

Predicting RSV efficacy for MK-1654 during post-COVID-19 pandemic RSV seasons with protracted transmission pattern using MBMA and clinical trial simulation approaches that account for RSV force-of-infection

Nele Plock¹; Jos Lommerse¹; Brian M. Maas²; Jingxian Chen²; Francesco Bellanti¹; Li Qin¹; Han Witjes¹; Philippe Pierrillas¹; Radha A. Railkar²; Antonios O. Aliprantis²; Kalpit Vora²; Wei Gao²; Luzelena Caro²; S. Y. Amy Cheung¹; Jeffrey R. Sachs²

¹Certara, Princeton, NJ, USA; ²Merck & Co., Inc., Rahway, NJ, USA

- Background
- Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis and hospitalization in infants
 - For most infants, RSV prophylaxis (vaccine or monoclonal antibody) is currently not available
 - MK-1654 is an 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 to 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
 - Precautions taken in response to the COVID-19 pandemic, such as masking and social distancing, have reduced seasonal transmission of respiratory viruses, including RSV
 - Removal of these precautionary measures was predicted to result in more severe and atypical outbreaks of RSV due to reduced population immunity accrued during periods with reduced transmission³
 - Delayed and more severe RSV patterns have already been observed⁴
 - These atypical transmission patterns can be reflected via force-of-infection (FOI) curves, which can be incorporated into the available MBMA framework to provide insight into potential impact on drug efficacy, informing the clinical development of prophylactic agents, including MK-1654
 - The objective of this work was to evaluate whether a protracted, delayed, and more intense RSV season could impact the predicted efficacy of MK-1654 as measured in the ongoing trial

- Methods
- RSV infection rate with integrated FOI function
- The risk of being infected with RSV over a season in a study, R, represents the percent incidence per study per season (incidence rate), 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 that particular day
 - Days with higher FOI add more to overall incidence rates calculated
 - On days with low FOI, even placebo arms have low risk of infection
 - FOI was described by fitting a 3-parameter Gaussian function plus baseline to published¹ FOI data from temperate regions in the US from 2007-2012^a

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

- FOI 1 Nov - 1 Apr in typical seasons was arbitrarily normalized to a mean of 1 per day.
- ^aThe 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.
- To simulate a COVID-19–impacted RSV season, we assumed a doubling in FOI AUC, a delay to peak season of 30 days, and an increase in standard deviation by 10 days

Definitions

R, the response (incidence rate expressed as %);
t_{last}, the last day of study;
t_{first}, the first day of study;
FOI(t), weighting function to account for the force of RSV infection over time;
N_{norm}(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;
amp, magnitude between the off-season and peak incidence rates;
baseline, relative off-season incidence rates.

- Clinical trial simulations for MK-1654
- Clinical trial simulations were conducted using the developed MBMA model and a virtual infant population to predict seasonal incidence rate (IR) of RSV lower respiratory tract infection (LRTI) and efficacies for MK-1654 in a regular and a COVID-19–impacted season
 - 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 January (original peak of the season)
 - Two simulation scenarios: Each infant was observed for RSV infection over a period of 5 or 7 months after enrollment to represent a typical clinical trial observation period and a prolonged interval due to COVID-19 impact, respectively
 - Infants were administered a single dose of MK-1654 at varying dose levels or matching placebo
 - 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.

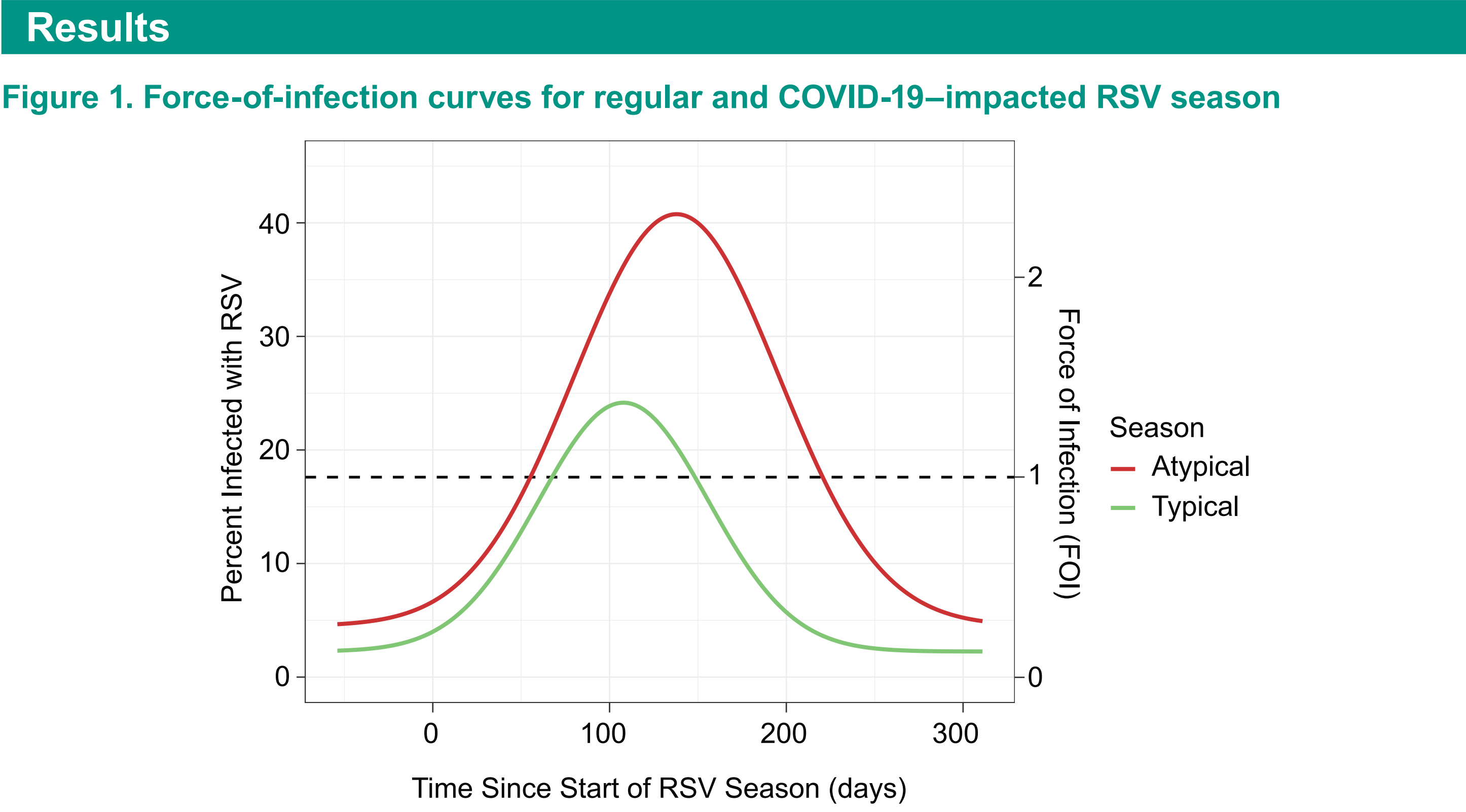
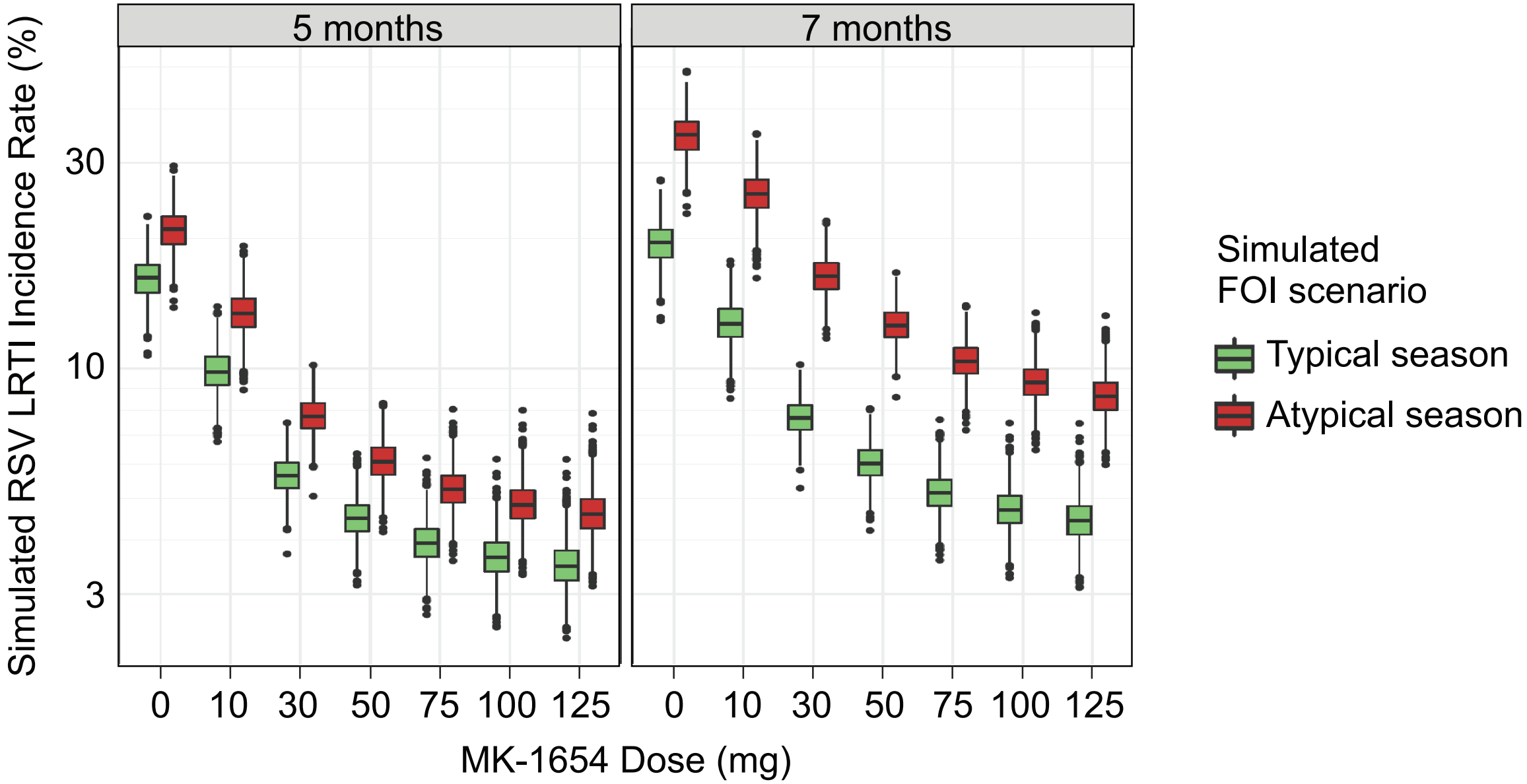


Table 1. FOI parameter values for regular and atypical season

Parameter	Regular season	COVID-19–impacted
σ (days)	48	58
μ (days)	162	192
amp	2,633	2,633
baseline	2.25	2.25
Scale	0.0568	0.114

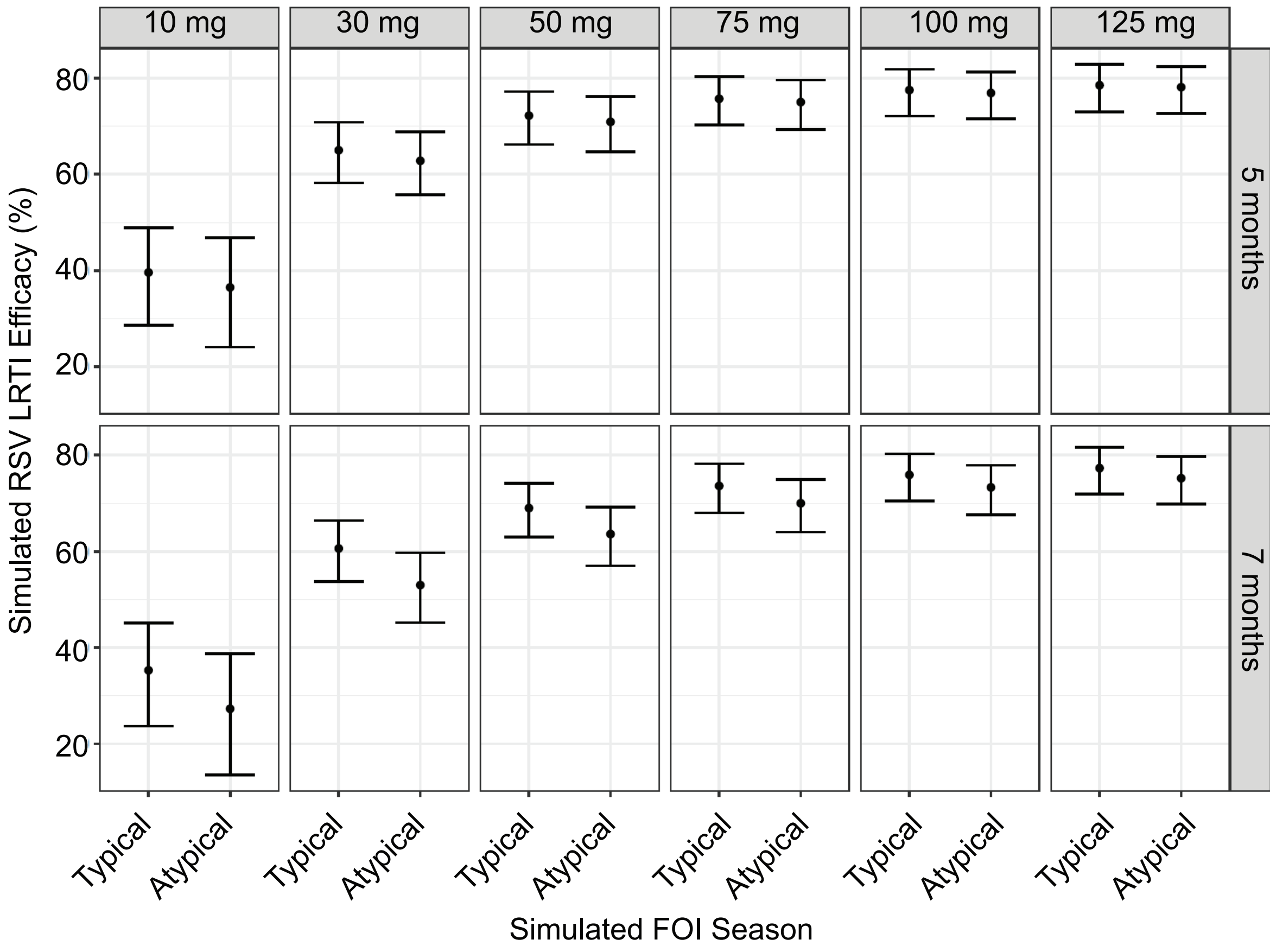
- The area under the FOI curve is doubled to represent a 2-fold increase in RSV seasonal intensity
- Changes in the FOI function mean and standard deviation lead to a delayed and prolonged season, respectively

Figure 2. Comparison of predicted RSV LRTI incidence rates for a virtual clinical trial in typical and COVID-19–impacted (atypical) RSV season (observation periods of 5 or 7 months)



- RSV incidence rates in an atypical, COVID-19–impacted RSV season are predicted, as expected, to be substantially higher than during a typical season
- Increasing the RSV LRTI observation period from 5 to 7 months leads to increases in predicted incidence rates in both simulated FOI scenarios

Figure 3. Comparison of predicted efficacy for MK-1654 in a virtual trial in typical and COVID-19–impacted season (observation periods of 5 or 7 months)



- For a typical RSV season not impacted by the COVID-19 pandemic, MK-1654 is predicted to maintain efficacy (>75%) for the prevention of RSV MALRI with doses of 75 mg or greater, through 150 days
- If the observation period is prolonged to 7 months in a typical RSV season, only a minor reduction in efficacy is expected (efficacy >70%)
- For an atypical RSV season impacted by the COVID-19 pandemic, MK-1654 is still predicted to yield efficacy of 70% at a dose of 75 mg for up to 7 months

Conclusions

- Atypical RSV seasonality patterns such as more intense, protracted, and delayed seasons can be incorporated into clinical trial simulation to account for variations in RSV disease
- Atypical RSV seasonality – caused by the removal of pandemic precautions – could result in lower MK-1654 efficacy in the ongoing trial, relative to a trial conducted during typical RSV seasons
- Simulation results suggest that MK-1654 is likely to demonstrate high efficacy against RSV MALRI through 150 days, even in the face of pandemic-driven changes to RSV seasonality

References

1. Balderston McGuiness C, et al. *Pediatr Infect Dis J*. 2014;33(6):589-594.
2. Maas BM, et al. Forward and reverse translational approaches to predict efficacy of the neutralizing respiratory syncytial virus (RSV) antibody MK-1654. Presented at: IDWeek 2021; virtual; October 2020.
3. Baker RE, et al. *Proc Natl Acad Sci USA*. 2020;117(48):30547-30553.
4. Agha R, Avner JR. *Pediatrics*. 2021;148(3):e2021052089.

Acknowledgments

We thank Maria Luisa Sardu and Anna Largajolli of Certara, Princeton, NJ, USA for important Quality Control support of the modelling data. The authors would also like to thank members from Certara Data Science Group at Hyderabad and Menlo Park led by Raj Thatavarti and Nancy Zhang, especially Niharika Gandhapuneti, Maheswar Ganta and Nina Tsuneda for database curation. Thanks also to Michelle Green (employed by Certara, Princeton, NJ, USA during the time of this study) for careful reading of the manuscripts and abstracts from the literature searches performed for this study. Thank you to Lyn Finelli and Yoonyoung Choi for epidemiological data support (each employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA).