Supporting Information for**: Improving the estimation of influenza-related mortality over a seasonal baseline**

Edward Goldstein [1], Cécile Viboud [2], Vivek Charu [2,3], Marc Lipsitch [1,4]

1) Center for Communicable Disease Dynamics, Department of Epidemiology, Harvard School of Public Health, Boston MA, USA
2) Division of International Epidemiology and Population Studies, Fogarty International Center, National Institutes of Health, Bethesda, MD, USA
3) School of Medicine, Johns Hopkins University, Baltimore, MD, USA
4) Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston MA, USA

## S1. Mortality data

**eTable 1:** List of underlying causes of death studied and associated international classification (ICD) of diseases codes, USA, 1997-2007. Indented causes are subset of those above with lesser indentation

| Description | ICD-9* | ICD-10** |
|---|---|---|
| Respiratory diseases | 460-519 | J00-J99 |
| Pneumonia and influenza | 480-487 | J09-J18 |
| Influenza | 487 | J09-J11 |
| Chronic lower respiratory disease | 490-494, 496 | J40-J47 |
| Cardiovascular causes | 340-459 | I00-I99 |
| Heart disease | 390-398, 402, 404, 410-429 | I00-I09, I20-I51, I11, I13, |
| Ischemic Heart Disease | 410-414, 429.2 | I20-I25 |
| Acute Myocardial Infarction | 410.0 | I21-I22 |
| Cerebrovascular diseases | 430-438 | I60-I69 |
| Malignant neoplasms | 140-208 | C00-C97 |
| Diabetes | 250 | E10-E14 |
| Renal diseases (nephritis, nephrotic syndrome, nephrosis) | 580-589 | N00-N07, N17-N19, N25-N27 |
| Chronic Liver Disease and Cirrhosis | 571 | K70, K73-K74 |
| Degenerative central nervous system diseases | 331 | G30-G32 |
| Alzheimer's | 331.0 | G30 |
| Septicemia*** | 038 | A40-A41 |
| Unintentional injuries*** | E800-E869; E880-E929 | V01-X59, Y85-Y86 |

*1997-1998
**1998-2007
*** Used as controls

## S2. A preliminary, Serfling-type approach relating influenza incidence proxies to excess mortality

As an initial step in our analysis, we visually inspected the feasibility of relating excess mortality to the influenza incidence proxies from  by comparing excess P&I mortality above a Serfling baseline, against influenza incidence proxies shifted forward by two weeks [1].

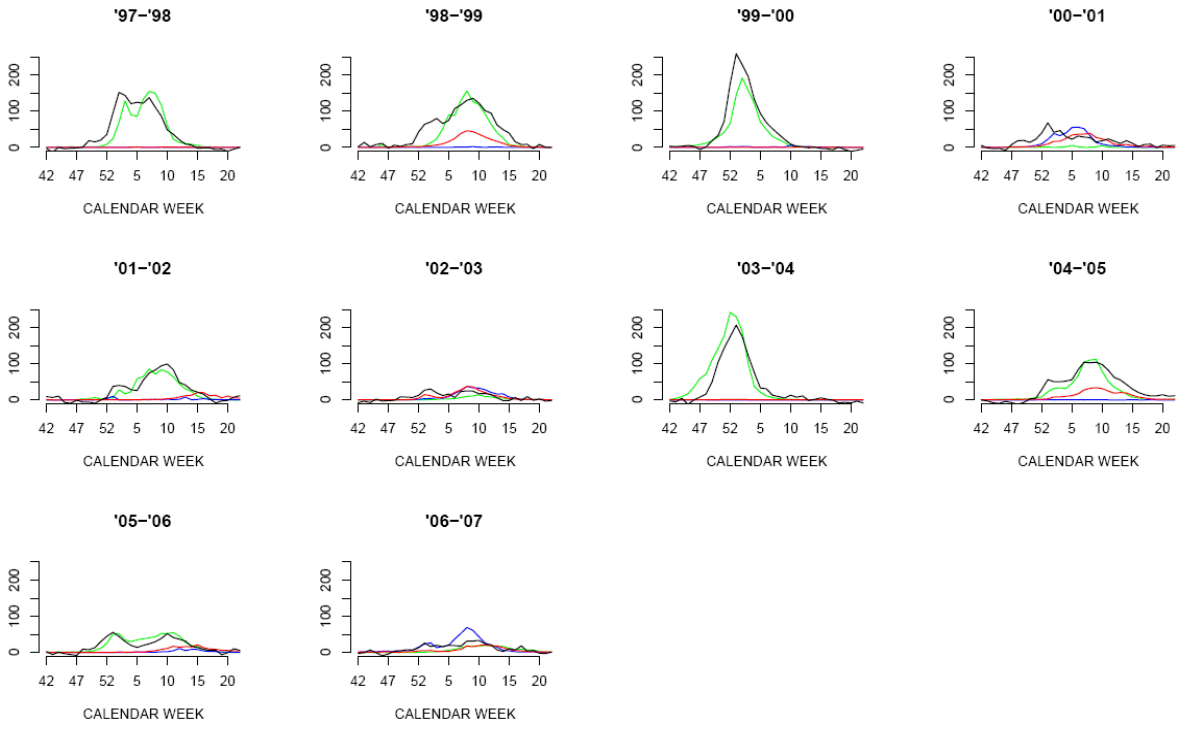
We have considered the weekly mortality counts $M^{a}_{P\&I}(t)$ for which P&I was mentioned anywhere on the death certificate (as opposed to merely being the underlying cause) [2]. Excess P&I mortality is defined as

$$EM^{a}_{P\&I}(t) = M^{a}_{P\&I}(t) - (\text{baseline} + \text{trend}) \qquad \text{(S1)}$$

The temporal trend is modeled by a (low degree) polynomial in the influenza season year, and the baseline is a periodic trigonometric function in the week $t$ (with an annual period) [2]:

$$baseline(t) = c_1 cos(\frac{2\pi t}{52}) + c_2 sin(\frac{2\pi t}{52}) \qquad \text{(S2)}$$

The coefficients for the baseline and trend were fit against the mortality data by linear regression during the warm months of each year between 1972-2006 [2]. Figure S1 relates excess P&I mortality $EM^{a}_{P\&I}(t)$ to the incidence proxies of influenza A/H3N2, A/H1N1 and B, shifted forward by two weeks during the influenza circulation periods for the '97-'98 through the '06-'07 seasons.




**eFigure 1:** Excess P&I mortality per 100,000 (black, multiplied by 250) and the incidence proxies of A/H3N2 (green), A/H1N1 (blue) and influenza B (red).

While there is a good visual relationship between the bulk of A/H3N2 incidence and excess mortality, one also sees a "bump" in excess mortality peaking around the first week of January which cannot be consistently explained by influenza. Moreover the magnitude of that bump appears to be larger during the first four seasons in the data, which is also coincidental with the introduction of the pneumococcal conjugate vaccination in 2000 [3,4]. Additionally, it appears from eFigure 1 that the ratio between excess mortality and A/H3N2 incidence might be bigger before than after the '03-'04 season when the Fujian strain of A/H3N2 appeared. Those considerations have affected our choices for the main inference model in the paper.

**S3. Analysis with A/H1N1 included**

In this section we repeat some of the analysis from the main body of the text with influenza A/H1N1 included in the model. Table S2 presents the results of the model with A/H1N1 included for the underlying causes studied in the paper.

Average mortality rates per 100,000 and the regression coefficients for A/H3N2 and B are mostly similar to the estimates in Table 3 in the main body of the text (particularly for all cause mortality and circulatory causes). Generally, the biggest differences are observed for the underlying causes where the A/H1N1 coefficients are relatively large. However given the wide confidence bounds on those coefficients, the results of the model with A/H1N1 are difficult to interpret. The biggest relative difference in average mortality rates is observed for chronic liver disease, though both estimates are quite small. Differences for other underlying causes are under 10% or less (less than 5% for respiratory causes and less than 2% for circulatory causes). Also the estimate for unintentional injuries is statistically significant for the model with A/H1N1 (and borderline significant for a model without A/H1N1).

**eTable 2:** Results of a model with A/H1N1 (described in Table 1) for various underlying causes between 1997-2007. Regression coefficients (with the 95% confidence bounds) are multiplied by 1,000. Indented causes are subset of those above with lesser indentation.

| CAUSES | $\beta^1_{H3}$ | $\beta^2_{H3}$ | $\beta_{H1}$ | $\beta_B$ | $R^2$ | $f$ (eq. 4) | Average mortality rate per 100,000 |
|---|---|---|---|---|---|---|---|
| All cause | 15 (12.7,17.36) | 10.81 (8.81,12.92) | -0.42 (-7.26,6.58) | 14.27 (5.96,22.49) | .9613 | .445 | 11.86 (10.02,13.71) |
| All circulatory | 6.05 (4.97,7.14) | 3.78 (2.84,4.74) | -0.14 (-3.25,3.08) | 5.63 (1.84,9.55) | .9777 | .545 | 4.58 (3.73,5.46) |
| Heart disease | 4.92 (4.09,5.74) | 3.11 (2.39,3.84) | -0.11 (-2.57,2.35) | 4.95 (2.07,7.85) | .9742 | .642 | 3.80 (3.17,4.47) |
| Ischemic heart Disease | 3.5 (2.87,4.13) | 2.14 (1.6,2.7) | -0.31 (-2.19,1.6) | 3.61 (1.38,5.82) | .9789 | .66 | 2.67 (2.16,3.17) |
| Myocardial infarctions | 1.4 (1.16,1.64) | 0.77 (0.56,0.98) | 0.13 (-0.61,0.83) | 1.24 (0.41,2.07) | .9809 | .791 | 1.03 (0.84,1.22) |
| Cerebrovascular disease | 0.93 (0.75,1.11) | 0.46 (0.31,0.63) | -0.00035 (-.54,0.54) | 0.76 (0.13,1.39) | .9697 | .149 | 0.65 (0.5,0.8) |
| All respiratory | 5.18 (4.46,5.88) | 3.82 (3.15,4.5) | -0.3 (-2.55,1.97) | 1.79 (-0.96,4.58) | .9597 | .277 | 3.54 (2.97,4.13) |
| Pneumonia & Influenza | 2.51 (2.25,2.76) | 1.99 (1.75,2.24) | 0.009 (-0.8,0.84) | 0.55 (-0.43,1.57) | .9597 | .138 | 1.73 (1.51,1.95) |
| Chronic lower Respiratory | 2.13 (1.82,2.43) | 1.48 (1.21,1.75) | -0.65 (-1.57,0.3) | 2.24 (1.16,3.36) | .9559 | .45 | 1.63 (1.38,1.87) |
| Cancer | 1.1 (0.84,1.36) | 0.59 (0.37,0.81) | -0.4 (-1.16,0.32) | 1.41 (0.53,2.27) | .8277 | 1 | 0.82 (0.62,1.03) |
| Diabetes | 0.33 (0.24,0.42) | 0.23 (0.15,0.3) | -0.22 (-0.47,0.03) | 0.70 (0.42,1) | .8939 | .563 | 0.3 (0.23,0.37) |
| Renal disease | 0.22 (0.15,0.28) | 0.19 (0.14,0.25) | 0.10 (-.09,0.29) | 0.23 (0.006,0.45) | .8946 | 0 | 0.20 (0.15,0.26) |
| Central nervous system disease | 0.24 (0.09,0.39) | 0.34 (0.21,0.47) | -0.26 (-0.7,0.2) | 1.20 (0.69,1.71) | .965 | .238 | 0.38 (0.27,0.51) |
| Alzheimer's disease | 0.24 (0.09,0.39) | 0.32 (0.19,0.45) | -0.36 (-0.79,0.1) | 1.26 (0.73,1.77) | .9632 | .215 | 0.38 (0.25,0.5) |
| Chronic liver disease | 0.06 (0.02,0.1) | 0.08 (0.045,0.11) | 0.12 (0.003,0.24) | -0.01 (-0.15,0.12) | .5131 | .33 | 0.063 (0.029,0.096) |
| CONTROLS | | | | | | | |
| Septicemia | -0.11 (-0.72,0.52) | 0.28 (-0.43,0.96) | 1.12 (-1.53,3.74) | -1.49 (-4.97,1.85) | .8219 | .464 | -0.08 (-0.59,0.45) |
| Unintentional Injuries | 0.13 (-0.02,0.28) | 0.18 (0.06,0.32) | 0.34 (-0.08,0.78) | -0.008 (-0.52,0.51) | .7812 | .946 | 0.15 (0.03,0.27) |

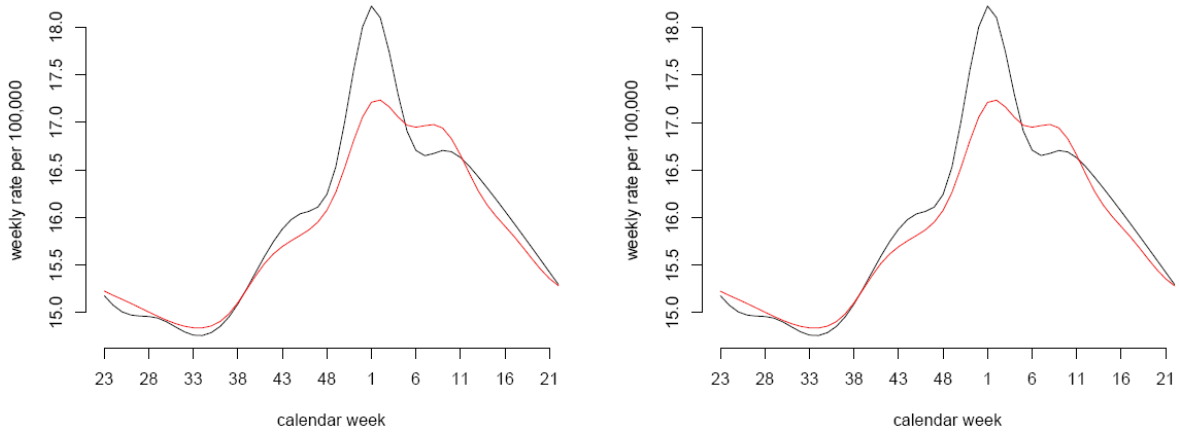
eTable 3 presents the estimates of annual mortality rates per 100,000 associated with each influenza strain, and with influenza overall in a model which includes A/H1N1. The

results for A/H3N2, influenza B and overall contribution are consistently similar with Table 2 in the main body of the text.

**eTable 3**: Annual mortality rates per 100,000 associated with each influenza strain, and with influenza overall

| | A/H3N2 | A/H1N1 | Influenza B | All influenza |
|---|---|---|---|---|
| '97-'98 | 16.32 | -0.002 | 0.072 | 16.39 |
| '98-'99 | 15.85 | -0.14 | 4.64 | 20.36 |
| '99-'00 | 14.95 | -0.002 | 0.08 | 15.02 |
| '00-01 | 0.28 | -0.14 | 4.74 | 4.88 |
| '01-'02 | 10.77 | -0.059 | 1.99 | 12.71 |
| '02-'03 | 1.40 | -0.11 | 3.87 | 5.16 |
| '03-'04 | 15.93 | -0.006 | 0.196 | 16.12 |
| '04-'05 | 8.83 | -0.13 | 4.45 | 13.15 |
| '05-'06 | 7.17 | -0.07 | 2.48 | 9.58 |
| '06-'07 | 2.28 | -0.085 | 2.88 | 5.08 |
| Overall average | 9.38 | -0.075 | 2.54 | 11.84 |

eFigure 2 presents the baselines for non-influenza associated all cause mortality, with and without A/H1N1 in the inference model. The results are very similar in the two models.




**eFigure 2:** Annual mortality baselines (black – $Base_1$ , red - $Base_2$ ) in a model with A/H1N1 (left) and without A/H1N1 (right)

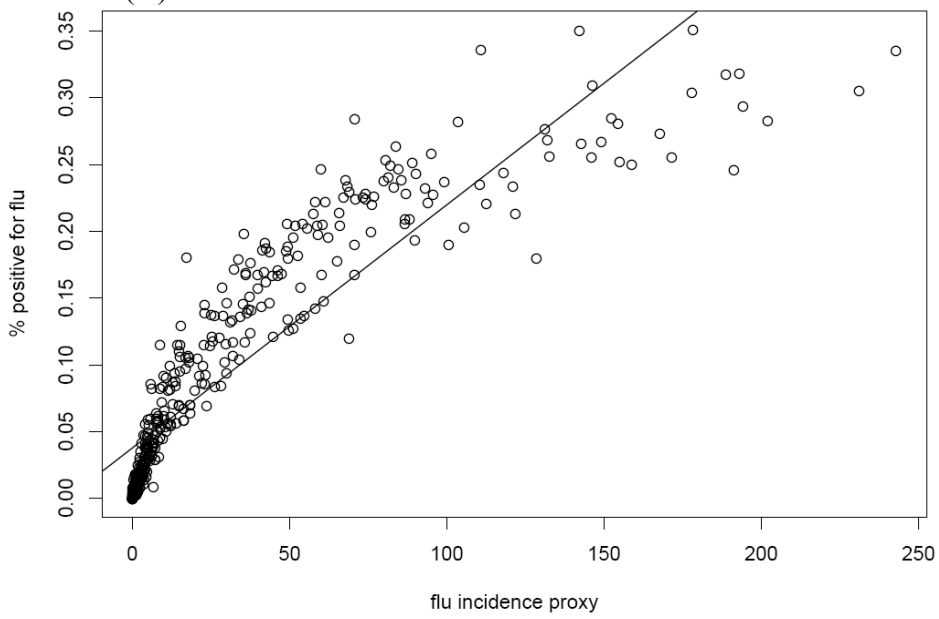
## S4. Sensitivity of the OLS inference with respect to the choice of an incidence proxy and baseline shape

In this section we examine the sensitivity of our main inference framework given by equation (3) with respect to the choice of incidence proxies and the model for baseline shape used in the inference process. In addition to (subtype-specific) incidence proxies used in the main body of the text (adopted from [5]) , we consider the weekly percent of

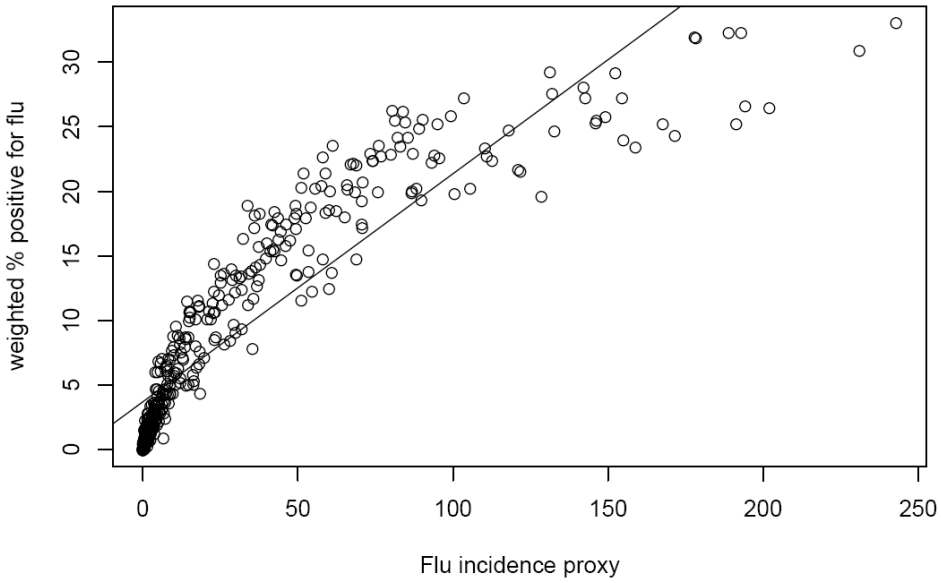
respiratory specimen from [6] testing positive for each influenza subtype (incidence proxy adopted from [7,8]), and the above percentages weighted by US regional populations. Two choices of a baseline shape are considered: a baseline modeled by periodic cubic splines with knots every four weeks (from the main body of the text); and a linear combination of a sine and cosine functions with a period of 52 weeks (adopted from [7,8]).

eFigure 3 (parts A, B, and C) is the scatter plot of the weekly influenza incidence proxy from the main body of the text (the sum of A/H3N2, A/H1N1 and influenza B incidence proxies) vs. the percent positive incidence proxy (A), the percent positive incidence proxy, weighted by regional populations in the US (B), and the weighted percent ILI (C).

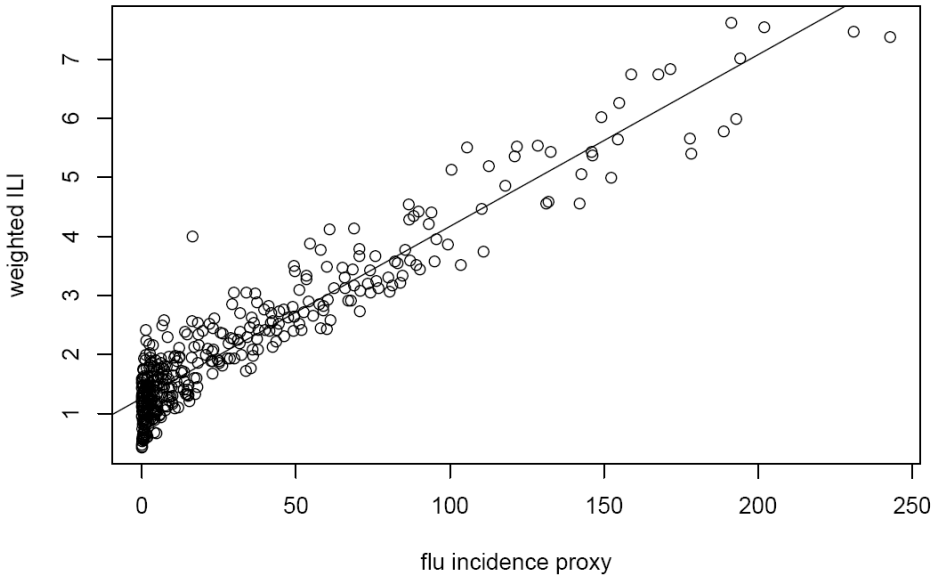
(A) Cor= 0.899




(B) Cor=0.903



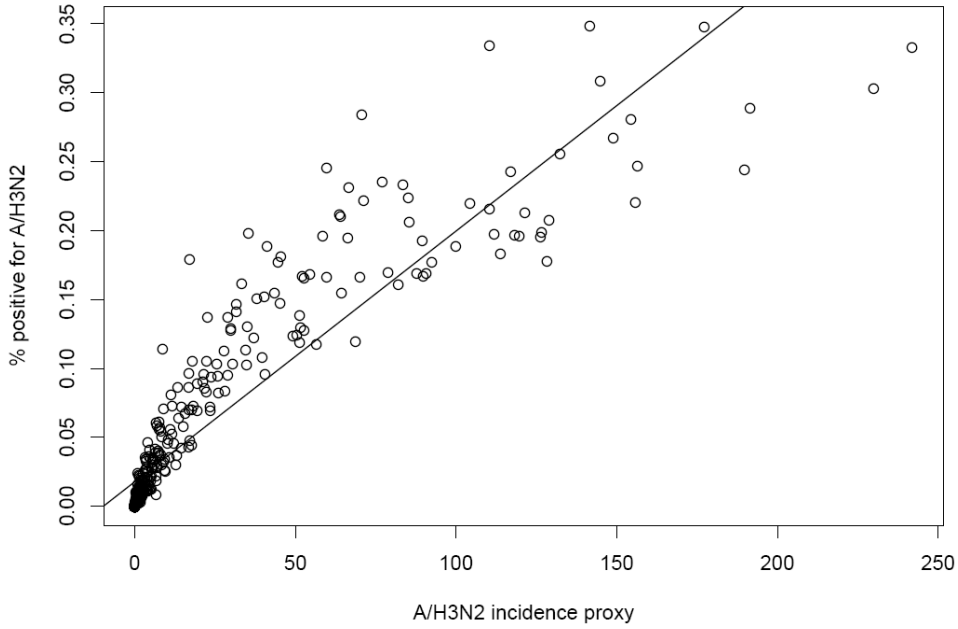

(C) Cor=0.948



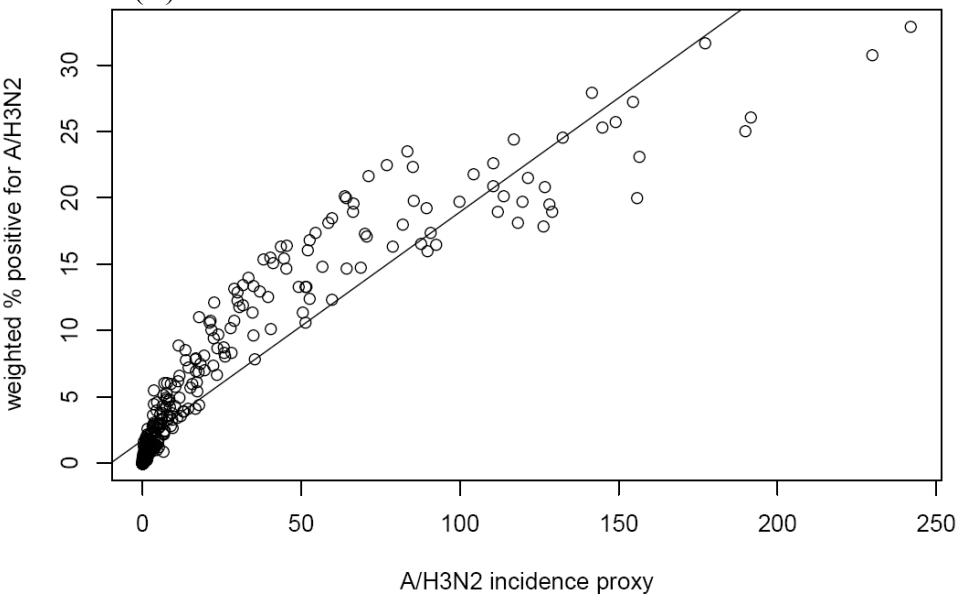

**eFigure 3**: Scatter plot of the weekly incidence proxy for influenza from our main model and various indicators of influenza activity. (A) Percent of respiratory specimens testing positive for influenza (B) Percent of respiratory specimens testing positive for influenza, weighted by regional populations (C) Percent of ILI doctor visits, weighted by regional populations

We see that the linear correlation is the strongest with the weighted percent ILI, while the relation with the percent positive incidence proxies is convex rather than linear. However percent of ILI doctor visits is not specific to the circulating influenza subtypes and therefore is not considered in the inference model. eFigures 4-6 plot the relation between our main incidence proxy and the (unweighted and weighted) percent positive incidence proxies for influenza A/H3N2 (eFigure4), A/H1N1 (eFigure 5) and B (eFigure 6).

(A) Cor= 0.914

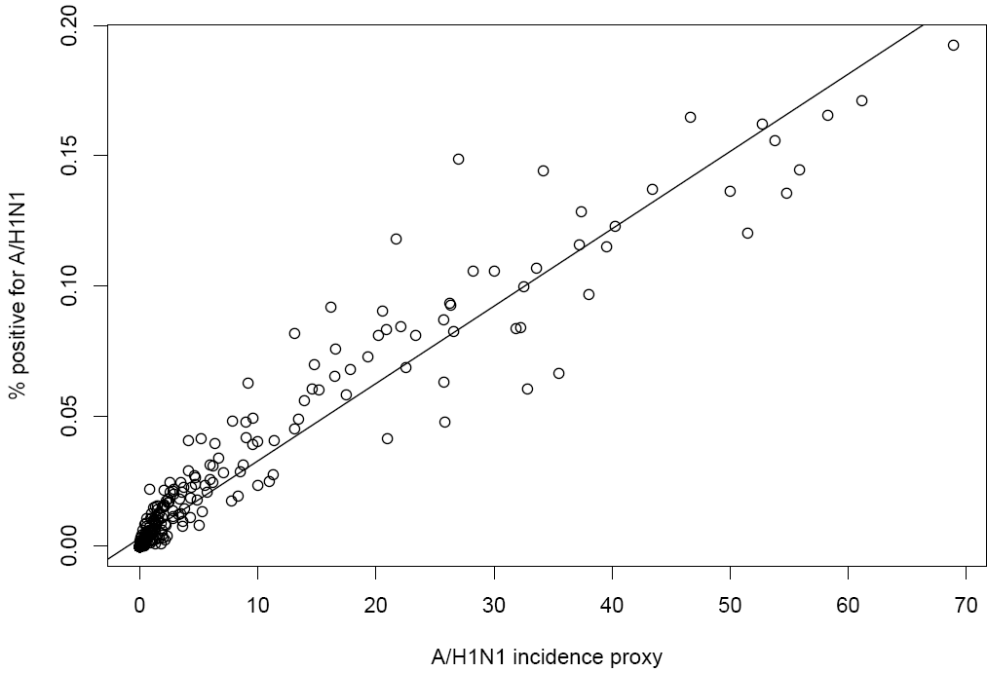



(B) Cor= 0.929

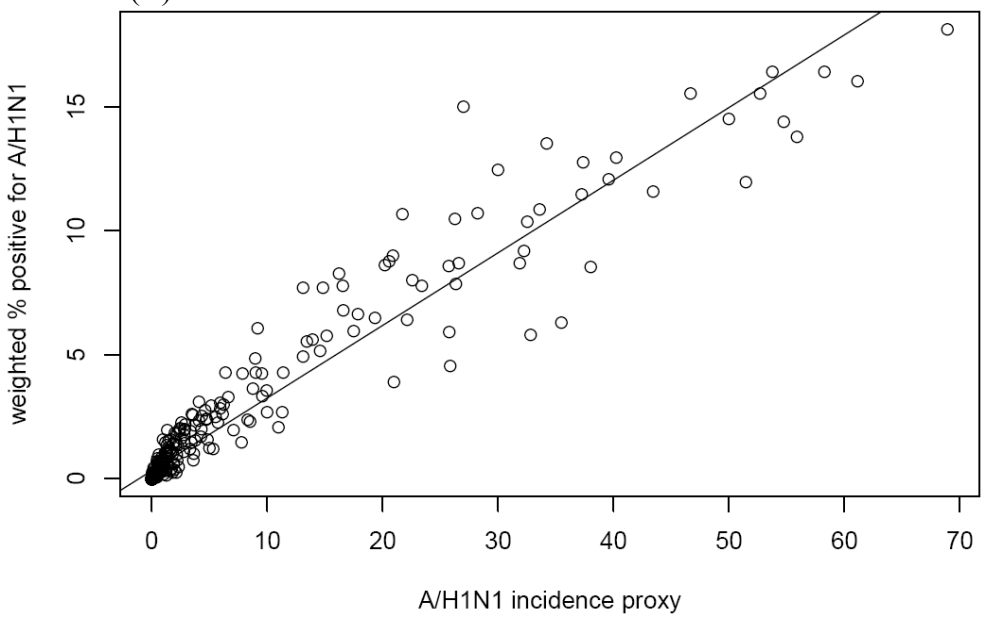



**eFigure 4**: Scatter plot of the weekly A/H3N2 incidence proxy from our main model and various indicators of A/H3N2 activity. (A) Percent of respiratory specimens testing positive for A/H3N2 (B) Percent of respiratory specimens testing positive for A/H3N2, weighted by regional populations

(A) Cor=0.963

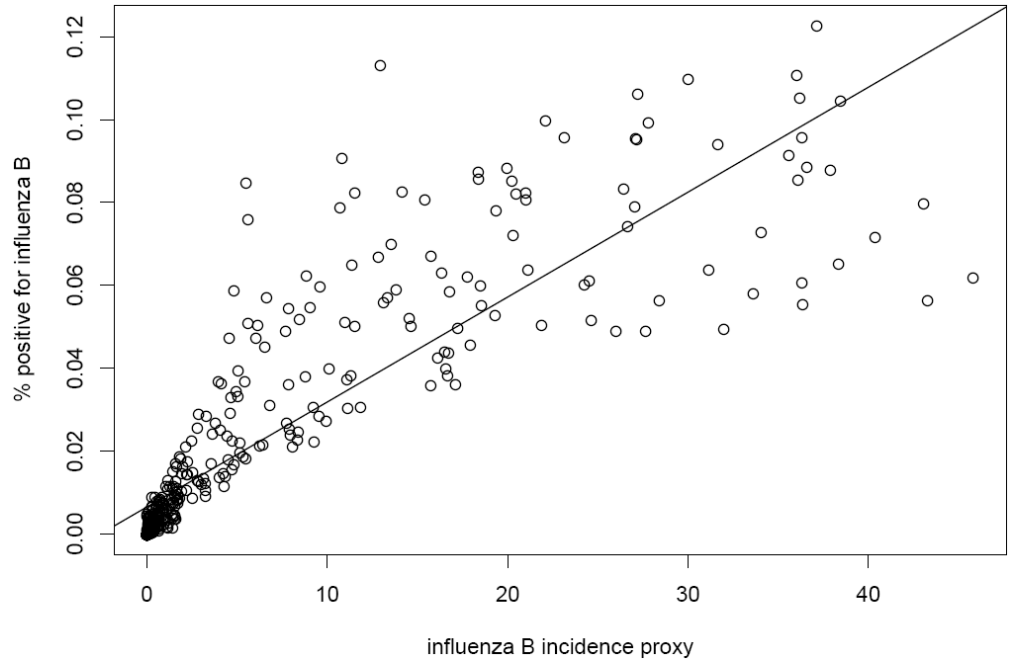



(B) Cor=0.962

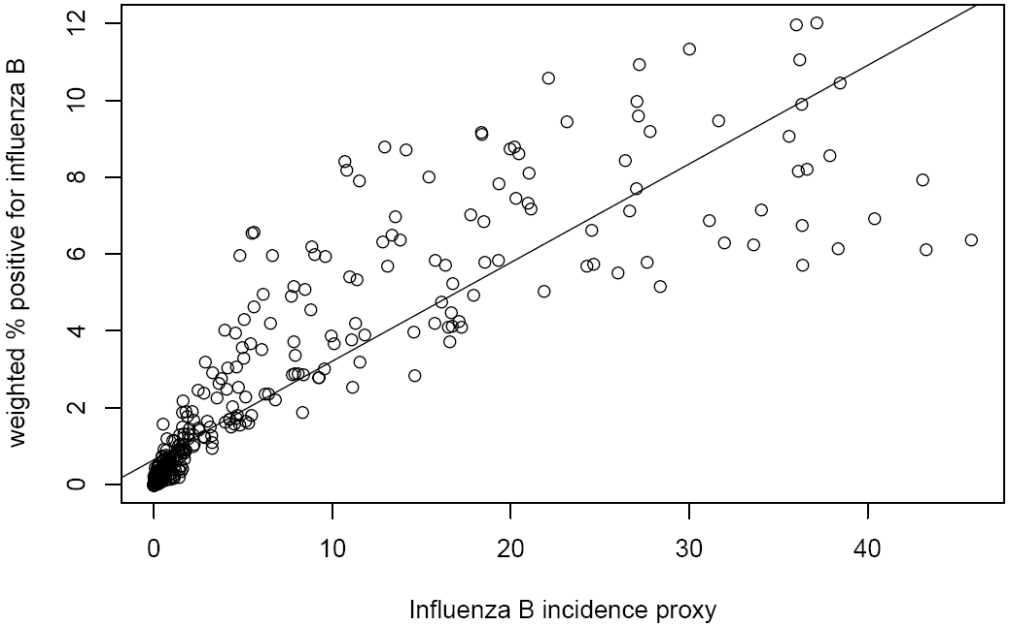



**eFigure 5**: Scatter plot of the weekly A/H1N1 incidence proxy from our main model and various indicators of A/H1N1 activity. (A) Percent of respiratory specimens testing positive for A/H1N1 (B) Percent of respiratory specimens testing positive for A/H1N1, weighted by regional populations

(A) Cor= 0.868




(B) Cor=0.881




**eFigure 6**: Scatter plot of the weekly the influenza B incidence proxy from our main model and various indicators of influenza B activity. (A) Percent of respiratory specimens testing positive for influenza B (B) Percent of respiratory specimens testing positive for influenza B, weighted by regional populations

The outcomes considered for each choice of the (subtype-specific) incidence proxies and each choice of a baseline shape are the accuracy ( $R^2$ ) of the OLS fit, as well as the

estimates of average annual all-cause mortality attributable to influenza. Table S4 summarizes those outcomes.

**eTable 4**: Average influenza-associated mortality and the accuracy of the OLS fit for various incidence proxies and baselines.

| | Spline baseline | | Trigonometric baseline | |
|---|---|---|---|---|
| Incidence proxies | Average mortality | $R^2$ for the OLS fit | Average mortality | $R^2$ for the OLS fit |
| Main incidence proxy | 11.92 | .9613 | 12.16 | .9261 |
| % positive | 15.99 | .9496 | 15.64 | .8986 |
| Weighted % positive | 17.66 | .9526 | 17.09 | .9044 |

We see that the incidence proxy from the main body of the text rendered the most accurate fits for each choice of a baseline, as well as the lowest estimates of flu-associated mortality during the study period (1997-2007) compared to other incidence proxies. Switching from a spline to a trigonometric baseline decreased the quality of the fit significantly for each choice of an incidence proxy; however that switch had relatively minor impact on the estimate of average annual flu-attributed mortality.

We want to point out that other incidence proxies were previously used to fit the mortality data not with a linear link but with an exponential link in the Poisson regression model – see below for a related comparison. Our main incidence proxy multiplies the % of doctor visits for ILI by the % of respiratory specimens testing positive for influenza sub-types. We see from eFigures 3-6 that the relation between our main incidence proxy and the percent positive incidence proxies is convex rather than linear. It is therefore not surprising that applying a convex (exponential) function to one of the alternative incidence proxies might yield a better fit for the mortality data than using a linear link.

**S5. Comparison of our method to Poisson regression models with a linear link**

In this section we compare the results of our main inference model, described by equation (3) with an inference model for which the expected weekly mortality rate per 100,000 is still described by equation (3), however the observed weekly mortality counts are modeled to be Poisson variables. More precisely, for the alternative inference model we use the same incidence proxies for influenza as in the main body of the text, and model the expected mortality rate per 100,000 underlying a certain cause, or a collection of causes $c$ as

$$E(M_c(t)) = \beta^1_{H3}\cdot S(H3^1)(t) + \beta^2_{H3}\cdot S(H3^2)(t) + \beta_{H1}\cdot S(H1)(t) + \beta_B\cdot S(B)(t) + .. \\ .. + Base_1(t) + Base_2(t) + \text{trend} + \text{noise} \qquad \text{(S3)}$$

Here $S$ is the forward shift operator as in eq. 4 in the main body of the text.
The weekly count in the whole US population is modeled as

$$M_c^{count}(t) = Pois(Population(t)/100,000 * E(M_c(t))) \quad \text{(S4)}$$

where $Population(t)$ is the US population on week t, estimated from the data in [9].

eTable 5 presents the annual estimates of influenza-associated mortality rates per 100,000 derived by the 2 method for all cause mortality, respiratory deaths, circulatory deaths, cancer deaths, and central nervous system disease deaths (the four underlying causes with the highest average annual flu contribution from Table 3).

**eTable 5**: Annual estimates for the main inference method (OLS inference) vs. the Poisson regression with a linear link method (given by equations (S3) and (S4)) of the influenza-associated mortality rates per 100,000 for all cause mortality, respiratory deaths, circulatory deaths, cancer deaths, and central nervous system deaths

| | All cause | | Respiratory | | Circulatory | | Cancer | | Central nervous system disease | |
|---|---|---|---|---|---|---|---|---|---|---|
| Season | OLS | Linear Poisson | OLS | Linear Poisson | OLS | Linear Poisson | OLS | Linear Poisson | OLS | Linear Poisson |
| '97-'98 | 16.44 | 16.43 | 5.68 | 5.63 | 6.63 | 6.64 | 1.25 | 1.25 | 0.3 | 0.3 |
| '98-'99 | 20.48 | 20.55 | 6.04 | 6.06 | 8.22 | 8.27 | 1.61 | 1.59 | 0.64 | 0.64 |
| '99-'00 | 15.08 | 15.06 | 5.2 | 5.16 | 6.07 | 6.09 | 1.15 | 1.15 | 0.28 | 0.28 |
| '00-01 | 4.95 | 5.04 | 0.64 | 0.7 | 1.96 | 2 | 0.42 | 0.41 | 0.36 | 0.36 |
| '01-'02 | 12.77 | 12.79 | 3.97 | 3.97 | 5.13 | 5.16 | 0.99 | 0.99 | 0.35 | 0.35 |
| '02-'03 | 5.22 | 5.29 | 0.93 | 0.98 | 2.07 | 2.11 | 0.43 | 0.42 | 0.31 | 0.31 |
| '03-'04 | 16.17 | 16.17 | 5.68 | 5.67 | 5.65 | 5.67 | 0.92 | 0.92 | 0.54 | 0.53 |
| '04-'05 | 13.24 | 13.31 | 3.65 | 3.7 | 4.82 | 4.87 | 0.88 | 0.86 | 0.62 | 0.62 |
| '05-'06 | 9.64 | 9.68 | 2.83 | 2.86 | 3.48 | 3.5 | 0.62 | 0.61 | 0.42 | 0.42 |
| '06-'07 | 5.13 | 5.18 | 1.14 | 1.18 | 1.92 | 1.95 | 0.37 | 0.36 | 0.29 | 0.29 |
| Overall average | 11.92 | 11.95 | 3.58 | 3.6 | 4.6 | 4.63 | 0.87 | 0.86 | 0.42 | 0.42 |

We see that the estimates are very similar for the two inference methods.

## S6. Comparison of our method to Poisson regression models with an exponential link

In this section compare the results of our main inference model with inference obtained through the Poisson regression method, considering an exponential link between incidence and mortality, [7,8]. We consider the following three choice of the Poisson regression inference model

**Model 1**: (adopted from [8]): The weekly influenza incidence proxies associated with the 3 major subtypes A/H3N2, A/H1N1 and B are defined as the percent of respiratory

specimens testing positive for those subtypes, and the baseline is modeled as a linear combination of the sine and the cosine functions.

**Model 2**: Same influenza incidence proxies as in Model 1 except the A/H3N2 proxy which is split into the pre and post-Fujian periods (before and starting the 2003-04 season). The baseline is modeled by periodic cubic splines, and separate baselines are considered before and starting 2001 (pre- and-post PCV baselines). The incidence proxies are shifted forward between 1 and 2 weeks as in equation (4) in the main body of the text.

**Model 3**: Same inference framework as in Model 1 except that the incidence proxies for the 3 major subtypes are defined as the percent of respiratory specimens testing positive for those subtypes, weighted by the regional populations in the US.

For each choice of a model, weekly estimates of influenza-associated deaths were obtained for each subtype by subtracting predicted values for the model where the virus subtype covariate is set to zero from predicted values for the full model. Weekly influenza-associated deaths were summed for each viral subtype across the influenza season to obtain seasonal estimates [8]. eTable 6 summarizes the comparison results for all cause, respiratory and circulatory deaths for models 1-3, and our main inference model. Since for our main inference model, the outcomes are mortality rates per 100,000, while for models 1-3, those are mortality counts in the US population, we have scaled the outcomes and the covariates and used weighted least squares to compare the AIC score in our main model with the AIC scores in models 1-3.

**eTable 6**: Poisson regression model estimates for the average flu-associated mortality rates per 100,000 for select underlying causes.

| | All cause | | Respiratory | | Circulatory | |
|---|---|---|---|---|---|---|
| Inference model | Annual average | AIC score | Annual average | AIC score | Annual average | AIC score |
| Model 1 | 13.52 | 23912 | 3.62 | 18896 | 5.06 | 14409 |
| Model 2 | 15.17 | 14034 | 4.49 | 10556 | 5.85 | 9754 |
| Model 3 | 17 | 13588 | 5.14 | 9888 | 6.59 | 9625 |
| Main model (equ. 3) | 11.9 | 8663 | 3.6 | 7234 | 4.6 | 7800 |

The estimates for our main model are 11.92 all cause deaths per 100,000, 3.58 respiratory deaths and 4.6 circulatory deaths, which are reasonable close to Model 1 estimates. We see that our main inference model gives the best fits for the data. Moreover Models 2 and 3 give significantly better fits to the data compared to the more "crude" Model 1 (with Model 3 giving better fits than Model 2). However the average mortality estimates in those models are higher than the ones in Model 1, and further away from the estimates for our main model.

Given that the regression coefficient associated with A/H1N1 was negative for some of the models (e.g. respiratory deaths in Models 1-3, all cause deaths in Model 2, etc., with

A/H1N1's contribution excluded from the corresponding estimates), we performed a separate analysis for the above model with A/H1N1 excluded from the inference framework (compare with section S3). eTable 7 summarizes the inference results.

**eTable 7:** Poisson regression model (with A/H1N1 excluded) estimates for the average flu-associated mortality rates per 100,000 for select underlying causes.

| | All cause | | Respiratory | | Circulatory | |
|---|---|---|---|---|---|---|
| Inference model | Annual average | AIC score | Annual average | AIC score | Annual average | AIC score |
| Model 1 | 13.07 | 23964 | 3.61 | 18900 | 4.74 | 14483 |
| Model 2 | 15.18 | 14033 | 4.49 | 10564 | 5.78 | 9753 |
| Model 3 | 16.74 | 13591 | 5.12 | 9887 | 6.42 | 9630 |
| Main model (equ. 3) | 11.9 | 8663 | 3.6 | 7234 | 4.6 | 7800 |

We see that overall that the exclusion of A/H1N1 had a modest effect on the average estimates, with the biggest impact being in Model 1.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