

Real-world data can estimate pre-exposure prophylactic drug effect in community-acquired respiratory infection trials

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INTRODUCTION

Pre-exposure prophylaxis (PrEP) drugs against influenza protect by ensuring efficacious drug concentrations at time of viral entry to inhibit virus replication. Current standard of care has a short half-life requiring daily dosing. Long-acting alternatives are attractive as they may allow sustained exposure after one administration. However, depending on the half-life and the potency of the drug under investigation, doses should be well selected to offer protective concentrations throughout a 6-month influenza season.

In community-acquired infection (CAI) trials, variation in time of seasonal disease peak (early or late) makes it not only difficult to interpret the actual protective effect of the drug in a phase 2 trial, but also to predict the effect in a subsequent multiple-season phase 3 study. Investigating protective effect of a compound during a season with early peak equates to testing the compound at high concentrations immediately post-administration, yielding no information on the effect at lower concentrations. Similarly, testing the compound in a season with a late peak does not inform about the drug effect at lower concentrations.

OBJECTIVES

- To predict CAI trial results through simulation:
- Predict the minimal required drug potency for a successful Ph3 trial using a given dose
 - Predict the selected dose in a Ph2 trial based on superiority to placebo
 - Predict the identified drug potency and recommended dose in a Ph2 trial

METHODS

Figure 1. Top: Concentration-time profile (median, 95% PI) for 5mg and 20mg doses of DrugX Bottom: Weekly hazard for influenza in the general population, scaled to 2% overall cumulative hazard per year, based on Real-World Data.

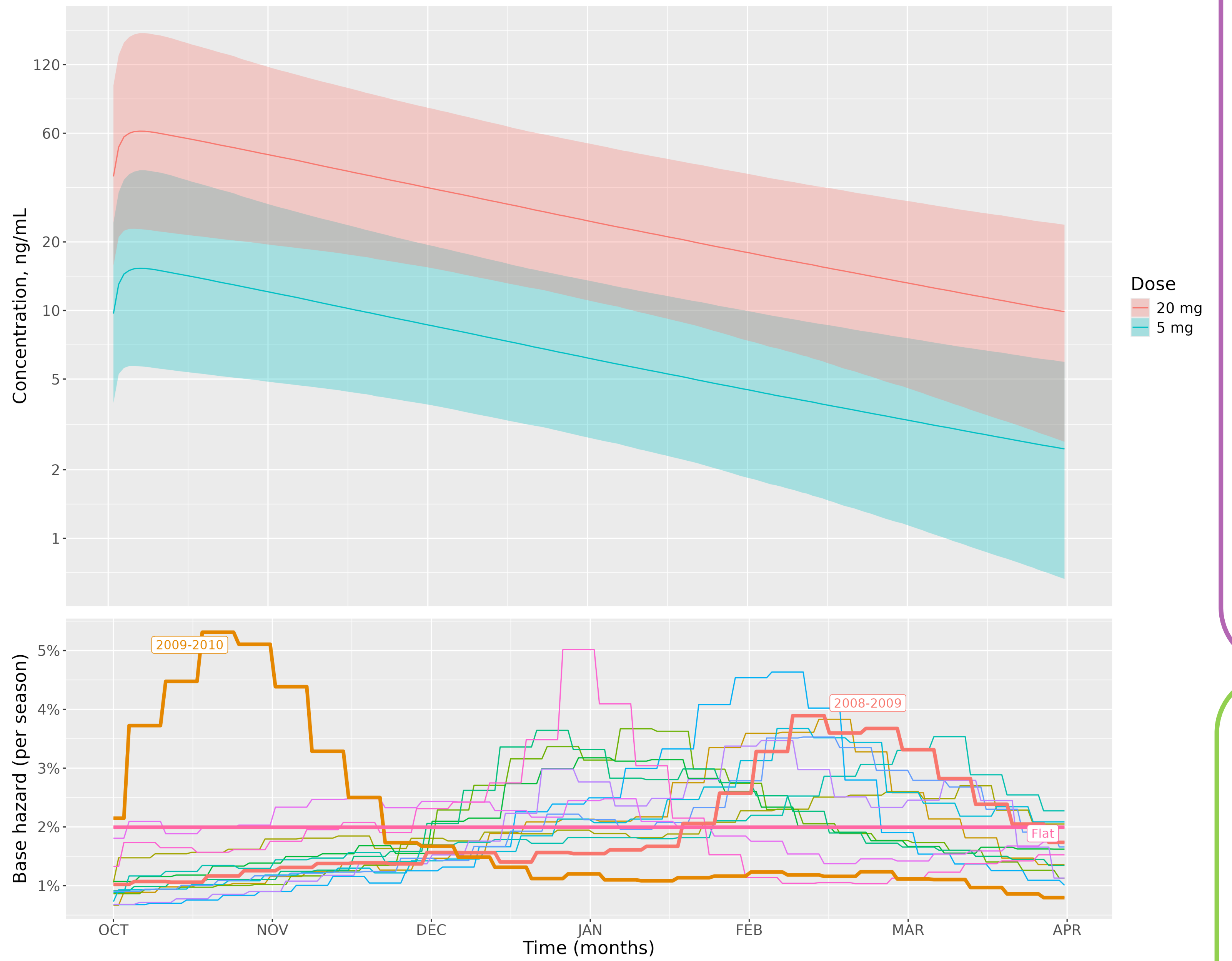


Figure 2. Schematic overview of simulation approach for a single trial

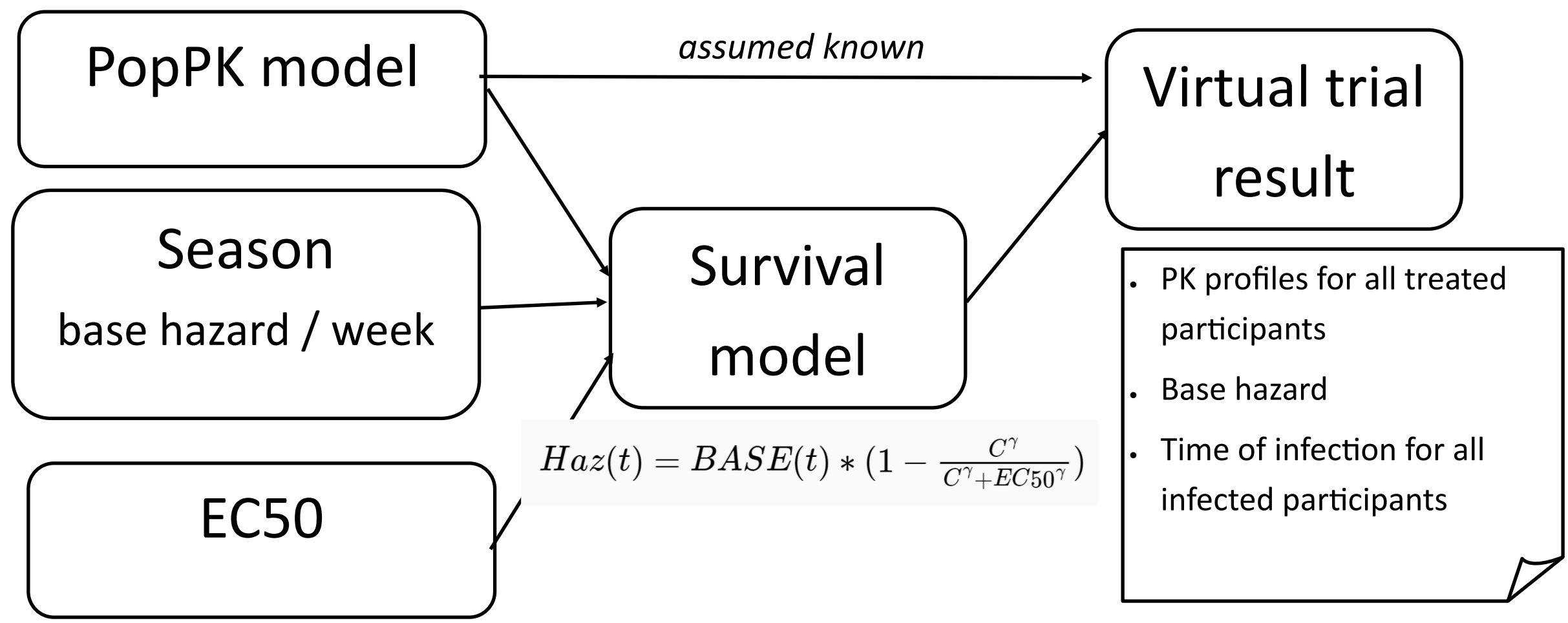
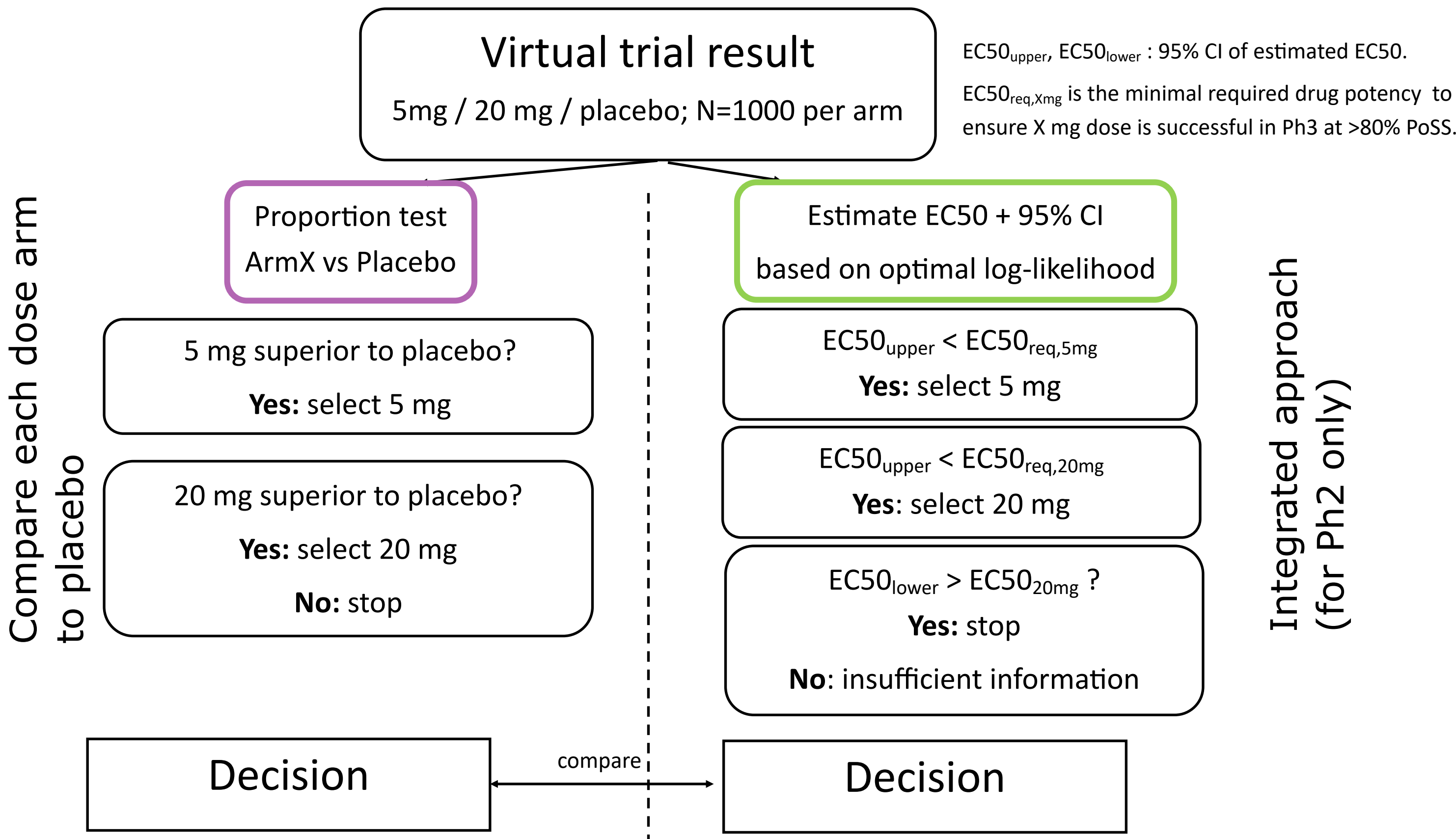
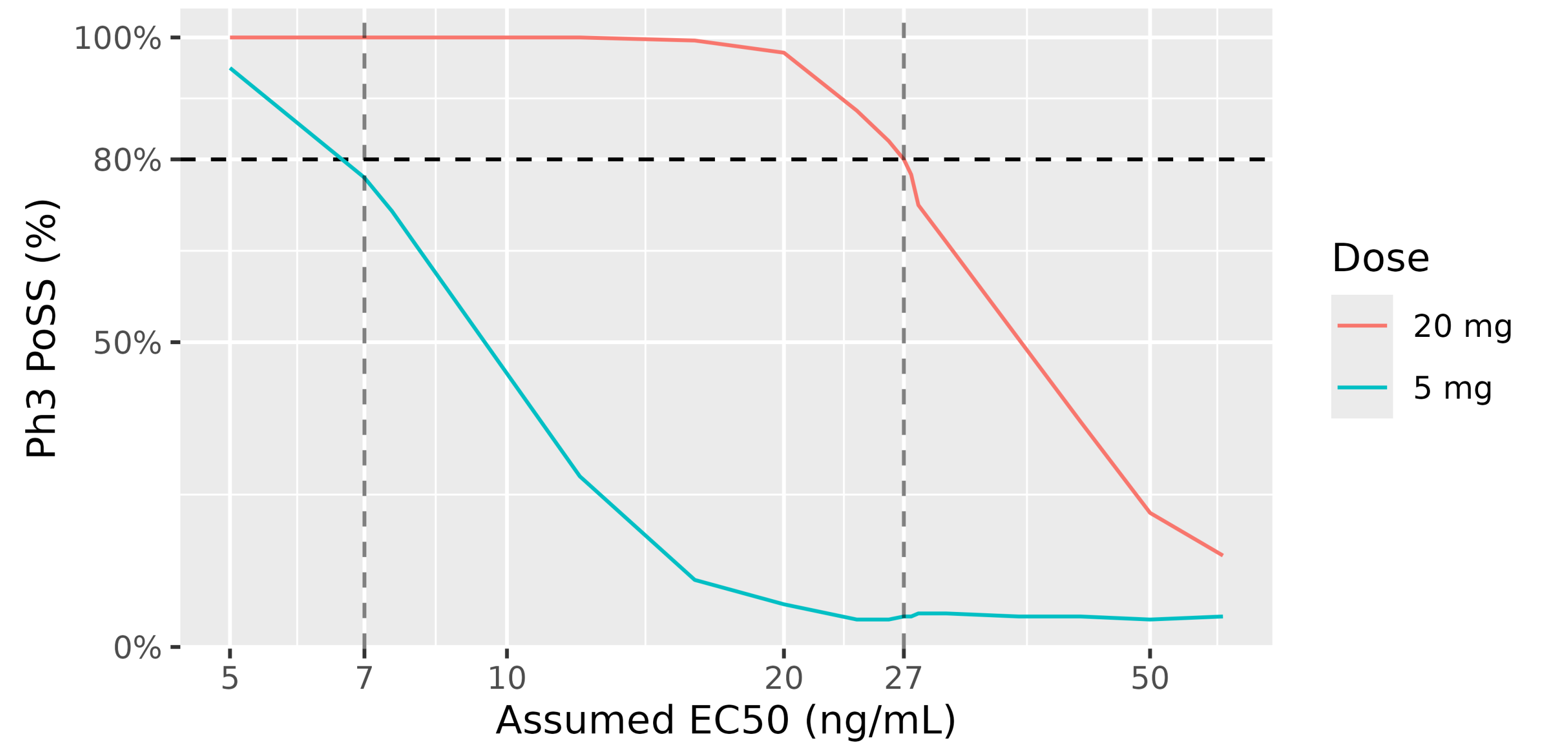


Figure 3. Clinical trial simulation approach.



RESULTS

Figure 4. Probability to show superiority to placebo in a N=6000 Phase 3 multi-year (flat season) study using proportion test, for drug potencies from 5 to 50 ng/mL. The EC50 should be lower than 27 ng/mL to have a PoSS of >80% for the 20 mg dose.



If a Ph2 trial identifies an EC50 significantly **below** 27 ng/mL, a 20 mg dose should work in Ph3 . If a Ph2 trial identifies an EC50 significantly **above** 27 ng/mL, a subsequent Ph3 trial becomes highly risky.

Figure 5. Probability of decision for assumed EC50 values from 1 to 120 ng/mL, and different influenza seasons, when comparing each arm to placebo separately.

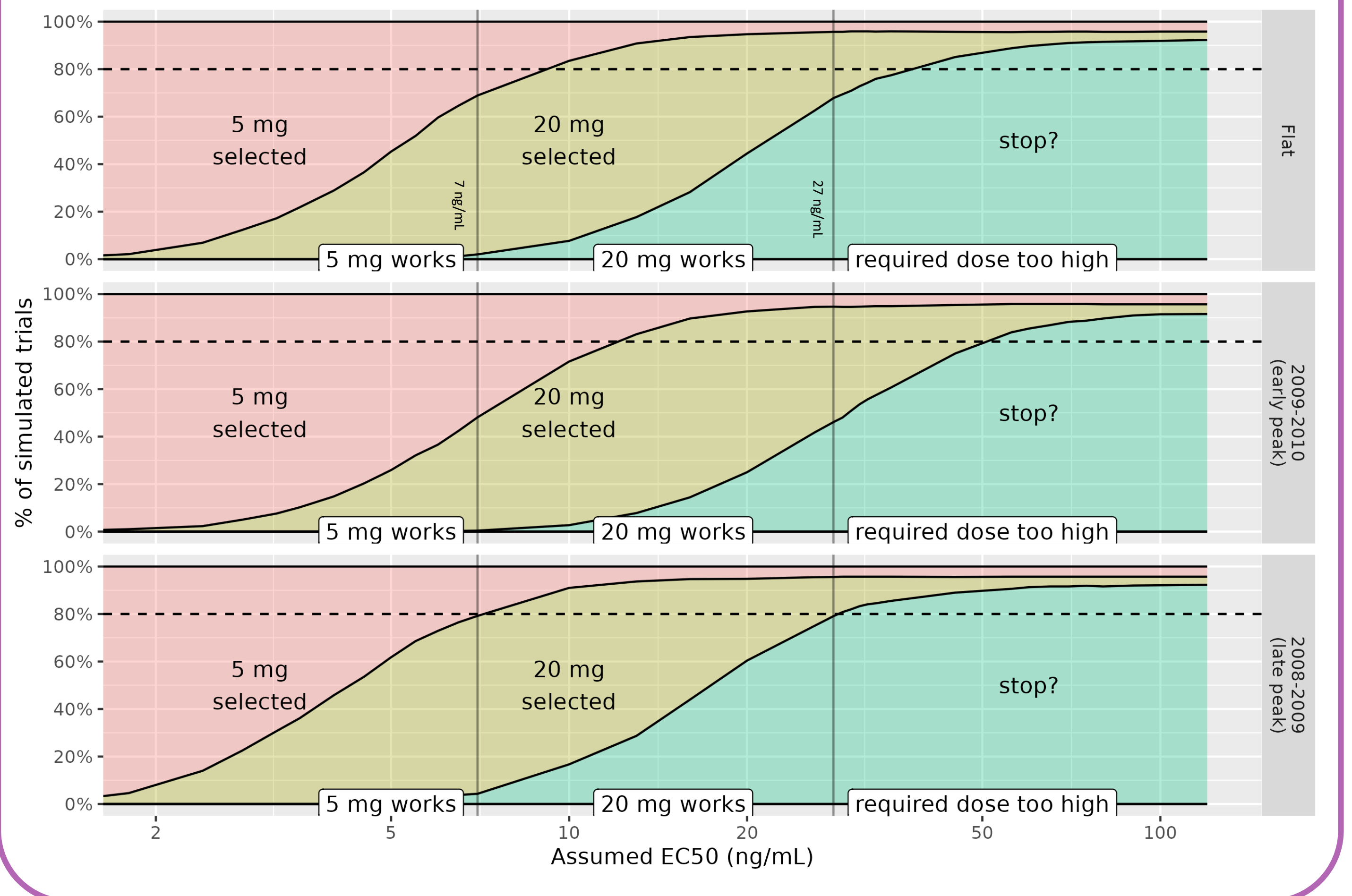
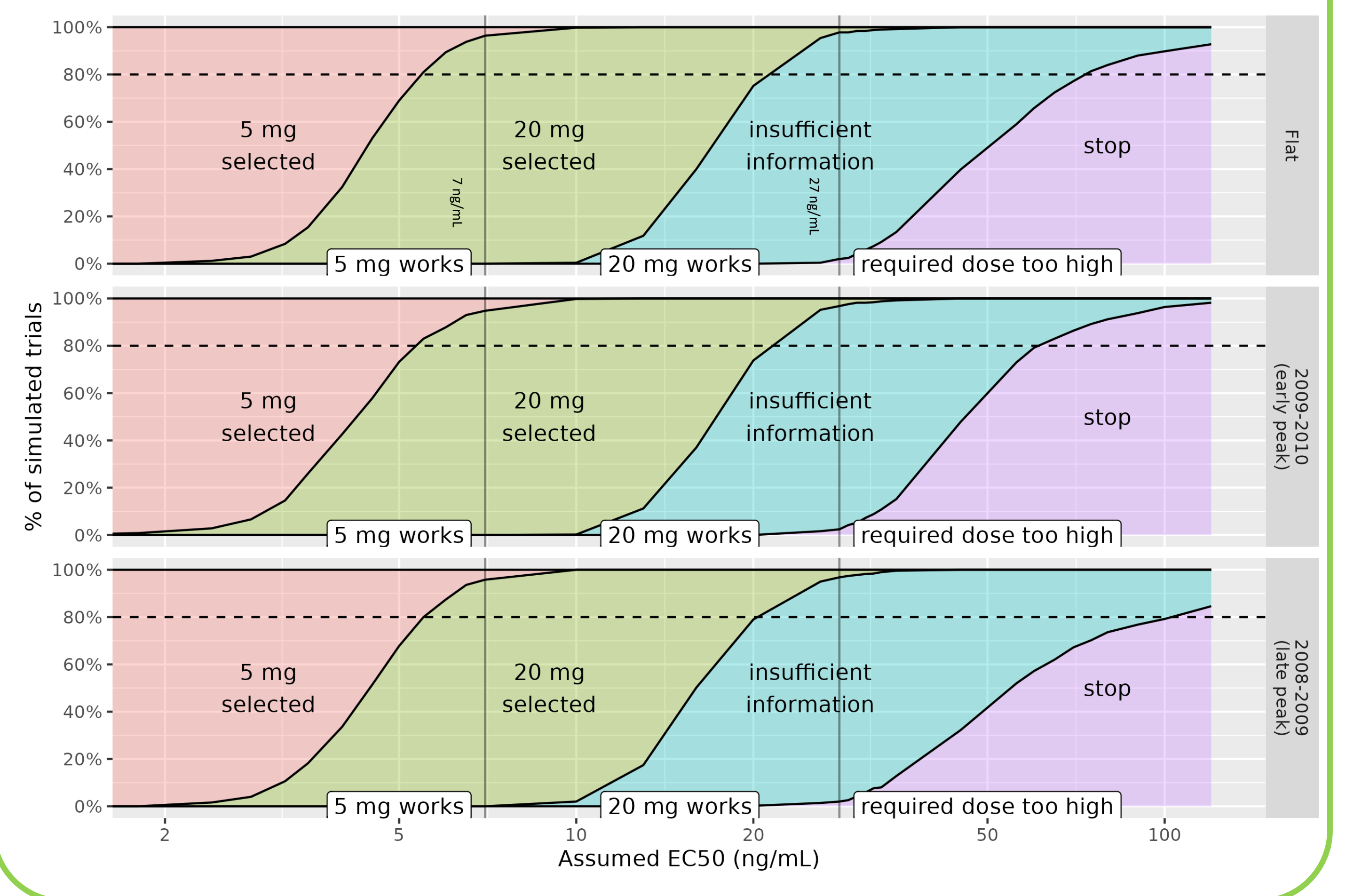


Figure 6. Probability of decision for assumed EC50 values from 1 to 120 ng/mL, and different influenza seasons, using an integrated approach estimating EC50.



CONCLUSIONS

- Comparing the incidence in a single dose arm to placebo leads to **high false positive rates** (continuing development of a drug with low potency) in case of early influenza peak, due to high early drug concentrations inflating the observed drug efficacy.
- **EC50 can be estimated** from a limited CAI trial by integrating RWD, individual PK data and time of infection, although precision is low. The estimated EC50 and associated 95% CI translates into a dose selection considering Phase 3 probability of study success.
- **The integrated approach is robust to influenza seasonality differences**, offers **lower false positive rates** as compared to evaluating each arm separately, and allows to stop drug development with confidence in case of low potency.
- This model can be extended to any PrEP for seasonal infectious diseases (such as RSV), where real-world data is available to model the infection risk over time.

REFERENCES

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2. Crowther, M. J., Abrams, K. R., & Lambert, P. C. (2013). Joint Modeling of Longitudinal and Survival Data. *The Stata Journal*, 13(1), 165-184. <https://doi.org/10.1177/1536867X1301300112>