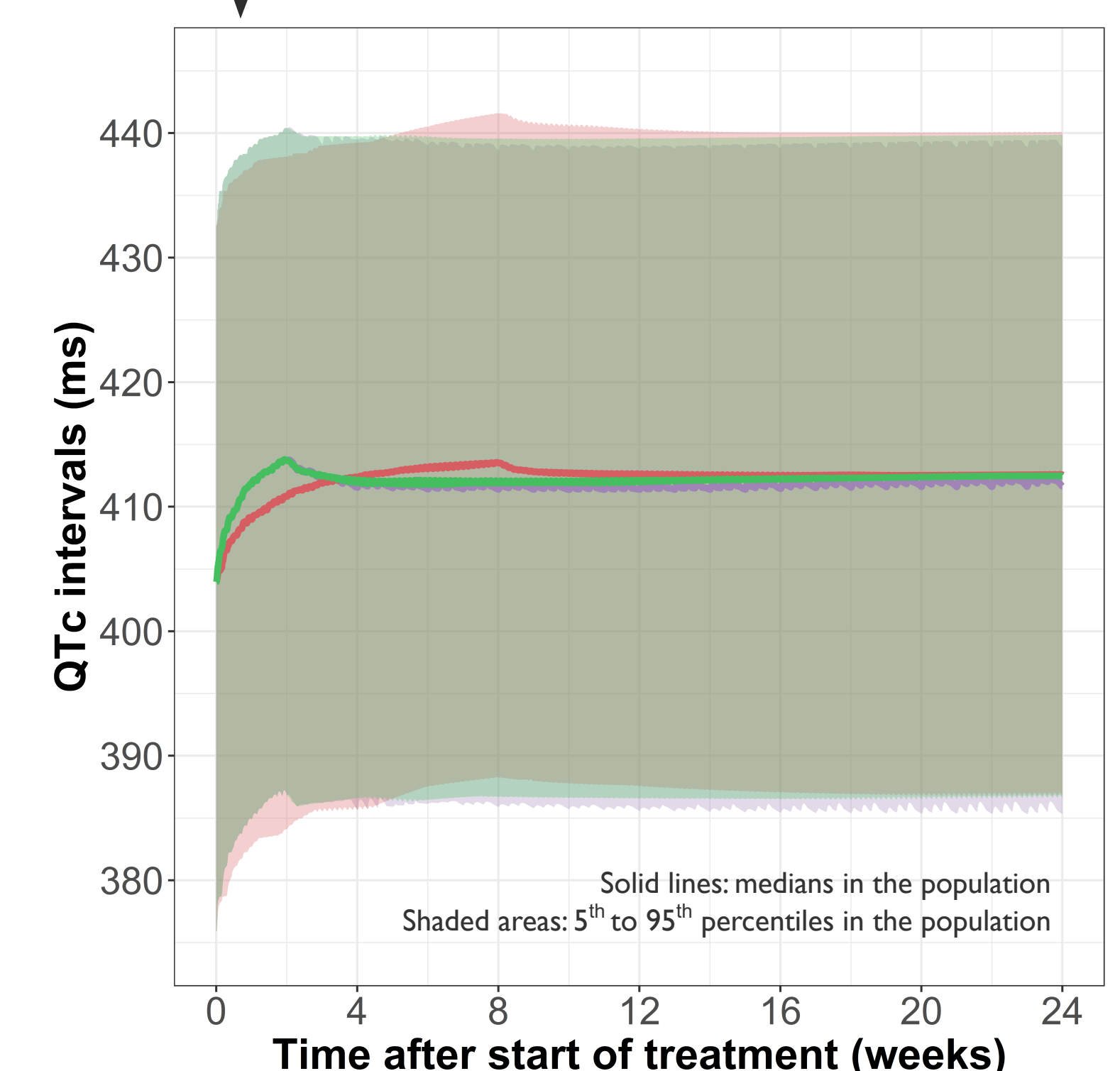
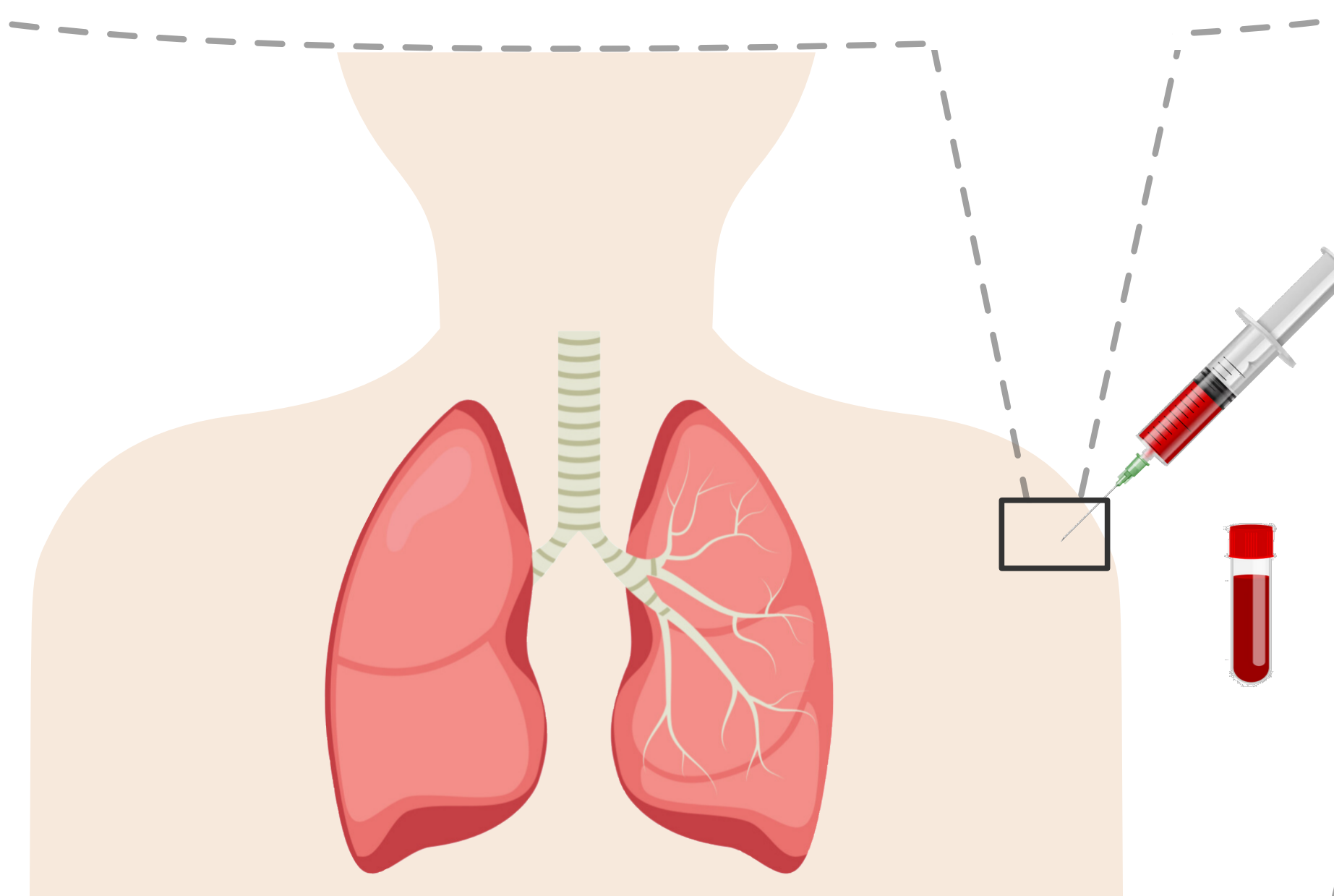
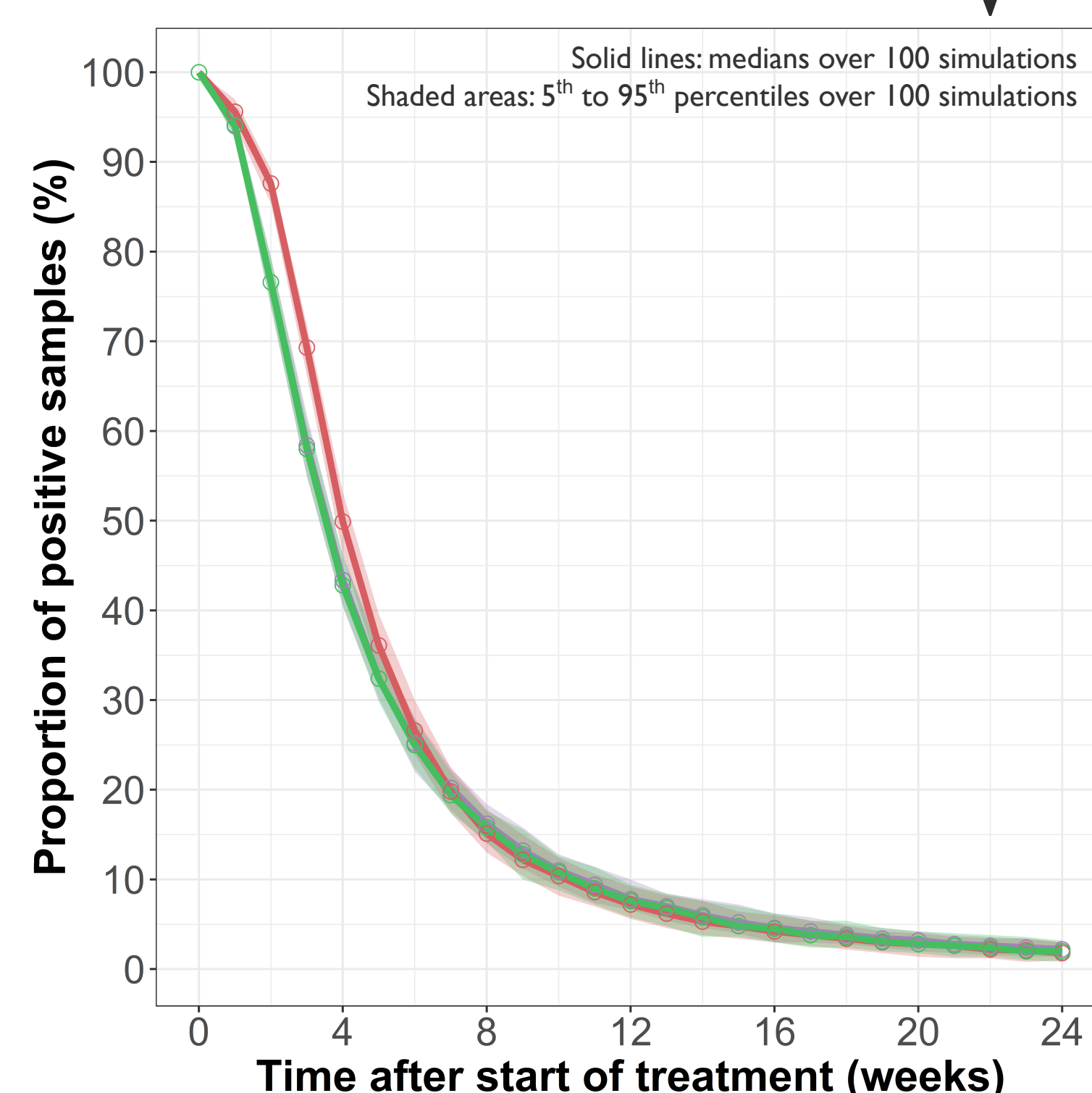
- Virtual population (n = 500/regimen): 50%/50% male/female, 40% black race
- Covariates were simulated using conditional distribution modeling^[5] based on 556 patients from 3 trials (TB-PACTS^[6])

PK (bedaquiline and M2)^[1]

- ~50% higher median cumulative AUCs of bedaquiline and M2 with registered and high-loading-dose dosing at week 2, compared to ZeNix dosing
- By 8 weeks, all 3 evaluated regimens yielded comparable cumulative AUCs of bedaquiline and M2

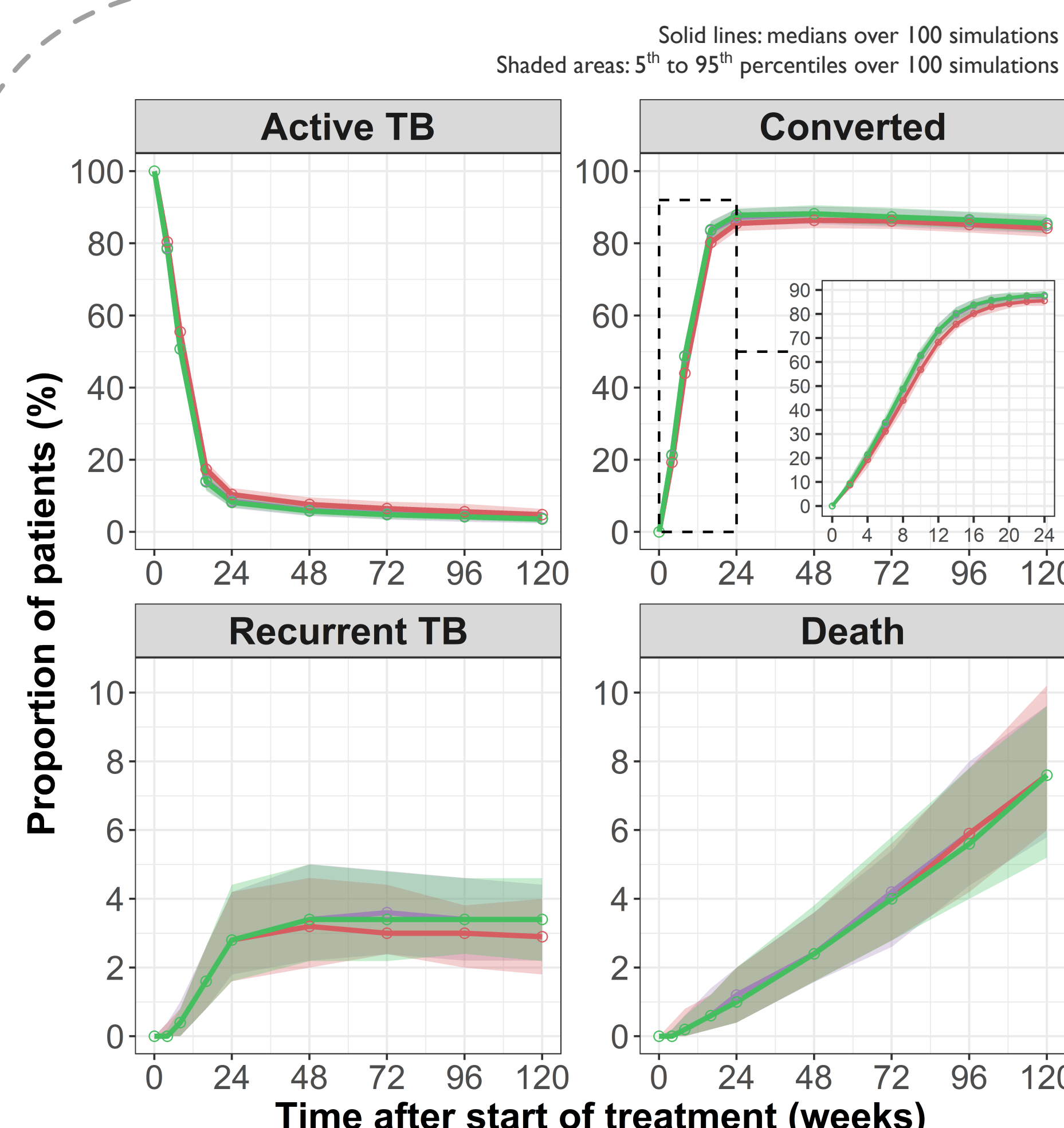


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Efficacy (sputum cultures)^[2]

- ~11% fewer negative samples under ZeNix dosing in the first month compared to registered and high-loading-dose dosing
- % of negative samples were similar under registered and high-loading-dose regimens



Long-term outcomes^[4]

- Up to 5.9% fewer patients in converted state under ZeNix dosing compared to registered/high-loading-dose regimens
- Similar % of patients having recurrence or died across 3 regimens over 120 weeks

Safety (QT prolongation)^[3]

- Predicted QTc intervals (376-442 ms from 5th to 95th percentiles) were similar for all 3 regimens, which were safe for use (< 500 ms)

Conclusion

- High-loading-dose once-daily dosing yielded earlier treatment response compared to ZeNix dosing. Safety profiles were similar across all the evaluated regimens
- The interactive R Shiny platform can be used for future exploration on different scenarios, e.g., dose interruption and re-initiation

[1] Svensson EM et al., CPT Pharmacomet Syst Pharmacol (2016).
[2] Svensson and Karlsson, J Antimicrob Chemother (2017).
[3] Tanneau et al., CPT Pharmacomet Syst Pharmacol (2021).
[4] Lin et al., J Antimicrob Chemother (2024).
[5] Smania and Jonsson, CPT Pharmacomet Syst Pharmacol (2021).
[6] Critical Path Institute. <https://c-path.org/tools-platforms/tb-pacts/>.

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