Forecasting Clinical Outcomes from Limited Real-World Data: A Comparative Simulation Study

MSR22

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BACKGROUND

- AstraZeneca's location-relevant real-world data (RWD) platform, ATLAS, captures retrospective longitudinal healthcare data to enable country-level informed decision across multiple disease areas.
- Estimating future trends in healthcare outcomes at national and sub-national levels is essential for effective local planning and can uncover opportunities where interventions can influence meaningful improvements.
- Using RWD to project clinical outcomes can be effective because it can be accessible, timely, robust, and representative across small geographies.
- Traditional forecasting methods struggle with structural breaks (e.g., COVID-19), compounded by limited historical location-specific RWD and disease-specific seasonality impacts.

OBJECTIVES

- Compare modeling approaches (indicated below) for forecasting key clinical outcomes from limited RWD.
- Assess robustness and short-horizon performance of:
  - Linear Model (LM)
  - Generalized Additive Model (GAM)
  - Autoregressive Integrated Moving Average (ARIMA),

  each combined with Interrupted Time Series (ITS) to capture COVID-related disruptions.[1,2]
- Evaluate separate vs pooled vs hierarchical analyses of sub-national regions.

METHODS

- **Study design**: Simulation study.
- Synthetic RWD data was generated to inform a simulation process. COVID-19 disruption was considered as the middle of available time points (as depicted in **Figure 1**).
- **Available RWD:**
  - Chronic obstructive pulmonary disease (COPD) hospital admission rates & counts.
  - One national series and 18 regional series considering both, with and without seasonality (using Spain real-world healthcare data as a framework)
  - T = 10 to 50 time points of follow-up (in synthetic RWD)
- **Outcomes**: hospital admission rates and counts
- **Evaluation**: Rolling-origin cross-validation at future time points: 1, 3, 5 (horizon)
- Time points are based on data availability (e.g. can be monthly, quarterly, annually)
- Analyses were conducted to investigate the accuracy and uncertain of the models, with and without seasonality considerations
- **Metrics**:
  - Accuracy: RMSE (Root Mean Squared Error), MAE (Mean Absolute Error), sMAPE (Symmetric Mean Absolute Percentage Error)
  - Uncertainty: 95% PI Coverage, PI Width

Key design feature: ITS component explicitly models the COVID-19 structural break, allowing all three base models to account for pandemic disruptions.

DATA-GENERATING PROCESS

Figure 1. Synthetic RWD presented as (A) Non-seasonal time series (B) Seasonal time series

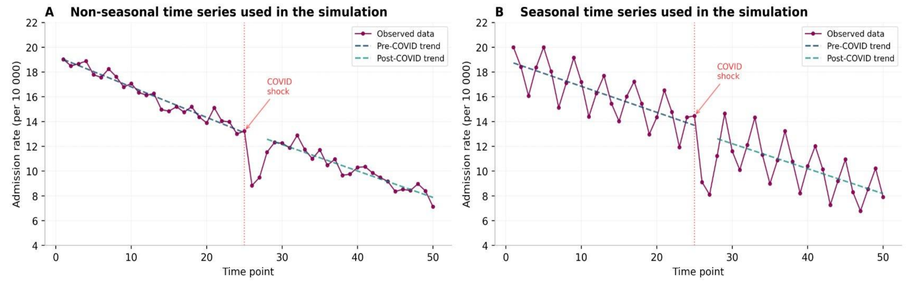


Figure 1A and **1B** describe the data-generating process for this simulation study.

The simulation is based on RWD observed for admissions rate and count to avoid arbitrary parameter choices and allow fair method comparisons.

RESULTS

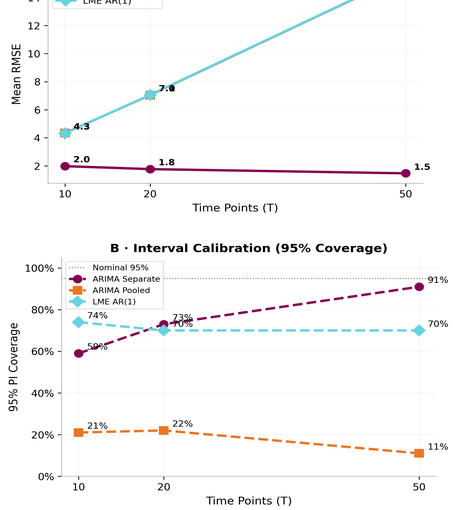
40 scenarios were evaluated, as depicted in **Figure 2**.

Figure 2. National level results: (A) RMSE without seasonality; (B) RMSE with seasonality; (C) 95% coverage without seasonality; (D) 95% coverage with seasonality; (E) MAE without seasonality; (F) MAE with seasonality; (G) sMAPE without seasonality; (H) sMAPE with seasonality

Without seasonality, across 10-50 time points, LM + ITS, GAM + ITS, and ARIMA + ITS achieved similar accuracy (e.g., for T = 10 and 3 future time points, RMSE were respectively 1.78, 1.79 and 1.80), **Figure 2A**.

With seasonality, ARIMA+ITS achieved overall lower accuracy (RMSE), **Figure 2B**.

Figure 3. Regional analysis – ARIMA + ITS applied separately in each region ("ARIMA Separate"), ARIMA + ITS applied to all regions combined ("ARIMA Pooled") and Hierarchical ("LME + AR (1)": (A) RMSE; (B) 95% coverage.



LME + AR (1): Linear Mixed-effects (LME) model where the residual errors follow an AR(1) autocorrelation structure

Figure 3 compares the regional analysis as a separated, pooled or hierarchical approach (considers correlation between regions).

The ARIMA + ITS Separate model outperform pooled and hierarchical approaches in RMSE **Figure 3A**.

Accounting for correlations between regions improved uncertainty (95% coverage) more than improving RMSE **Figure 3B.**

KEY INSIGHTS

- Without seasonality: all three ITS models are interchangeable for point prediction.
- With seasonality: ARIMA + ITS demonstrated superior performance, especially with shorter time points in data.
- Regional forecasting: ARIMA + ITS applied for reach region separately delivers the best point accuracy across all time points of observed data.
- Pooling across regions helps uncertainty, not point error — hierarchical fits improve interval calibration when T is large, but adds complexity without reducing RMSE.

CONCLUSIONS

- ARIMA + ITS was found to be a flexible and reliable approach for timely, informed decision-making. It adapts to different data configurations and can account for seasonality and structural interruptions in the time series.
- Separate region-by-region fitting is preferred for heterogeneous panels.
- Even with shorter time horizons, pooling/hierarchical structures is preferable for uncertainty, yet performed poorly for accuracy, compared to ARIMA Separate.
- ITS was successful in correctly handling COVID-era disruptions in health outcome data.
- A key limitation is the synthetic RWD based on one disease and one healthcare metric. Yet, we incorporated various follow-up time points and potential seasonality impacts.

REAL WORLD APPLICATION

This work will directly inform AstraZeneca's location-relevant RWD platform, ATLAS, and will be considered for additional markets and outcomes.[3]

Generating forecasts for key outcomes of interest is critical for planning purposes and can enable an urgency to act now to minimize future burden.

Demonstrating region-specific future trends, which have accounted for COVID-19 disruptions, is valuable to unlock value for healthcare decision making.

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