Stochastic Assessment of Adaptive Volunteer Infection Study (aVIS) Designs in Malaria - A Case Study with Artefenomel

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ABSTRACT

Background: Optimal dose selection for Phase 2 malaria clinical trials requires a well described quantitative dose-response (DR) relationship. We propose the probability of recrudescence (pR) versus dose as a functional structure for dose optimization. Fisher Information Matrix based optimization was used to select doses for subsequent cohorts in a reduced aVIS study design. Artefenomel published results[1] were used for a case study stochastic assessment of aVIS trial designs and the impact of a 2nd optimized cohort on pR vs dose definition.

Methods: Artefenomel aVIS trials were simulated over 3 dose ranges: literature reported doses (100, 250, 500 mg), doses at the ow end of the DR curve (50, 100, 200 mg), and high doses (1000, 1500, 2000 mg). 100 trials of 2-4 (n=8 subjects) and 3-3-6 (n=12) designs[2] were evaluated for cohort 2 using a Hill function for pR vs dose. Optimal cohort 2 doses were selected for each cohort 1 dose range. Maximum slope of parasite descent was evaluated as a predictor of pR. Impact of definition of cure (parasite level = 0.0002, 0.0003, 0.003, 0.01 parasites/mL at 336 h post drug) in model simulations was evaluated.

Results: Literature (2% bias) and low dose (14 and 10% bias); range results were well estimated ED50; bias was larger for high dose group (79 and 89%). A 2nd cohort markedly improved pR predictions when original dose range did not contain EC50 (bias = 0.4 for both low dose designs and 22 and 31% for high dose designs). Definition of cure had small impact on ED50 (ED50 = 491, 490, 494, 490 mg, for the cure definitions, respectively).

Conclusions: Effective methods for dose selection of 1st cohort aVIS studies are needed. Inclusion of a 2nd cohort with optimized dose selection has greatest benefit when the cohort 1 doses do not include a dose near the true ED50. Slope of parasite decline is correlated with pR, but lacks separation around dose = ED50.

INTRODUCTION

Traditional Malaria Volunteer infection studies use three consecutive single dose level cohorts (n=8). If selected doses do not capture information necessary to evaluate the Dose-Response relationship there is little ability to correct in the current methodology. In prior work we developed a platform to evaluate the performance of a single cohort adaptive design compared to the reference which gave good estimates of fixed parameter effects and standard errors. Building upon this platform we developed a methodology for defining the Dose-response relationship and additional cohorts for adaptive Volunteer Infection Studies.

METHODS

Simulated data was from an artefenomel PK/PD model (**Figure 1**).[1] Ten trials of a traditional design (8 low, 8 middle, and 8 high dose per trial) were simulated with *mrgsolve[3]* v0.9.0 for 3 different dose ranges: 1) 100, 250 and 500 mg (Literature), 2) 50, 100, 200 mg, 3) 1000, 1500, 2000 mg. From the reference trial, ten cohorts of two designs of adaptive trials were randomly selected (100 total per design):

1) Design 1 : 2-2-4,
2) Design 2 : 3-3-6.

Subsets of reference trials were estimated with NONMEM7.3/KIWI v3.0. Runs were evaluated for minimization and covariance. Viable runs, with both minimization and covariance steps, were carried on to next step. Percent recrudescence (pR) at dose ranges from 0-2000 mg and then fit using **Equation 1**.

$$pRec \sim 1 - \frac{Dose^a}{Dose^a + ED_{50}^a}$$

Using PFIM, optimal doses were selected for each cohort based on fit. These new cohorts with the doses selected were simulated and parameters were re-estimated with original cohorts. pR curves were re-simulated with new estimates. These results were then compared back to the True estimates and bias between first and combined cohorts were compared. Also simulations were run with different definitions of cure (0.003, 0.01, 0.0002 and 0.0003) to determine impact.

RESULTS

Results of estimation for each cohort were evaluated for minimization and covariance. Runs that had successful minimization and covariance were evaluated for Cohort 2, in total 88 runs for both Design 1 and Design 2 were evaluated for a second cohort in the first subset of doses, 87 and 92 runs for the second subset of doses, and 37 and 36 runs for the third subset of doses for Design 1 and Design 2 respectively. Each run that was carried on to next cohort was evaluated for doses selected and summarized. Below is the most common doses selected among regimens (**Table 1**).

Cohort 1 Doses	PFIM Doses Most Selected
100, 250, 500 mg	600, 800, 1000 mg
50, 100, 200 mg	600, 800, 1000 mg
1000, 1500, 200 mg	450, 600, 8000 mg

Table 1: Summary of doses selected by design

Comparison of pR cuves for both Cohort 1 and combined Cohorts were compared back to the true simulation values. Median and 90% Confidence interval were computed and plotted comparing first cohort, combined cohorts and true value (**Figure 1 and 2**). Estimated ED50 values for each cohort were also calculated and compared back to the true simulation value (489 mg) (**Table 2**). When Initial doses were near the ED50 then there was not significant change in the central values with some increase in precision (Literature doses). However when the true ED50 was not contained in the dose range selected, then there was significant improvement in the median ED50 (low and high dose values)

Cohort 1 Doses	Median	90% Confidence Interval	Design	Cohort
100, 250, 500 mg	501	480-561	1	1
	513	473-555	1	2
	501	471-561	2	1
	513	473-555	2	2
50, 100, 200 mg	559	470-673	1	1
	491	472-530	1	2
	538	470-563	2	1
	491	471-530	2	2
1000, 1500, 2000 mg	875	594-1249	1	1
	597	532-702	1	2
	932	618-1220	2	1
	643	534-702	2	2

Table 2: Median and 90% Confidence Intervals for 1st and 2nd cohorts of Designs 1 and 2

Figure 1: Percent Recrudescence curves for low dose simulations addition of a second cohort improves median EC50 estimate and improves precision
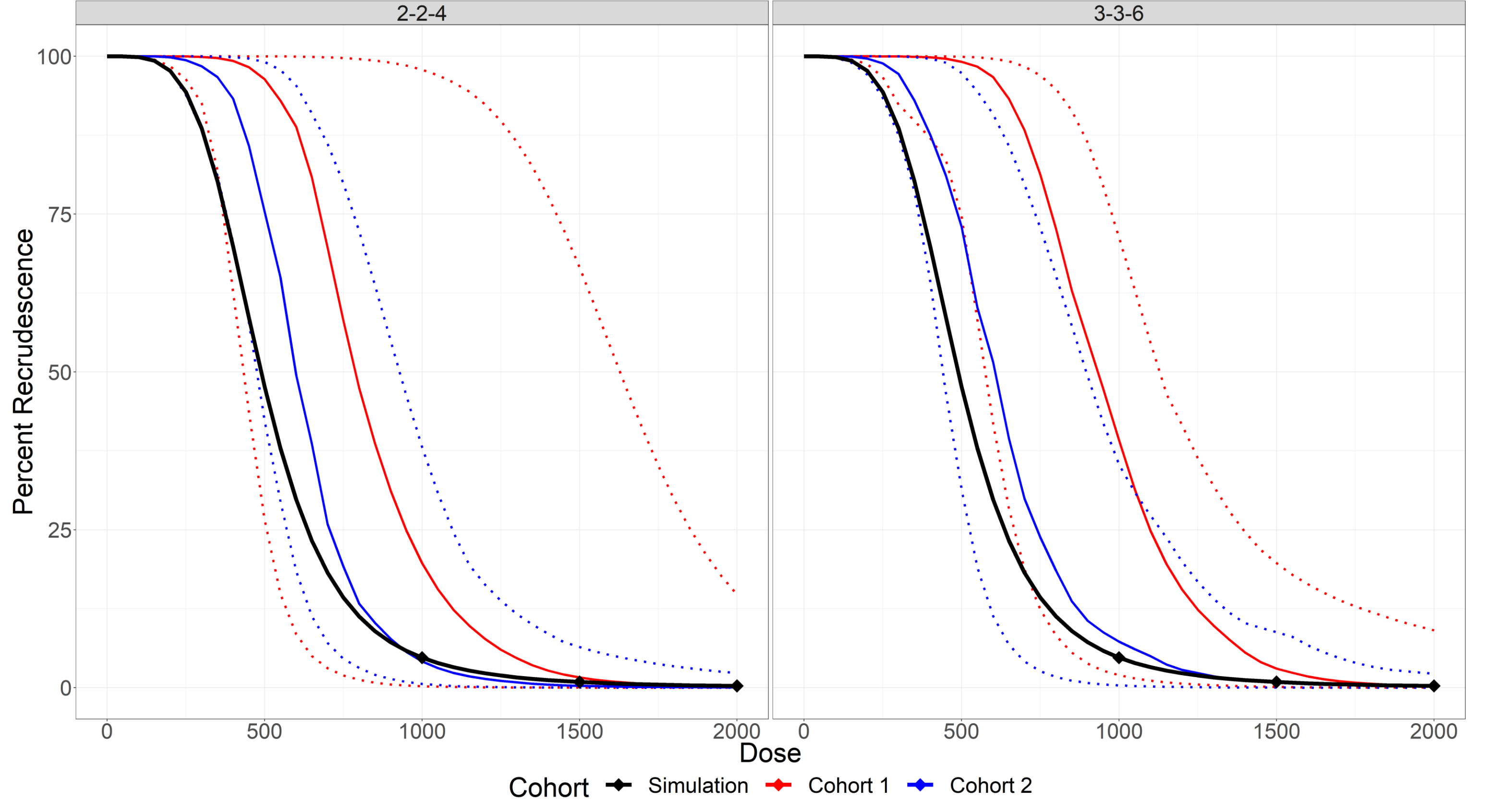
Figure 2: Percent Recrudescence curves for high dose simulations show addition of a second cohort improves median EC50 estimate

Definition of cure did not have a significant impact on EC50 (489 mg, 490 mg, 494 mg, and 490 mg).

SUMMARY

This example shows a case where the doses chosen represented a good estimate of the recrudescence curve profile. Addition of a second cohort added to the literature values did not significantly improve the fitting of the pR curve. A second cohort was beneficial when the first cohort did not contain a dose near the true ED50. This was much more apparent in both the low and high dose simulations. In combination with the simulation engine the ability to evaluate doses prior to starting additional doses can help reduce number of subjects needed, as well as save time and resources.

REFERENCES

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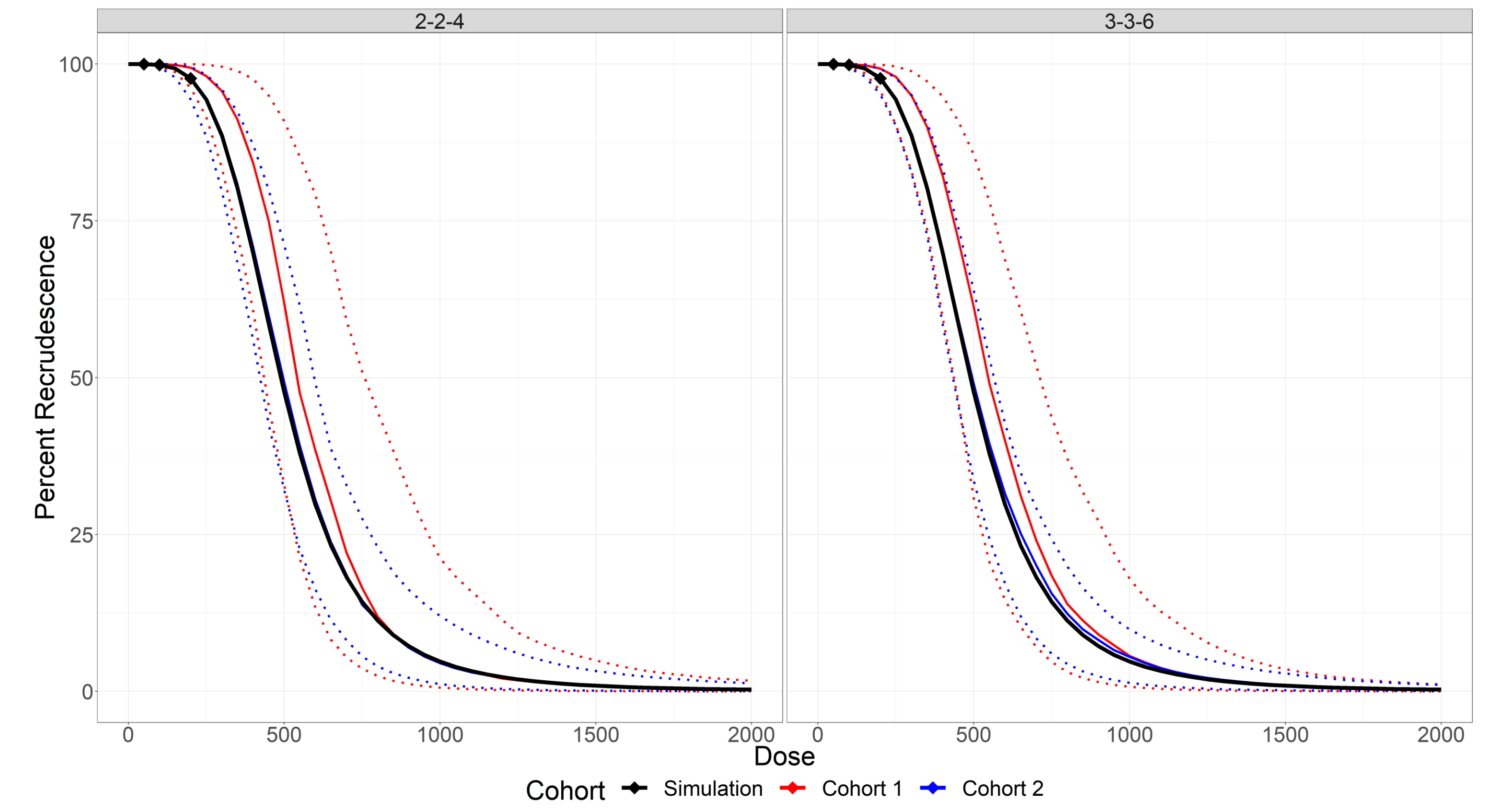3. Baron, K, et al. 2015. JPKPD 42:S84-S85