

Predictive Probability of Success (PPOS) in longitudinal endpoint to predict trial outcome: What can we learn from a retrospective interim analysis?

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Objective

To provide an example of Predictive Probability of Success (PPOS) using a longitudinal endpoint, at various stages of recruitment, and show how the convergence to the eventual outcome can be model and time dependent.

Background

We used a pharmacometrics model at interim time points to allow prediction of likely outcomes for each individual subject, regardless of how much data had been gathered. We had planned to implement this analysis as the trial was accruing but the Data Monitoring Committee (DMC) did not agree to allow early unblinded data, hence we performed a retrospective interim analysis at various points in the presence of full knowledge of the trial outcome.

Data and methods

Data used in this analysis is from the six-month trial, Mumta Lactating Women (LW), of 957 lactating mothers who were breastfeeding their newborns in the peri-urban slums of Karachi, Pakistan. Mothers were randomized in equal numbers to receive their usual diet (denoted as C for control later); receive a nutrition supplement made from locally sourced materials (AFZ); receive AFZ and the infant would receive a prophylactic dose of azithromycin at day 42 (AZM), sponsored by the Bill & Melinda Gates Foundation, and conducted by the VITAL Pakistan Trust. The trial focused on improving growth outcomes for infants, i.e., Length for Age Z-score (LAZ).

Individual predictions were based on whether or not subjects had data at the interim analysis. If a subject had data, their individual posterior was used to predict the missing outcomes through the final observation period. Two imputation models (linear and cosine) were used to impute data and were compared to an observed cases change from baseline to month 6 for each interim analysis.

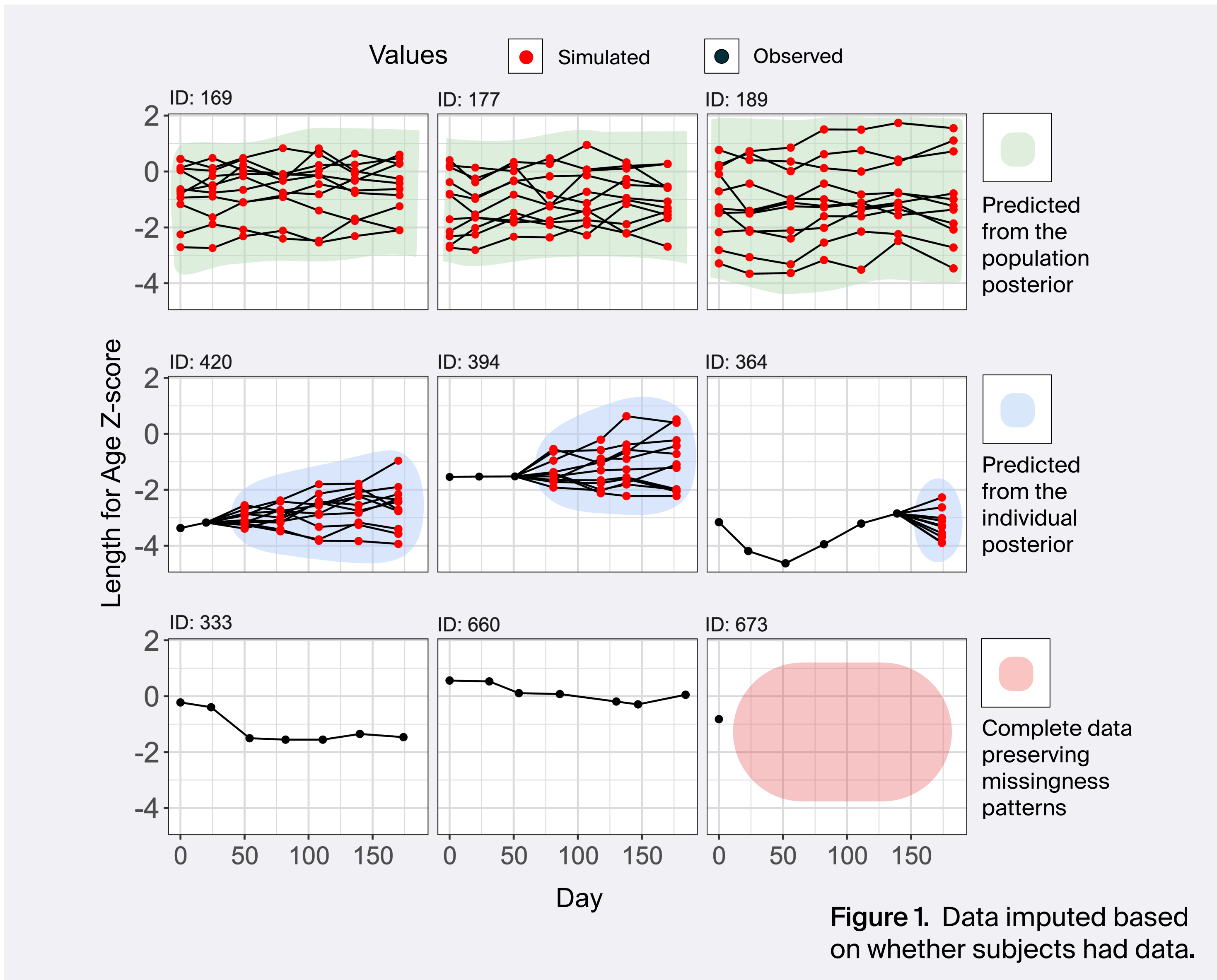


Figure 1. Data imputed based on whether subjects had data.

For subject having no data at the interim analysis, the population posterior was used to predict the unobserved outcomes. In this way individuals with observed data would drive their outcomes while the assumption was that those who had not been observed would behave as the typical subject. Comparisons are made to what we would have known if we ran this exercise live rather than retrospectively to inform considerations for implementation.

Conclusions

PPOS is a viable means of predicting trial outcome with interim data. The degree and timing of how early adequate confidence in the predictions were dependent on the quality of the model used. This approach could be considered for applications where much is known about the longitudinal trajectory of the outcomes.

Results

Prediction of the outcome in the final analysis could be done very early on but these predictions were somewhat dependent on the model chosen, where better models predicted eventual outcomes earlier. In all cases, longitudinal models outperformed the planned statistical analysis of month 6 change from baseline.

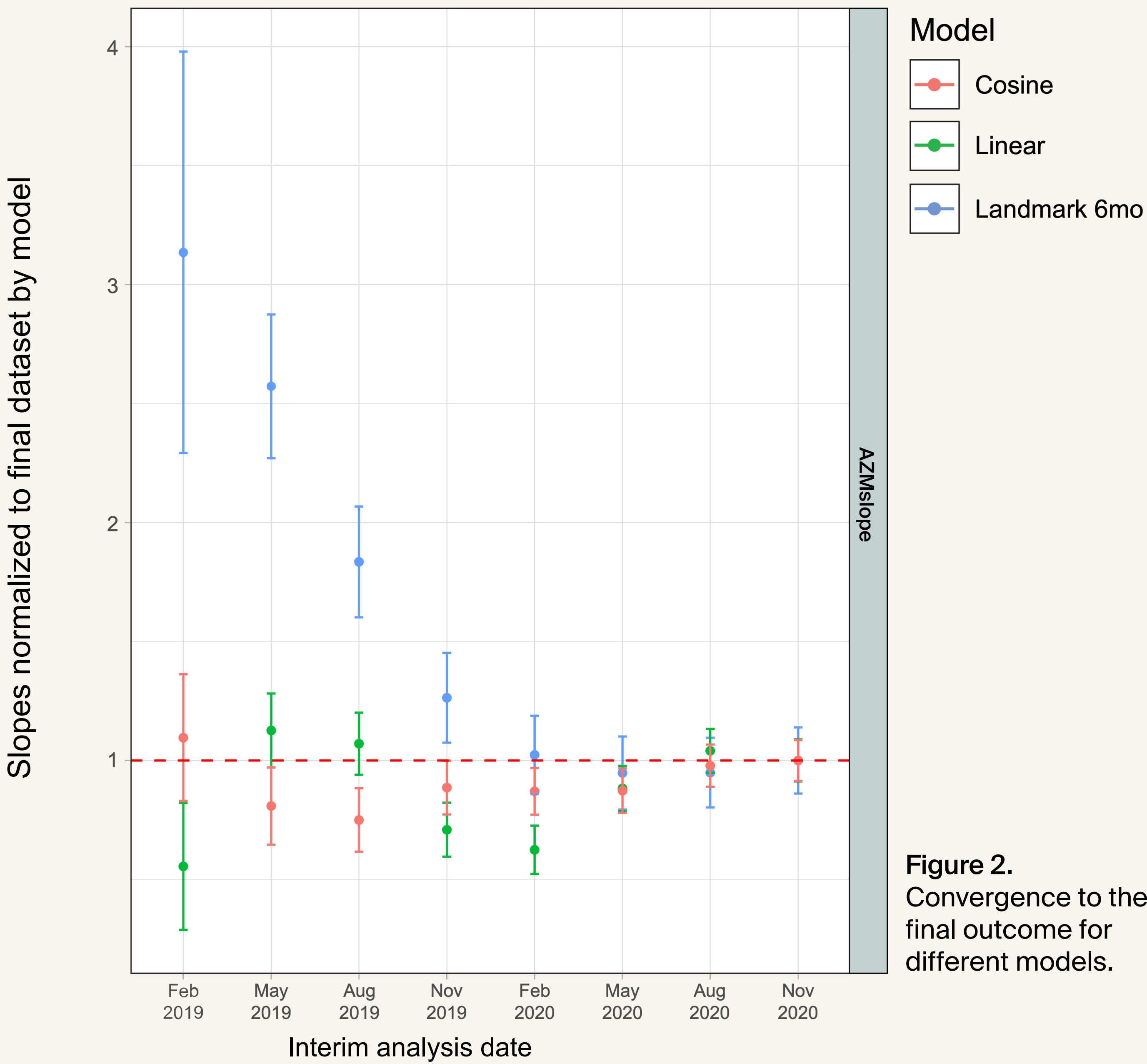


Figure 2. Convergence to the final outcome for different models.

A model (noted below) that takes into account the seasonal variability in infant growth had the earliest convergence while the six-month landmark analysis was the slowest to converge to the final outcome.

Linear:
$$y_i(t) = \theta_1 + \eta_1 + \frac{(Slope(t) + \eta_2) * t}{180} + \epsilon$$

Cosine:
$$y_i(t) = \theta_1 + [\theta_3 * \cos(\frac{2\pi}{365}(\text{DOY}(t) - \theta_4)) + \eta_1] + \frac{(Slope(t) + \eta_2) * t}{180} + \epsilon$$

Equations 1. Where Slope(t) was a different θ for each of control, AFZ and AZM up to day 42, and AZM after day 42.

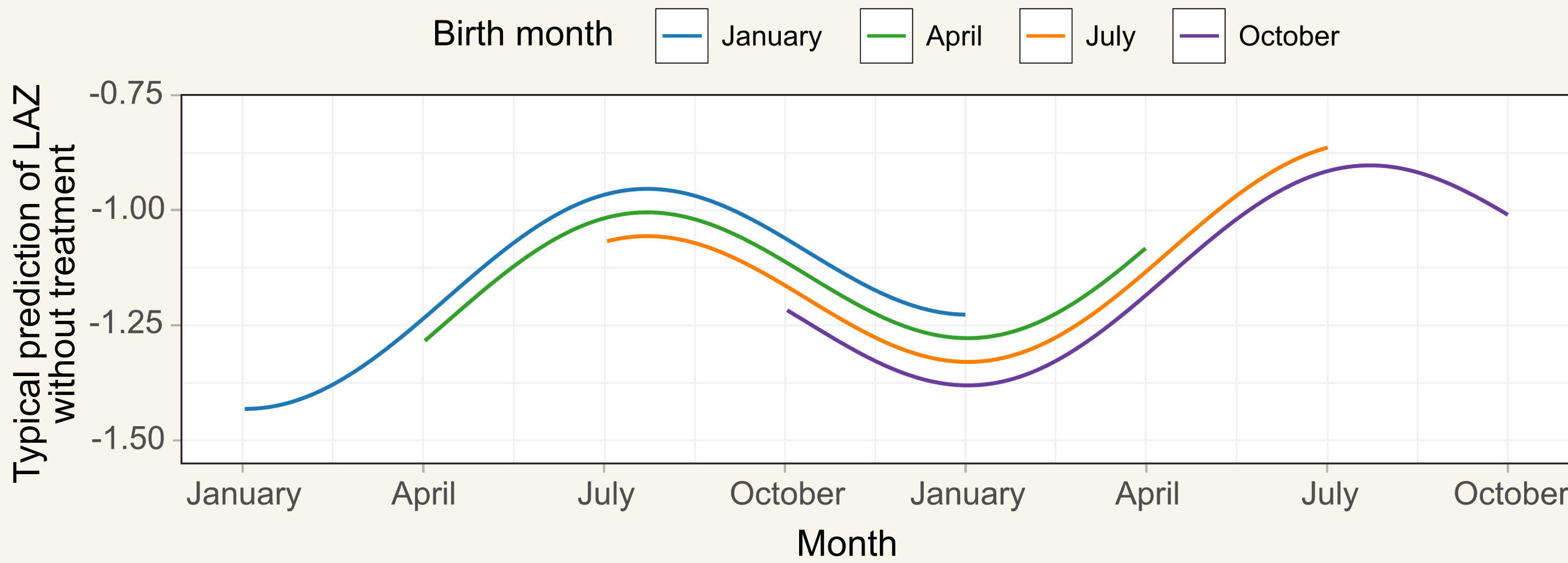


Figure 3. Seasonal growth in infants was observed and fit with a cosine term.

References

1. Zhou M, Tang Q, Lang L, Xing J, Tatsuoka K. Predictive probability methods for interim monitoring in clinical trials with longitudinal outcomes. Stat Med. 2018 Jun 30;37(14):2187-2207

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