Predicting Seasonal Influenza Hospitalizations

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Purpose

To determine which of a set of simple candidate statistical models (CSM) most closely fits a series of hypothetical influenza hospitalization curves (HIHC), stratified by season severity (Centers for Disease Control and Prevention, 2016).

Which of these simple CSMs would provide the best severity forecast at the beginning of the flu season (i.e., epiweek 40) based purely on fit to the HIHCs described below?

Subquestion: Which model best predicts the proportion of flu-attributable hospitalizations?

General approach

1. Fit a quadratic trend filter model (Brooks et al., 2015) to FluSurv-NET hospitalization data for the seasons 2003–2004 through 2017–2018, based in part on the approach described by Brooks et al. (Brooks et al., 2015).

2. Simulate 3,000 HIHCs using the empirical Bayes model as a "generative model".

3. Stratify these HIHCs into groups representing High/Moderate and Mild severity HIHCs, based on the CDC's categorization (Biggerstaff et al., 2018; Centers for Disease Control and Prevention, 2018).

4. Fit each CSM within each severity stratum and test for goodness of fit. Systematically alter the functional form of epiweek indicators as in Wang et al.'s study of influenza mortality (Wang et al., 2012).

Forecasting targets

All weeks will be specified using the *MMWR* Week convention (Centers for Disease Control and Prevention, a):

1. Peak week
2. Peak number of hospitalizations
3. Total hospitalizations

These targets follow in part from (Brooks et al., 2015).

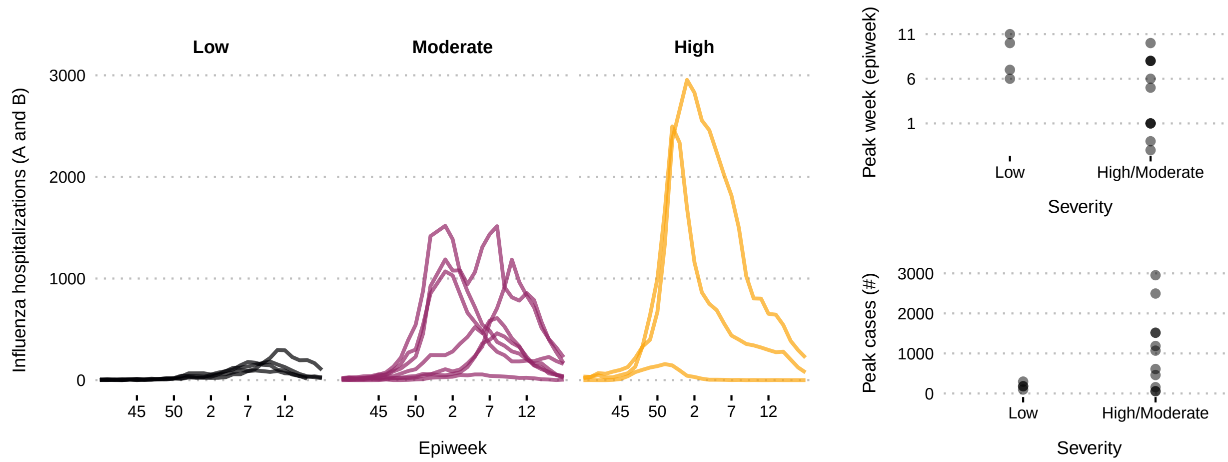

Figure 1: Empirical hospitalization curves, peak weeks, and peak number of cases — 2003–2017 (Source: FluSurv-NET, CDC). Data excludes 2009–2010 pandemic influenza season and 2017–2018 due to no official severity designation.

Curve fitting and simulation

We will simulate HIHCs using a modified version of the curve-fitting approach described by Brooks et al. (Brooks et al., 2015).

First, we fit a quadratic trend filter to historical hospitalization curves released by the CDC (beginning with the 2003–2004 season), using the R package `glmgen` (Brooks et al., 2015; Centers for Disease Control and Prevention, 2016). This model is fit within flu severity group (Mild, High/Moderate).

For each season s and each week i, Brooks et al. conceptualize a seasonal influenza curve as some function plus noise[1]:

$$y_i^s = f^s(i) + \epsilon_i^s, \epsilon \sim N(0, \tau^s),$$

where

$$f^s(i) = \frac{\theta}{\max_j f(j)}\left[f\left(\frac{i-\mu}{v} + \underset{f}{\text{arg max } j}(j)\right)\right]$$

Based on fitting the quadratic trend filtering model to empirical data (i.e., historical CDC flu hospitalization data), we estimate error τ^s:

$$(\hat{\tau}^s)^2 = \underset{i}{\text{avg}}\left[y_i^s - \hat{f}^s(i)\right]^2$$

and then sample from the model, introducing noise for each weekly observation based this estimate of τ^2.

We impose a lower bound of 0 hospitalizations via the following transformation of $\hat{y}_i^s$, which we denoted below as $\hat{z}_i^s$:

$$\hat{z}_i^s = 0.5\left(|\hat{y}_i^s| + \hat{y}_i^s\right)$$

[1] Brook et al. use their method to forecast a current flu season, where b represents the current season's epidemic threshold of weighted influenza-like illness percent. Because hospitalization curves have a lower bound of 0, we drop b from the original equation.

Note: In the Brooks paper, exactly what j stood for was a little unclear. I believe the only sensible interpretation is that it is the indicator for the week in the trend filter predictions $f(j)$ conducted as part of each curve simulation.

Parameters in quadratic trend filtering model

The HIHCs are simulated using the following sampling scheme for each parameter represented in the model for hospitalization count (y_i^s) at each week. Note that all equations are either adapted from or appear in (Brooks et al., 2015).

$$\langle f, o, \nu, \theta, \mu \rangle$$

Shape (f)

$$f \sim U\{\hat{f} : \text{historical season } s\}$$

Noise (σ)

$$\sigma \sim U\{\hat{\tau}^s : \text{historical season } s\}$$

Peak height (θ)

$$\theta \sim U\left[\theta_m, \theta_M\right]$$

Results in the following curve:

$$f_3(i) = f_2(i - \mu + \text{arg max}_j f_2(j))$$

Note: Brooks et al. say they get "unbiased estimators" for the minimum and maximum peak heights θ_m and θ_M, respectively. However, given the notation does not indicate these parameters are estiamtes, I am using the observed minimum and maximum heights based on CDC data.

Pacing (ν)

Curve-stretching around peak week:

$$\nu \sim U[0.75, 1.25]$$

Results in following curve:

$$f_4(i) = f_3\left(\frac{i - \text{arg max}_j\ f_3(j)}{\nu} + \text{arg max}_j\ f_3(j)\right)$$

Candidate models

Incidence-rate difference models

- Generate a set of predicted flu-related hospitalizations based on a standard incidence rate difference model typically used to model flu cases. Implement in flumodelr based on (Izurieta et al., 2000; Thompson et al., 2009).
- Thresholds: 0.1 and 0.15 as in (Thompson et al., 2009).

Question for Kevin: Does it make sense to use the rate-difference model in the context of hospitalizations? We essentially have a rate of 0 (or very close to it) at the beginning of each flu season, unlike with wILI.

Serfling model (least squares)

Modified from (McConeghy et al.):

$$Y = \beta_0 \alpha + \beta_1 t + \beta_r X_r + ... + \beta_p cos\left(\frac{2\pi t}{52}\right) + \beta_q sin\left(\frac{2\pi t}{52}\right)$$

Where t = time (epiweek), subscript r denotes a vector of β coefficients and variables, and subscripts p and q take on particular numbers based on the length of r.

Modified Serfling model

Modified from (McConeghy et al.):

$$y = \alpha_0 + \beta_1 t + \beta_2 Flu_t + \beta_p X_p + ... + sin\left(\frac{2\pi t}{period}\right) + cos\left(\frac{2\pi t}{period}\right) + u$$

Where t = time (epiweek) and subscript p denotes a vector of $beta$ coefficients and variables.

Generalized additive model (Prophet)

This model will be implemented using the R package *prophet* (Taylor and Letham, 2018), which implements a generalized additive modeling approach developed by engineers at Facebook, Inc.

The general form of the equation that will be fit to the HIHCs:

$$y(t) = g(t) + ... + h(t) + \epsilon_t,$$

where $g(t)$ models nonperiod trends and $h(t)$ stands for a vector of holidays or other events that are known to correlate with flu hospitalization (Brooks et al., 2015). As with the Serfling and modified Serfling models, the Prophet model will include additional model terms included to improve fit.

Question for Kevin: Do you agree that we won't need seasonality terms here? We are essentially modeling one flu hospitalization season at a time, so it's unclear to me where seasonality would come into the picture. Consequently, does this fact obviate the need for cyclical terms in the Prophet model and perhaps any need for the Serfling models? The curves look as if they could be modeled simply as quadratic functions.

Model terms

The following model terms will be entered into the vector of covariates considered for each model:

a) Cyclical terms (Serfling, Fourier, etc.)

b) Historical (empirical) flu hospitalizations

c) Historical data on viral activity (NREVSS), outpatient surveillance (ILI-Net)

d) Average weekly temperature

e) Climate factors (e.g., prior summer temperatures)

f) Lags and leads of c) or d)

g) Indicators for weeks of Thanksgiving and/or Christmas (Brooks et al., 2015; Taylor and Letham, 2018)

Goodness of fit

- Root mean squared error (RMSE)
- Bayesian information criterion (BIC)
- Relative bias

Question for Dr. Naimi: Should we be doing cross-validation or sample-splitting given the aims of this analysis? We can simulate an arbitrary number of hypothetical hospitalization curves, so the limited number of historical flu season available may not be an issue.

Sensitivity analysis

Challenge
The composition of institutions reflected in the FluSurv-NET has changed over time (Centers for Disease Control and Prevention, b; Kandula et al., 2019), meaning the FluSurv-NET estimates for influenza-related hospitalizations may not be comparable across time.

Response
Redo the analysis three times: one for each set of years in which the same participating institutions reported flu data to CDC. See (Centers for Disease Control and Prevention, b) for more information.

Limitations

Brooks et al. showed that their empirical Bayes model improved upon standard lagged CDC predictions for several forecasting targets of the overall influenza curves (season onset, peak week, peak rate/count, duration of season). In adapting their approach to hospitalizations, we should ensure we can achieve similar accuracy.

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