

Predicting RSV efficacy for moderate and tropical climates considering seasonal differences in RSV force-of-infection: Application of an MBMA and clinical trial simulation framework to support MK-1654 decision-making

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Background

- Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis and hospitalization in infants
- MK-1654 is a RSV F glycoprotein neutralizing monoclonal antibody in phase 2/3 development to prevent RSV infection in infants
- RSV is a seasonal disease, with outbreaks typically occurring between November and March in the temperate US¹
- Serum neutralization (SN) titer is a measurement of RSV neutralization activity in the serum
- A model-based meta-analysis (MBMA) model was developed using published clinical data to establish the relationship between SN titers and different levels of RSV disease severity; it was subsequently used to predict the efficacy of RSV mAbs, like MK-1654²
- Tropical regions show distinct differences in the pattern of circulating RSV over the course of the year, relative to temperate regions, which can be reflected in differences in force-of-infection (FOI)
- Considering FOI in MBMA-based predictions can provide insight into potential differences in drug efficacy between climates, informing the clinical development of prophylactic agents, including MK-1654
- The objective of this work was to:
 - Outline how an FOI function can be applied to represent epidemiological data to account for differences in RSV seasonality
 - Develop a framework to apply this methodology through efficacy simulation to evaluate whether variations in regional seasonality impact the efficacy of different hypothetical compounds
 - Perform a sensitivity analysis to investigate – through simulation of various SN profiles – if timing of SN titer peak relative to maximum FOI can impact predicted efficacies in tropical regions

Methods

The FOI function

- The risk of being infected with RSV over a season in a study, R, represents the percentage incidence rate per study, and is calculated via integration of the probability p(t) of contracting RSV at a particular day, t:

$$R = 100 \cdot \int_{t=t_{first}}^{t=t_{last}} p(t) \cdot FOI(t) \cdot N_{norm}(t) \cdot dt$$

- The overall predicted incidence rate per season is the sum of daily probabilities of being infected
- The daily probability depends on the FOI on this particular day
- Days with higher FOI add more to overall incidence rates calculated
- On days with low FOI, even placebo arms have low risk
- FOI was described by fitting a 3-parameter Gaussian function plus baseline to published¹ FOI data
 - Epidemiological RSV data from temperate regions in the United States between 2007 and 2012 were used to describe temperate RSV seasonality, while data from Puerto Rico (2010-2012) was used to describe tropical RSV seasonality³

$$FOI(t) = baseline + amp * \frac{1}{\sigma \cdot \sqrt{2\pi}} \cdot e^{-\frac{(t-\mu)^2}{2\sigma^2}}$$

FOI of 1 Nov - 1 Apr in temperate region was arbitrarily normalized to a mean of 1 per day; tropical FOI was scaled relative to this normalized FOI.

³The approach assumes that reported “percent positive” cases is a direct reflection of overall circulating RSV in the population. Changes in testing over time or region may violate this assumption. However, extreme FOI scenarios can be used to assess potential impact on efficacy, even if the scenarios are unlikely to occur.

Definitions
R, the response (incidence rate expressed as %).
tlast, the last day of study; tfirst, the first day of study.
FOI(t), weighting function accounting for force of RSV infection change over time, normalized to 1/day for RSV season in northern hemisphere starting 1 November and lasting 150 days.
Nnorm(t), fraction of subjects present at day t divided by the maximum number of subjects present at any time during the study.
σ, standard deviation of the Gaussian curve.
μ, time to FOI peak since 10 August for temperate and since 1 February for tropical climate.
amp, magnitude between the off-season and peak incidence rates.
baseline, relative off-season incidence rates.

Clinical trial simulations using hypothetical compounds in temperate and tropical regions

- Clinical trial simulations were conducted using the MBMA model and a virtual infant population to predict seasonal incidence rate of RSV lower respiratory tract infection (LRTI) and efficacies in both **temperate and tropical regions**
 - Infants born prior to the start of RSV season^b were enrolled at the start of the season
 - Infants born during the season were allowed to be enrolled up to the peak of the season
 - Each infant was observed for RSV infection over a period of 5 months after enrollment
- Infants were treated once at the time of enrollment either with placebo or with **various hypothetical compounds**
 - Compound potencies were selected to cover a broad SN titer range in the simulations and half-lives were approximately 50 days
 - Infant SN titers were simulated as the sum of predicted endogenous maternal titer time course and predicted external titer time profiles resulting from treatment

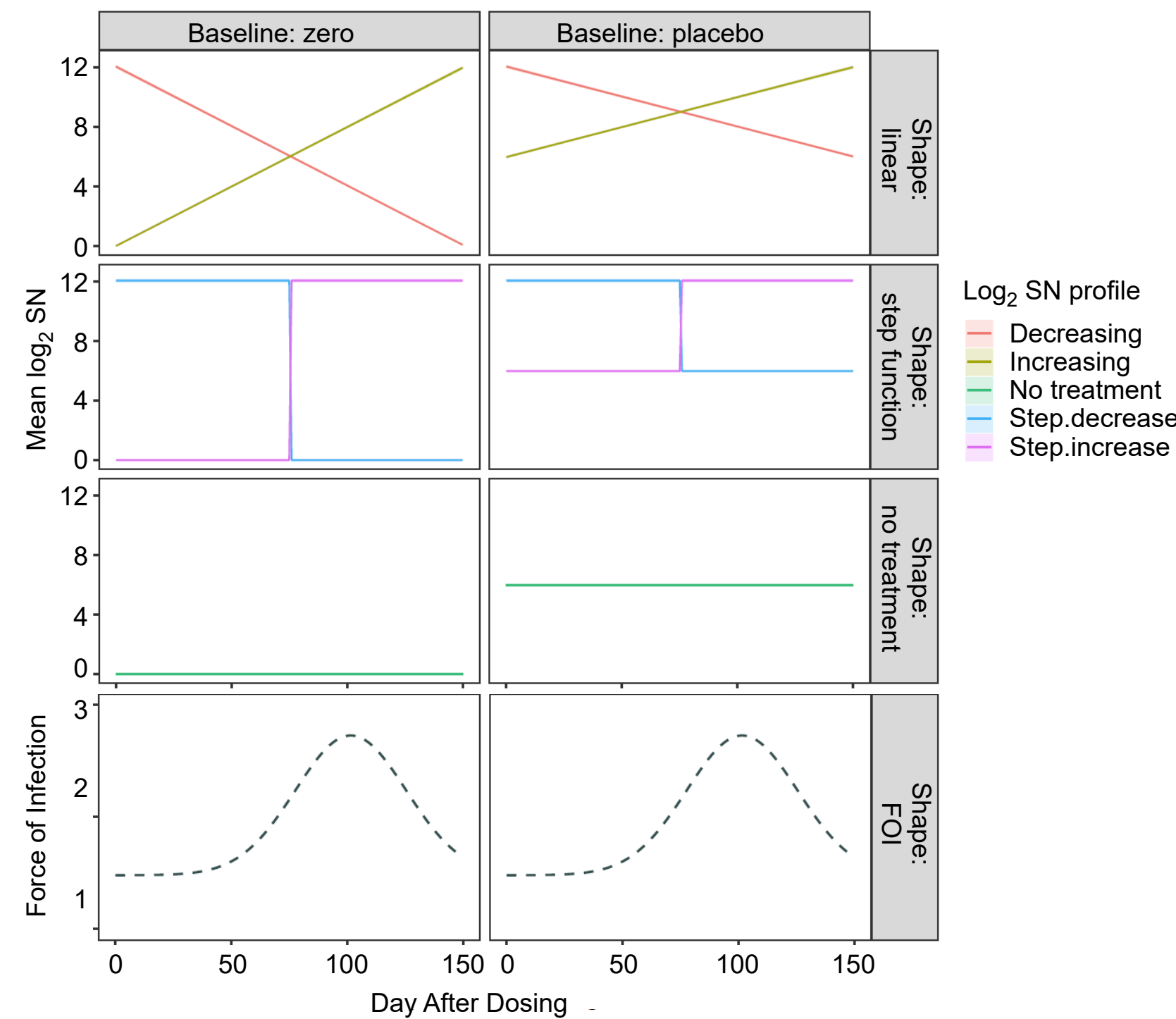
^bStart of the season is assumed approximately 3-4 months prior to RSV peak.

Sensitivity analysis for theoretical SN scenarios

- An analysis was conducted to evaluate how sensitive incidence rate and efficacy predictions are to various, non-physiologic SN titer profiles (**Figure 1**)
- The following assumptions were made:
 - The maximum SN titer is an arbitrary value high above the model-estimated IT50
 - The minimum SN titer corresponds to either 2⁶ (approximate baseline value of endogenous titer) or zero
 - The SN titer profile is the duration of a typical RSV season (150 days)
- Efficacies were simulated for two FOI scenarios
 - Tropical FOI
 - Flat FOI (constant throughout season, with similar average [AUC] as tropical)

Figure 1. Theoretical SN titer profiles used for sensitivity analysis, compared to FOI profile

SN titer profiles are presented in upper three rows, while row 4 (FOI) is included to enable assessment of interplay between SN titers and FOI at each time point.



Results

Figure 2. FOI curves for temperate and tropical climates

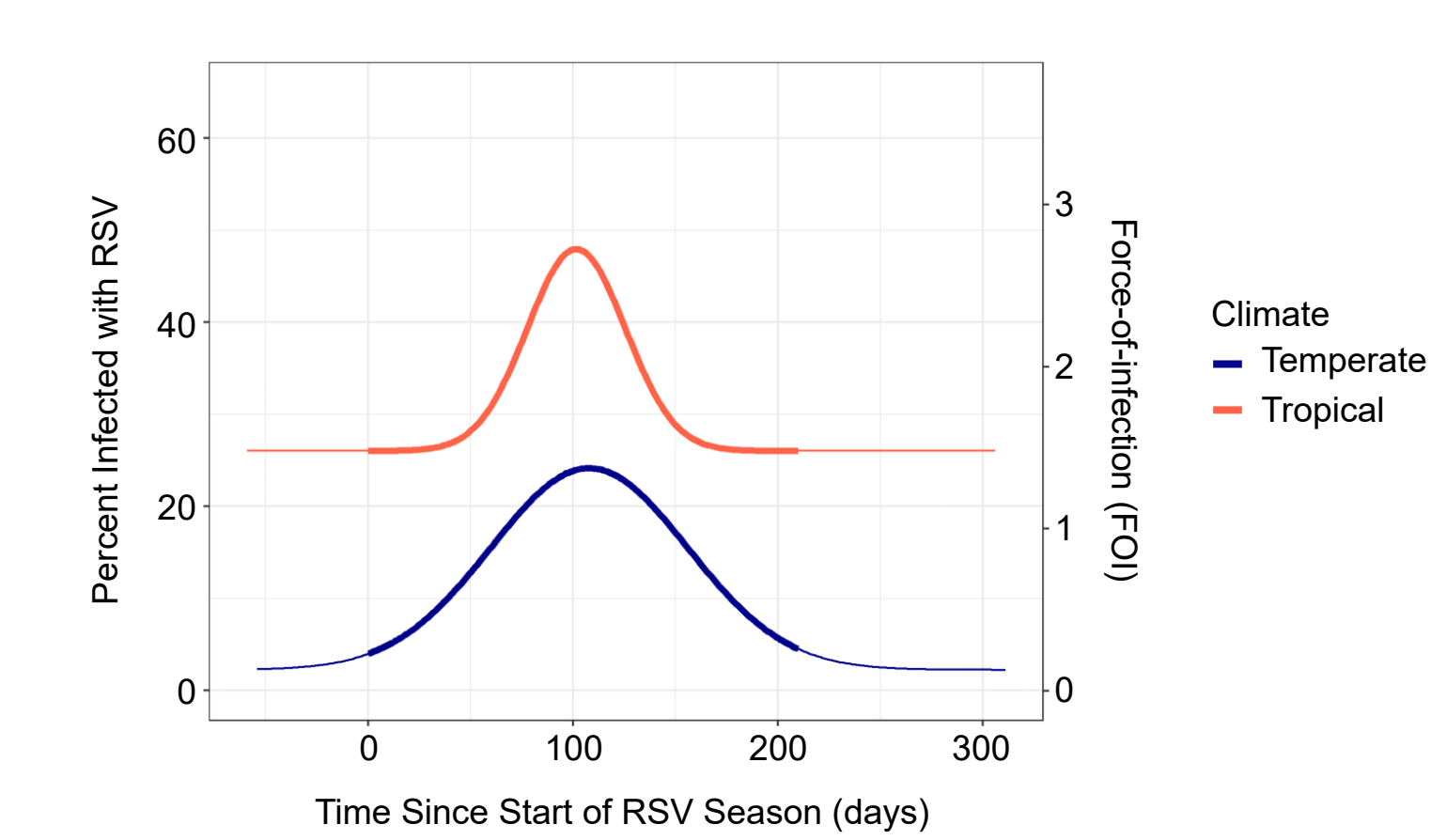
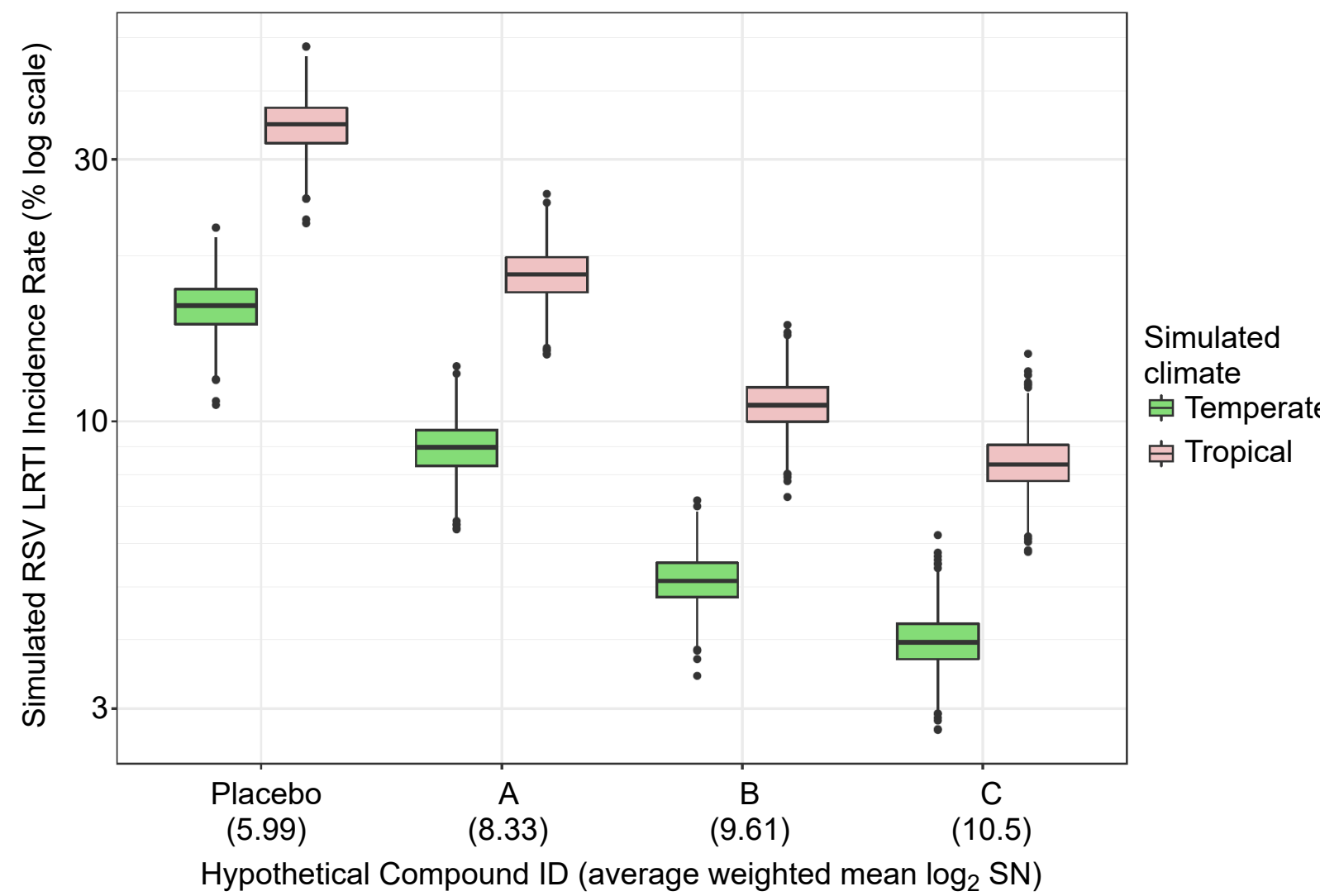


Table 1. Estimated FOI parameter values for different climates

Parameter	Temperate Region	Tropical Region
σ (days)	48	23.9
μ (days)	162	160.6
amp	2633	1314
baseline	2.25	26.1

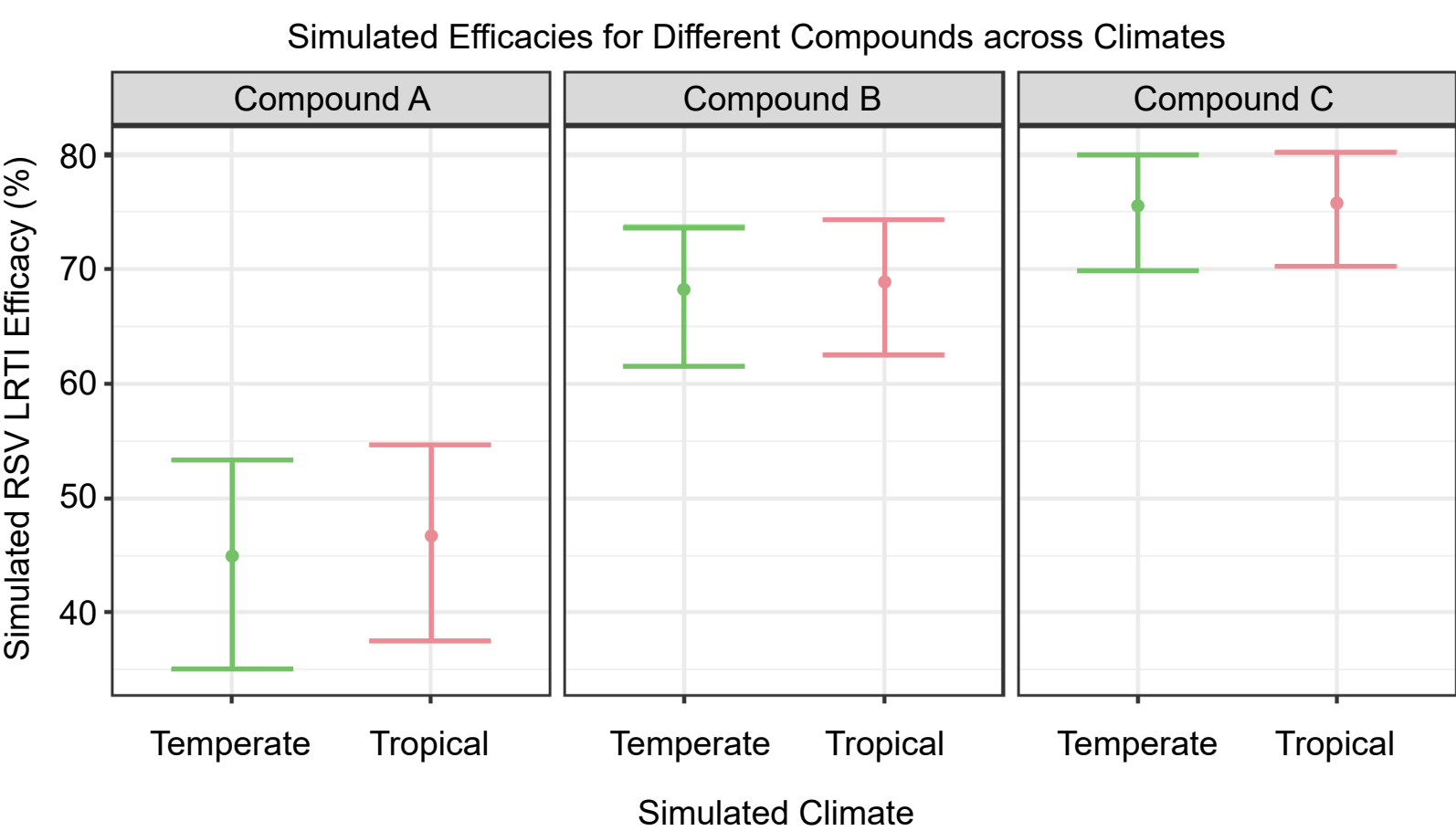
- Epidemiological data were captured using the estimated parameters (**Table 1**, **Figure 2**)
- Data from Puerto Rico between 2010 and 2012 were leveraged to represent seasonality in a tropical region with high FOI
 - In this case, FOI in a tropical climate has a higher peak and a substantially higher baseline with constant RSV exposure over the course of the year
 - Because these data are derived from a single country (Puerto Rico), the application of this FOI to other countries with a tropical climate may be limited

Figure 3. Comparison of predicted RSV LRTI incidence rates for a virtual clinical trial in temperate and tropical climates



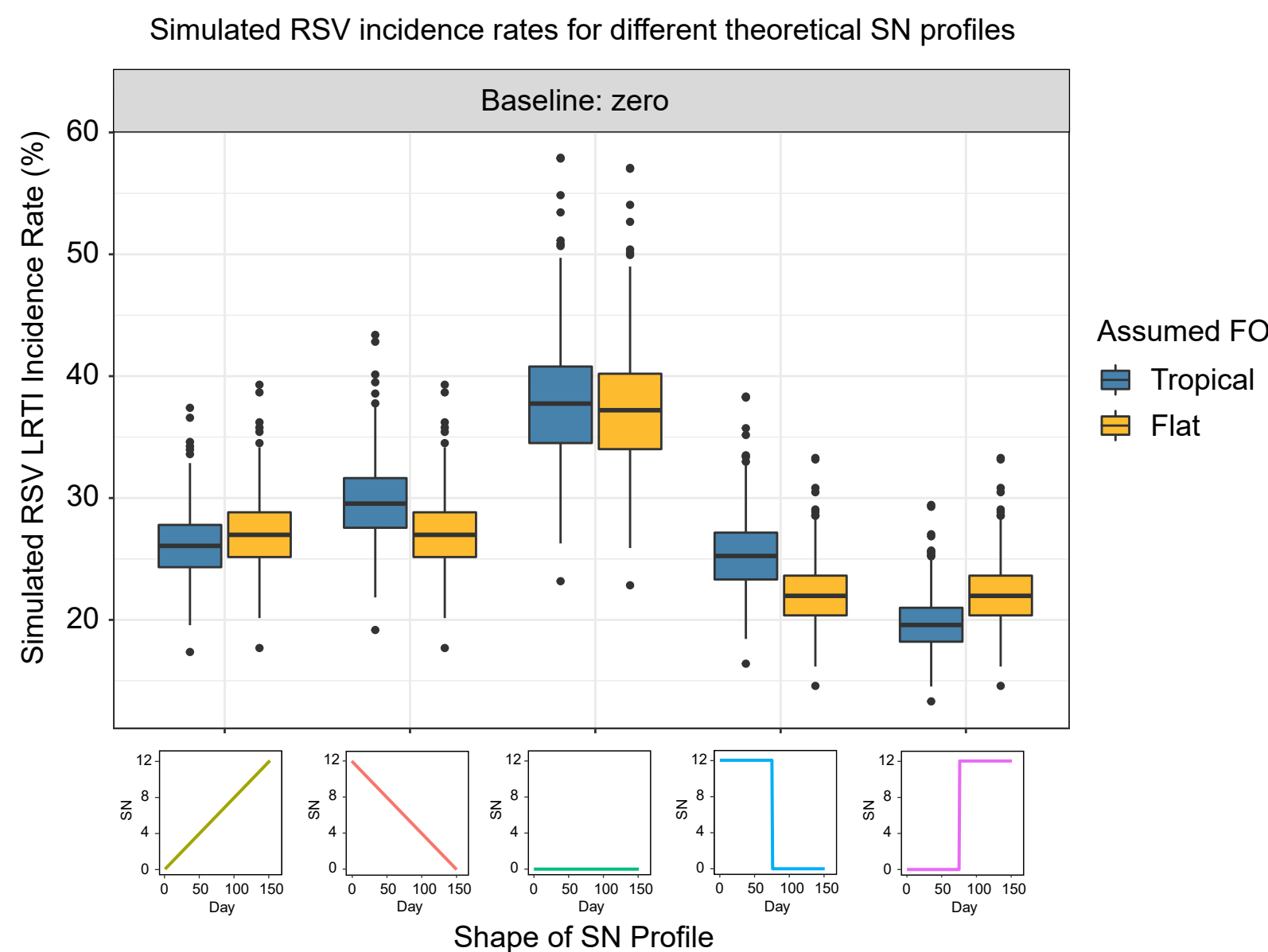
- Incidence rates of RSV LRTI were predicted to be approximately 2-fold higher in a region with a tropical climate vs. a region with a temperate climate for the simulated clinical trial, regardless of SN titer

Figure 4. Comparison of predicted efficacy for hypothetical compounds in a virtual trial in temperate and tropical climates



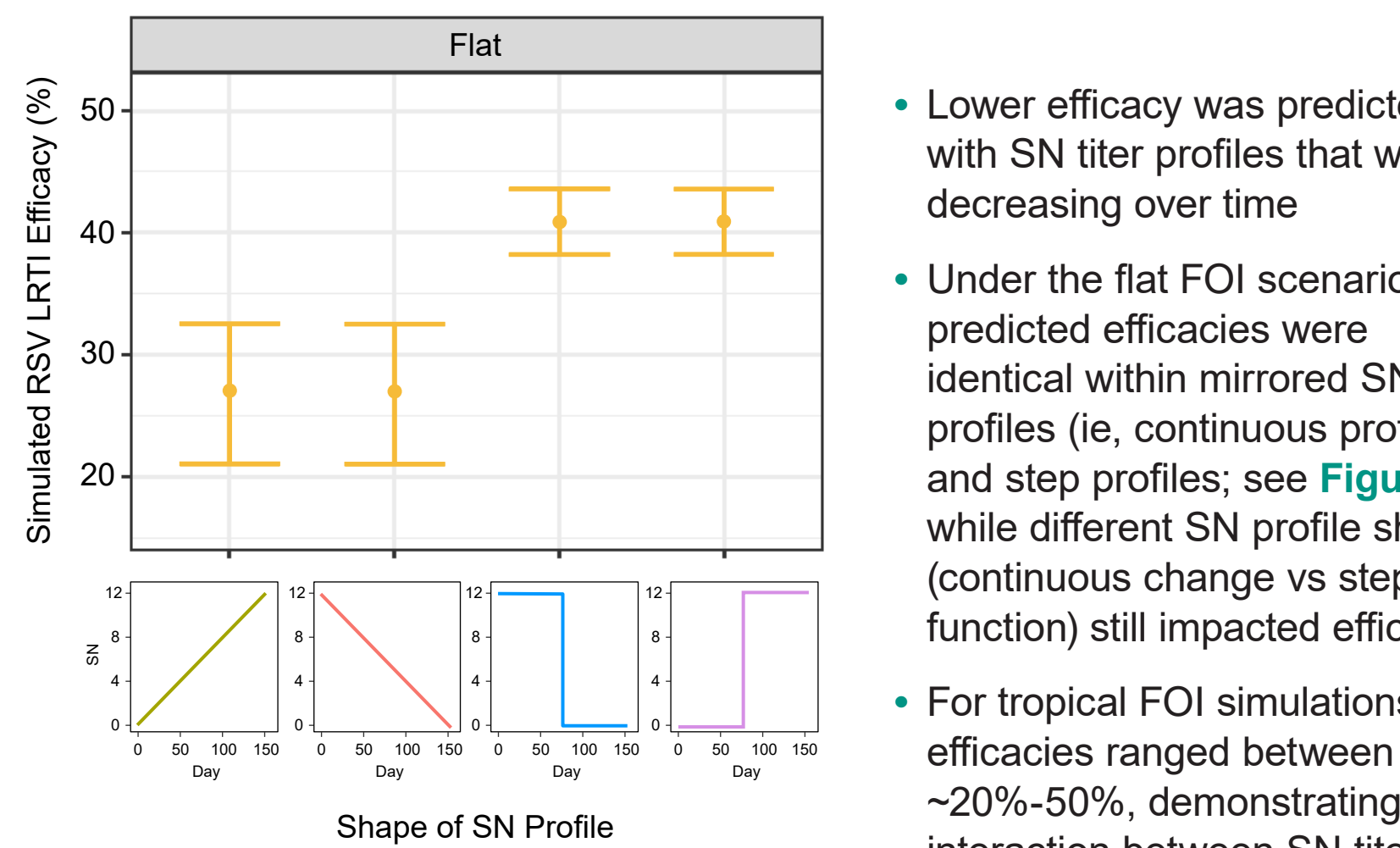
- Despite differences in predicted incidence rates between climates, predicted efficacy for the hypothetical compounds remains similar

Figure 5. Predicted incidence rates of RSV LRTI for theoretical SN titer profiles in regions with tropical and flat seasonality



- The SN titer profiles that reflect a step function lead to overall lower incidence rate compared to the continuous profile scenarios
 - This observation holds for both tropical and flat FOI
- The timing of SN peak relative to FOI peak impacts simulated incidence rate
 - Decreasing SN profiles results in higher incidence rate, as peak of FOI occurs closer to end of simulated period
- The timing of SN peak was irrelevant when assuming flat FOI profile, as evidenced by identical incidence rates within each pairwise scenario of SN titer in-/decrease
- Results were qualitatively similar when assuming a placebo baseline (not shown)

Figure 6. Predicted efficacy for theoretical SN titer profiles in regions with tropical and flat seasonality



- Lower efficacy was predicted with SN titer profiles that were decreasing over time
- Under the flat FOI scenario, predicted efficacies were identical within mirrored SN profiles (ie, continuous profiles and step profiles; see **Figure 1**), while different SN profile shapes (continuous change vs step function) still impacted efficacy
- For tropical FOI simulations, efficacies ranged between ~20%-50%, demonstrating the interaction between SN titer profiles and FOI and its potential impact on drug efficacy
 - SN titer time profiles had identical AUCs
- Results were qualitatively the same when assuming a placebo baseline (not shown)

Conclusions

- Trends in RSV seasonality across different climates can successfully be incorporated into clinical trial simulation to account for regional variations in RSV FOI
- Simulations indicated that while FOI is a substantial driver of overall RSV incidence rates, efficacy results of late-stage clinical trials for temperate and tropical regions may be comparable
- A sensitivity analysis based on various SN profiles shows that timing of SN titer peak relative to maximum FOI can impact predicted efficacies
- These results were incorporated into MK-1654 decision-making and will be further expanded by future efficacy simulations for MK-1654

1. McGuiness CB, et al. *Pediatr Infect Dis J*. 2014;33(6):589-594.
2. Maas BM, et al. Closing the gap: Using MBMA to make informed decisions on anti-RSV drug development. Presented at: American Conference on Pharmacometrics (ACoP11); November 2020.