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## Revisiting the Relationship between Weather and Interannual Variation in Human Plague Cases in the Southwestern United States

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### Abstract

Plague is a rare, potentially fatal flea-borne zoonosis endemic in the western United States. A previous model described interannual variation in human cases based on temperature and lagged precipitation. We recreated this model in northeastern Arizona (1960–1997) to evaluate its capacity to predict recent cases (1998–2022). In recreating the original model, we found that future instead of concurrent temperature had inadvertently been used for the presented fit. Prediction from our revised models with lagged precipitation and temporally plausible temperature relationships aligned with low observed cases in 1998–2022. Elevated precipitation associated with high cases in historical data (>6 inches combined precipitation over two previous springs) was only observed once in the last quarter century, so we could not assess if these conditions were reliably associated with elevated (four or more) human plague cases. Observed weather conditions were similar to those previously associated with low (fewer than or equal to two) case counts, suggesting “baseline” conditions in the last quarter century.

Plague is a rare but potentially fatal flea-borne zoonosis caused by *Yersinia pestis*. In the United States, plague occurs episodically in western states, with most cases reported from the Southwest.<sup>1</sup> Human plague is often associated with sporadically occurring epizootics, periods of time when *Y. pestis* spreads rapidly in susceptible rodent populations. Widespread rodent mortality during epizootics forces infected rodent fleas to seek new hosts, including humans.<sup>2</sup>

The timing of epizootics and increases in human plague cases have often been associated with increased rainfall and moderate summer temperatures.<sup>3</sup> In the American Southwest,

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above-average precipitation was associated with higher-than-average reported cases.<sup>4,5</sup> Similar trends were described for plague cases among companion animals, which were significantly correlated with human cases in New Mexico.<sup>6</sup> Temperature also played a significant role,<sup>5,6</sup> with cooler summer temperatures favoring transmission and very hot temperatures having a negative impact. The trophic cascade hypothesis provides a biological rationale for these associations. Specifically, increased precipitation is hypothesized to set the stage for epizootic transmission by building up food sources that promote increased rodent reproduction and populations in the next summer and that provide favorable conditions for the survival and reproduction of fleas. Increased contact between fleas and rodents is thought to increase the rate of *Y. pestis* transmission, resulting in epizootics. Extreme heat is proposed to counteract this by decreasing flea survival, *Y. pestis* transmission, and human–flea encounters, thereby reducing the number of human plague cases.<sup>3,7</sup>

Understanding the relationship between weather and plague occurrence (weather–plague relationship) could be useful for forecasting periods of elevated risk. Given the generalizability of the trophic cascade hypothesis in the Southwest, we sought to 1) recreate a previous well-fitting model<sup>5</sup> from northeastern Arizona (Climate Division 2; 1960–1997) and 2) assess if these relationships could predict observed case counts in the next 25 years (1998–2022). Although separate models were previously developed for Arizona and New Mexico,<sup>5</sup> changes in case reporting prevented us from identifying which cases occurred in the New Mexico climate division in the recent 25 years (see Supplemental Text), so we focus only on Arizona.

To recreate this trophic cascade model,<sup>5</sup> we fitted a Poisson generalized linear model (GLM; using the stats R package<sup>8</sup>) of human plague cases per plague year (defined previously<sup>5</sup> as June 16–June 15) relative to temperature and lagged precipitation. We used lagged February to March precipitation (one- and two-plague year lags), lagged July to August precipitation (one-plague year lag), and “degree days” (90°F [32.2°C] and 95°F [35°C] thresholds) as covariates (Figure 1A, schematic). For this, we acquired monthly precipitation data for the climate division<sup>9</sup> and calculated “degree days” (the annual number of days at least certain temperature thresholds) using maximum daily temperatures from Winslow Municipal Airport.<sup>10</sup> We tabulated human plague data from case reports sent to CDC.<sup>1,11</sup> See Supplemental Figure 1 and Supplemental Text for case, temperature, and precipitation data details.

We were unable to recreate the model fit (Figure 1B, fit) using the presented description<sup>5</sup> (Figure 1A, schematic). To produce the previous fit, degree days needed to correspond to the calendar year in which the June-to-June plague year ended (i.e., shifted forward in time) (compare Figure 1A and B). This resulted in a temporal mismatch between case and temperature data, with plague cases associated with future temperatures; each year, most days with temperatures  $\geq 32.3^{\circ}\text{C}$  (mean: 87.6%, range: 78.0–100%) and  $\geq 35^{\circ}\text{C}$  (mean: 93.3%, range: 75.8–100%) occurred after June 16 (1960–1997). Additionally, one-plague year lagged July to August precipitation was included in the original model, but we found it to be not significant here ( $P = 0.86$ ) and thus, dropped the variable (Figure 1C) without degradation of fit (Supplemental Table 1). See Supplemental Text for additional details.

With the described temporal mismatch, the implemented model (Figure 1B) used future conditions that could not impact case occurrence. Therefore, we fitted a variety of models with biologically plausible relationships of temperature and plague occurrence to assess their relative fit and predictive performance (Table 1). These models included degree days for the calendar year in which the June-to-June plague year began (as intended in the original model; model 1) (Figure 1C), for the winter/spring of the plague year (January 1–June 15; model 3) (Figure 1D), for the summer of the plague year (June 16–September 30; model 4) (Figure 1E), and aligned to the plague year (June 16–June 15; model 5) (Figure 1F). The precipitation covariates as originally presented were not impacted by the mismatched timing, so we included both one- and two-plague year lagged February to March precipitation; one-plague year lagged July to August precipitation was not significant in any model and thus, was dropped (Supplemental Table 1). We also fitted a version of the model with the plague data aligned to the calendar year (January 1–December 31; model 8) (Figure 1G) for more intuitive temporal relationships and because it aligns with broad plague seasonality in the United States (Supplemental Figure 2). This model included lagged February to March precipitation (one- and two-year lags) and concurrent degree days (90°F and 95°F). Covariates for July to August precipitation were not significant at either one-year ( $P = 0.13$ ) or two-year lags ( $P = 0.53$ ) and were removed (Supplemental Table 1). Using both the June-to-June and calendar plague years, we fitted models without degree days (only lagged precipitation; models 6 and 9) and no weather covariates (“simple”; models 7 and 10) as comparisons for model training performance with less weather information. Model 7 was an autoregressive order-1 Poisson model to remove residual autocorrelation. Model 10 was an intercept-only Poisson GLM because we did not detect residual autocorrelation (Supplemental Text). We used each fitted model to predict human plague cases for 1998–2022, calculating training (1960–1997) and testing (1998–2022) error (Table 1). We assessed predictive accuracy of all models by determining the proportion of observations contained within 95% prediction intervals (PIs) (Supplemental Text).

Across models, the magnitude and direction of fitted coefficients were similar (Supplemental Figure 4; Supplemental Tables 2–11) and aligned with the trophic cascade hypothesis; increased February to March precipitation, more days  $\geq 32.3^{\circ}\text{C}$ , and fewer days  $\geq 35^{\circ}\text{C}$  were associated with increased plague cases. All models had similar fit and predictive capacity as measured by mean absolute error (MAE) (Table 1). For example, with all training MAE between 0.79 and 1.36 cases, average fitted values differed from observed values by  $\leq 1.36$  plague cases per year.

Inclusion of future temperature (our recreation of the originally presented model<sup>5</sup>; model 2), inclusion of temperature from the summer of the plague year (model 4), or using a calendar plague year (model 8) resulted in the lowest training error (“best” model) (Table 1) and fitted well to the spikes in plague years 1983 and 1994 (Supplemental Figure 3A and C). Other models underpredicted the 1983 spike. For models with June-to-June plague years, model 1, our correctly time-matched recreation of the originally intended model<sup>5</sup> (Figure 2A), had the best predictive performance (lowest testing MAE) (Table 1). For models that used a calendar plague year, model 8 had the best prediction (Figure 2B). “Simple” models had the worst fit (poor training performance), so we did not focus on their predictive capacity.

All models accurately predicted few human cases (fewer than or equal to two) with all observations within the 95% point-wise PIs, indicating “good” prediction. There were no instances when models failed to predict or incorrectly predicted elevated cases (four or more). Weather conditions associated with elevated cases (four or more) during the training period (1960–1997), >6 inches of combined precipitation over the two previous springs, were only observed in 2021 in the testing time frame (Supplemental Figure 7). No cases were reported that plague year, as was the case in 1980. We did not identify a difference in degree days between years with low or elevated cases (Supplemental Text). Thus, although this cumulative amount of spring precipitation may represent a threshold for increased human plague risk, additional factors are needed for elevated cases to occur. Identification of such conditions would provide useful information for public health.

In the original study,<sup>5</sup> models were developed to describe historical trends and were not intended for prediction. The good fit of the trophic cascade model to the historical data included plausible biological relationships (increased precipitation before years with increased case counts mediated by high temperatures during the transmission season) but relied on an inadvertent temporal shift in degree day covariates. Our model recreation using the intended, biologically plausible relationships agreed with the trophic cascade hypothesis and accurately predicted low counts. Weather conditions were similar between low (fewer than or equal to two cases) years in the training and testing periods. As elevated precipitation totals previously associated with elevated cases (four or more) did not occur in the recent quarter century, we were unable to fully test the predictive accuracy of proposed trophic cascade associations in these more extreme cases. Thus, although weather appears to impact *Y. pestis* transmission,<sup>12–16</sup> conditions in northeastern Arizona did not enable us to fully test the accuracy of the proposed weather drivers of elevated plague cases; the impact and any underlying thresholds might be more apparent if evaluated in counties across the western United States where plague is endemic. Consideration of human socioeconomic risk factors might also improve prediction.<sup>17,18</sup> Additional work to identify factors associated with above-average cases across a wider area could further improve the usefulness of predictions for public health.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

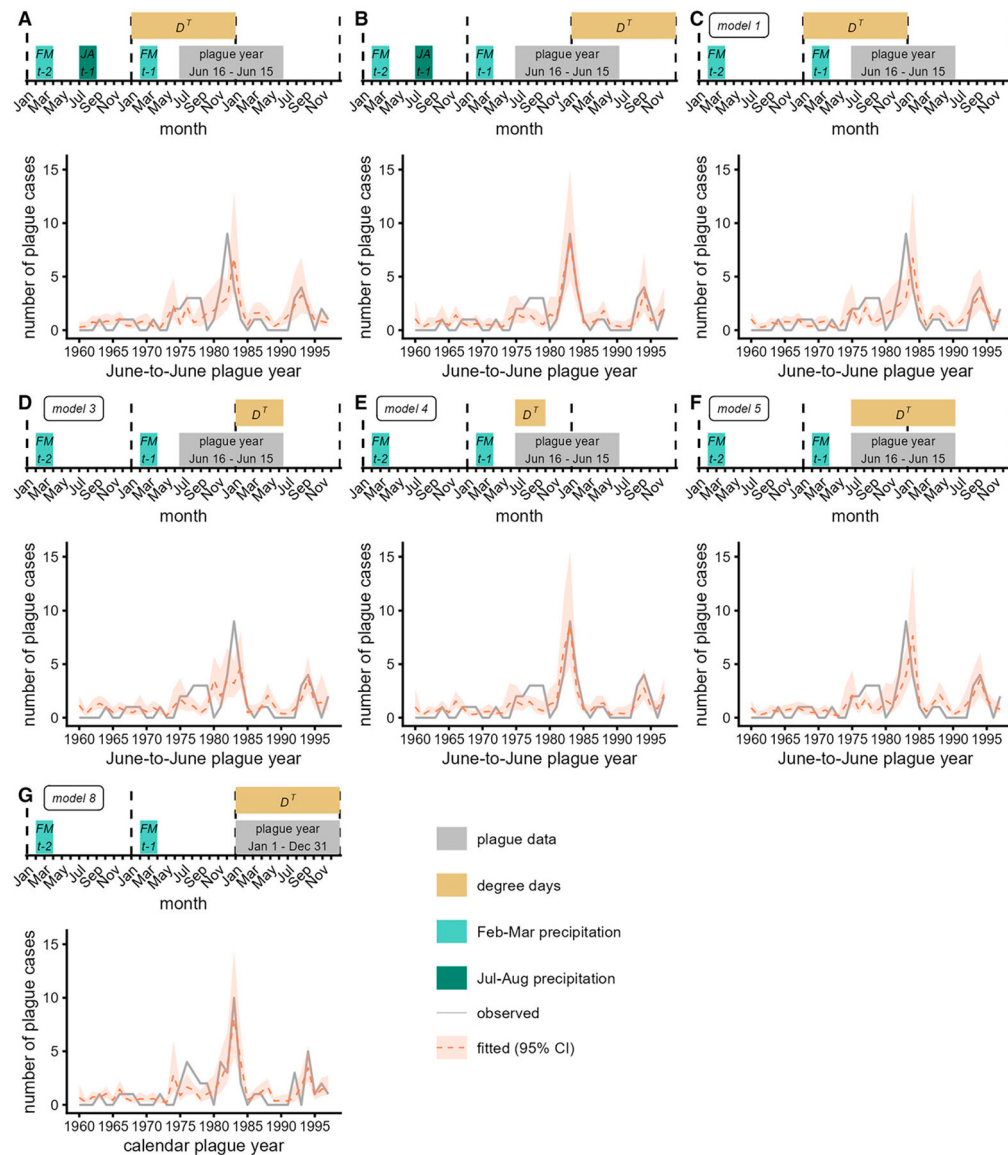
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**Figure 1.**

Temporal relationship of model parameters and the resulting fitted number of human plague cases in Arizona Climate Division 2 (1960–1997). The original model is as (A) described and (B) likely implemented. Recreated models (C) are based on the original description, (D–F) are shown with biologically plausible temperature relationships, and (G) use plague cases on a calendar year. Recreated models annotated with model numbers correspond to Table 1. In the panels, the schematics in the upper panels illustrate the temporal relationships between model parameters, and the lower panels illustrate the observed vs. fitted number of human plague cases for the indicated parameters:  $FM_{t-x}$  (February to March total precipitation [inches],  $x$ -plague year lag),  $JA_{t-1}$  (July to August total precipitation [inches], one-plague year lag),  $D^T$  (days at least temperature  $T$ , “degree days”), and the plague year  $t$ . The lagged July to August precipitation covariate was not significant in model

recreations, so it was not included in the models presented in **C–G**. Vertical dashed lines in the schematic indicate the start of a calendar year for context.

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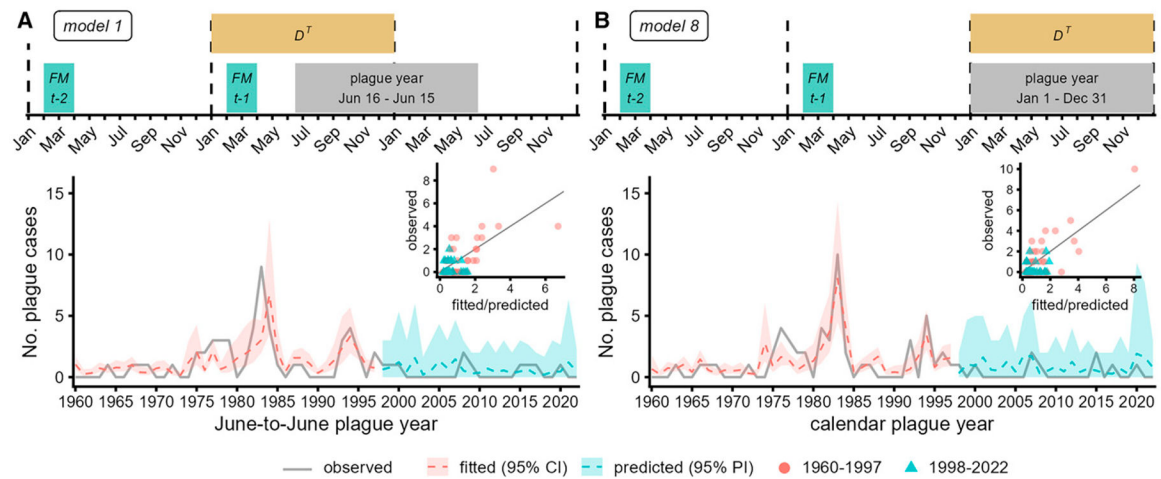


**Figure 2.**

Fitted and predicted estimates of human plague cases using degree days and lagged spring precipitation. Case data are from a (A) June-to-June or (B) calendar plague year. The panels are annotated with model numbers from Table 1. Insets provides scatterplots of observed vs. expected (fitted or predicted) cases, with the diagonal representing the 1:1 relationship. The schematics in the upper panels illustrate the temporal relationships between model parameters:  $FM_{t-x}$  (February to March total precipitation,  $x$ -plague year lag),  $D^T$  (days at least temperature  $T$ , “degree days”), and the plague year  $t$ . See Table 1 for more details on model performance metrics. PI = prediction interval.

**Table 1:** Composition and metrics of models of human plague cases in Arizona Climate Division 2 (1960–2022)

| Model | Plague Year  | Precipitation Covariates* Included | Time Frame for Degree Days†                               | AIC (Δ)‡       | R²§  | MAE       |         | Prop. 95% PIs Contain Truth# |
|-------|--------------|------------------------------------|-----------------------------------------------------------|----------------|------|-----------|---------|------------------------------|
|       |              |                                    |                                                           |                |      | Training¶ | Testing |                              |
| 1     | June-to-June | Yes                                | Original intended calendar year                           | 161.75 (57.74) | 0.34 | 0.99      | 0.59    | 1.00                         |
| 2     | June-to-June | Yes                                | Original actual calendar year                             | 104.01 (0.00)  | 0.52 | 0.75      | 0.92    | 1.00                         |
| 3     | June-to-June | Yes                                | Winter/spring of original plague year (January 1–June 15) | 120.42 (16.41) | 0.32 | 1.00      | 0.77    | 1.00                         |
| 4     | June-to-June | Yes                                | Summer of original plague year (June 16–September 30)     | 103.80 (20.21) | 0.52 | 0.79      | 0.79    | 1.00                         |
| 5     | June-to-June | Yes                                | Original plague year (June 16–June 15)                    | 112.10 (8.09)  | 0.42 | 0.98      | 0.68    | 1.00                         |
| 6     | June-to-June | Yes                                | NA                                                        | 123.10 (19.09) | 0.24 | 1.05      | 0.73    | 1.00                         |
| 7     | June-to-June | No                                 | NA                                                        | 116.09 (12.08) | NA   | 1.08      | 0.67    | 1.00                         |
| 8     | Calendar     | Yes                                | Calendar year                                             | 110.96 (6.95)  | 0.47 | 0.95      | 0.80    | 1.00                         |
| 9     | Calendar     | Yes                                | NA                                                        | 125.58 (21.57) | 0.26 | 1.08      | 0.99    | 1.00                         |
| 10    | Calendar     | No                                 | NA                                                        | 144.17 (40.16) | 1.00 | 1.36      | 1.09    | 1.00                         |

AIC = Akaike information criterion; MAE = mean absolute error; NA = not applicable; PI = prediction interval; Prop. = proportion. The interpretation of pseudo- $R^2$  values differs between modeling frameworks such that values are not directly comparable (NA). Therefore, we did not present a value for the June-to-June plague year “simple” model as it used an autoregressive framework (autoregressive order-1), whereas the other models used a generalized linear modeling framework. See Figure 1 for schematics of the temporal relationships between model parameters. See Figure 2 and Supplemental Figure 3 for model fits during training and testing periods. See Supplemental Tables 2–11 for fitted coefficients.

\* Precipitation covariates for February to March total precipitation (inches) at one-plague year lag ( $FM_{t-1}$ ) and two-plague years lag ( $FM_{t-2}$ ).

† Covariates for the numbers of days at 90°F (32.2°C) and 95°F (35°C) thresholds during the indicated time frame. Models without degree day covariates are indicated with NA.

‡ Mean AIC of three models fitted to imputed datasets. No imputation is needed when degree day covariates are not included (models 6, 7, 9, and 10), so a single model is fitted in these instances. The difference in mean AIC is calculated relative to our recreation of the originally presented<sup>5</sup> model fit (model 2), the model that most closely represented the original.

§ Mean of pseudo- $R^2$  of models fitted to imputed datasets. No imputation is needed when degree day covariates are not included (models 6, 7, 9, and 10), so a single model fitted in these instances.

Pseudo- $R^2$  is a goodness-of-fit metric where a value of zero indicates that the model captures no interannual variation (i.e., predicts the same number each year) and a value of one indicates that the model perfectly matches the observed cases (i.e., fully captures interannual variation).

|| MAE of the model fitted to data from plague years 1960–1997. Lower MAE indicates better fit. The average number of cases for this period was 1.32 cases/year (June-to-June plague year) or 1.34 cases/year (calendar plague year).

¶ MAE of model predictions for plague year 1998–2022. Lower MAE indicates better prediction. The average number of cases for this period was 0.40 cases/year (June-to-June plague year) or 0.36 cases/year (calendar plague year).

# Proportion of 95% PIs containing reported human plague cases (1998–2022). PIs containing observations indicate reliable predictions. All generalized linear modeling had point-wise prediction intervals, whereas the PIs for the autoregressive order-1 model (model 7) were calculated recursively.