Epidemiology of influenza strains: competition, prediction, and associated mortality

Joint work with:

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Data

US CDC data between 1997-2008 on weekly doctor visits associated with influenza like illness (ILI) and sub-typing of collected respiratory specimens.

Hypotheses tested

- Dynamics of influenza A/H3N2, A/H1N1 and B, are interdependent
  - High incidence of one strain limits same-season incidence of others
- Proxies for incidence of each strain early in a season predict cumulative magnitude of these same proxies for the remainder of the season.

Prior evidence on interference between strains

- H3N2 infection reduced same-season risk of H1N1 infection in schoolchildren (Sonoguchi et al. 1985)
- Seasonal influenza A in 2008-9 associated with lower risk of lab-confirmed pandemic H1N1 infection (Cowling et al. 2010)
- Strong, transient, subtype-transcending immunity required to produce realistic patterns of sequence diversity in simulations (Ferguson et al. 2003 and Tria et al. 2005)
- Transmission model estimated cross-immunity among H3N2, H1N1 and B (Cobey et al. in preparation)

Weekly incidence proxy

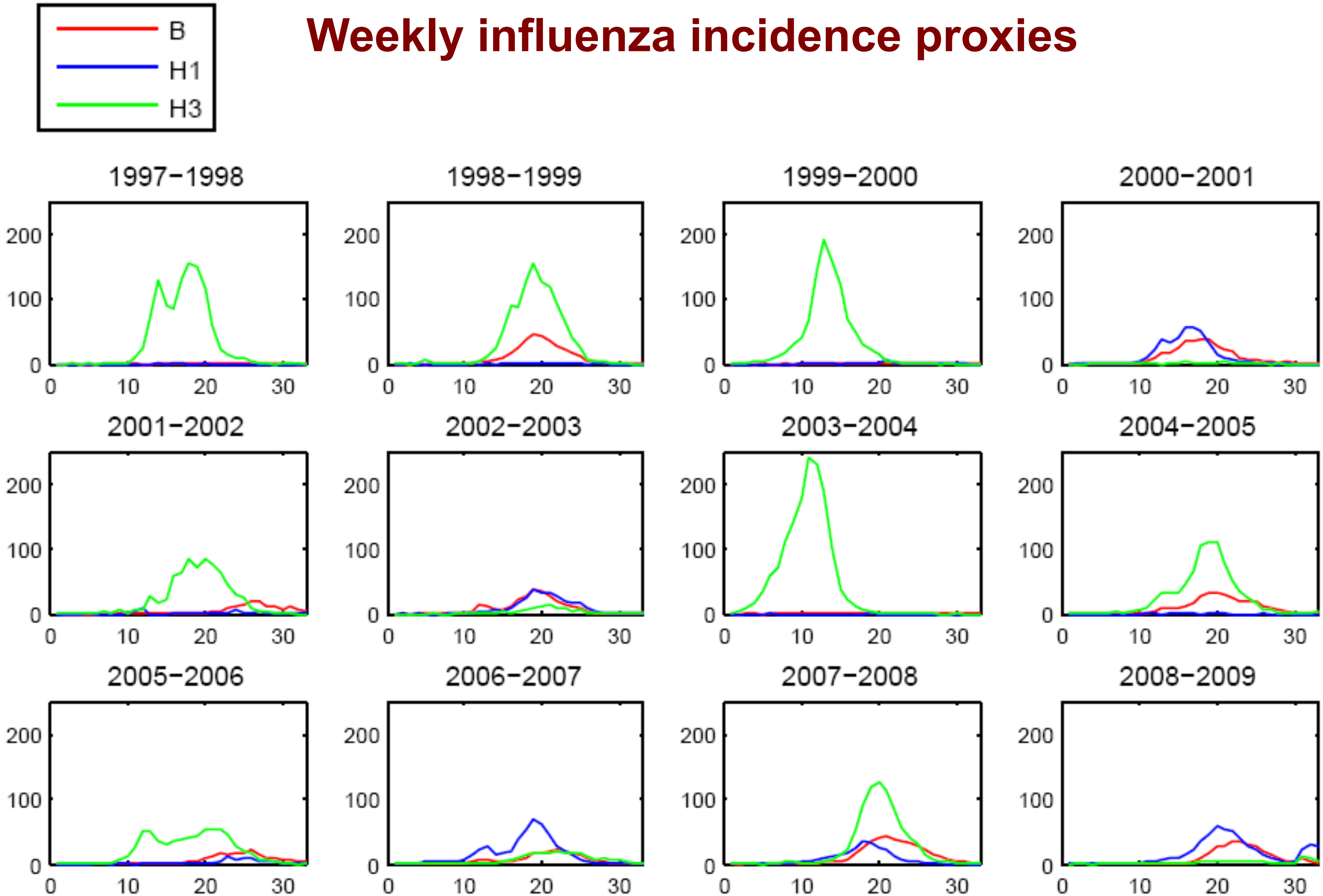
- Season runs calendar week 40 – week 20 (CDC definition)
- Proxy measure of weekly strain-specific incidence:

proportion of ILI among all visits to sentinel practices x

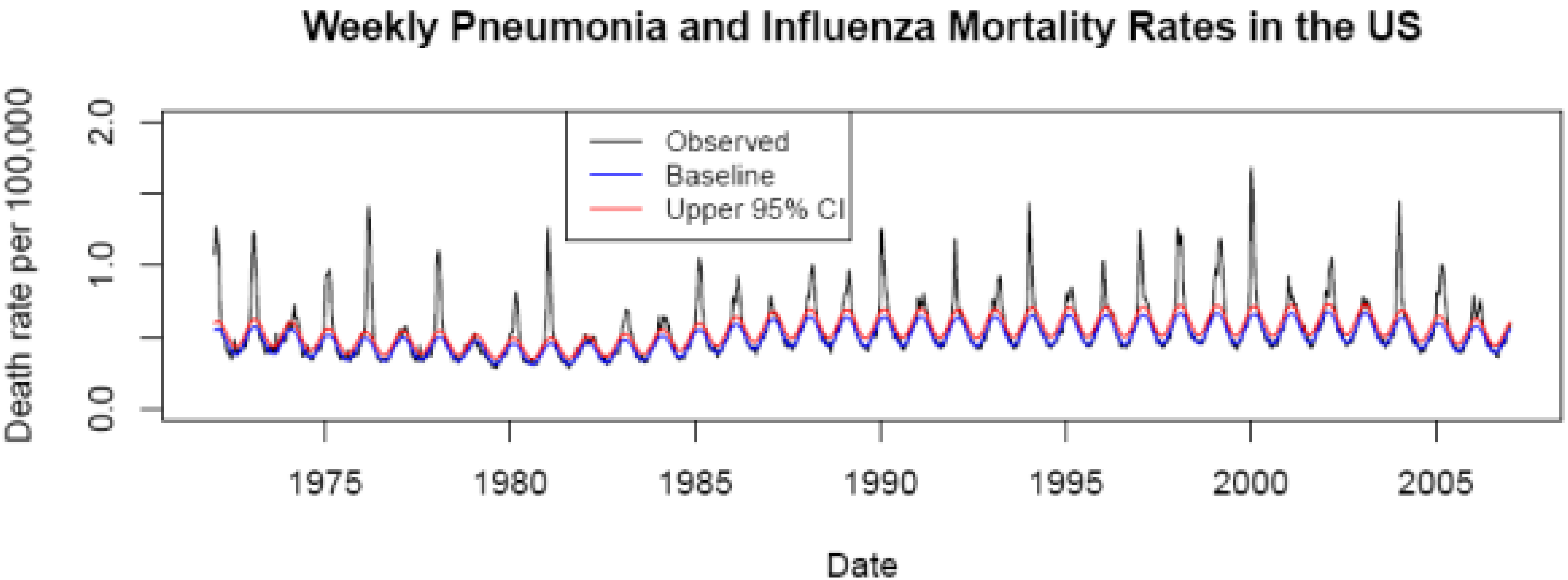
proportion of respiratory viral isolates tested that are positive for a particular strain

  - Population-weighted average across CDC regions
- Proxies cannot be compared across strains, only within strain across time

Weekly influenza incidence proxies



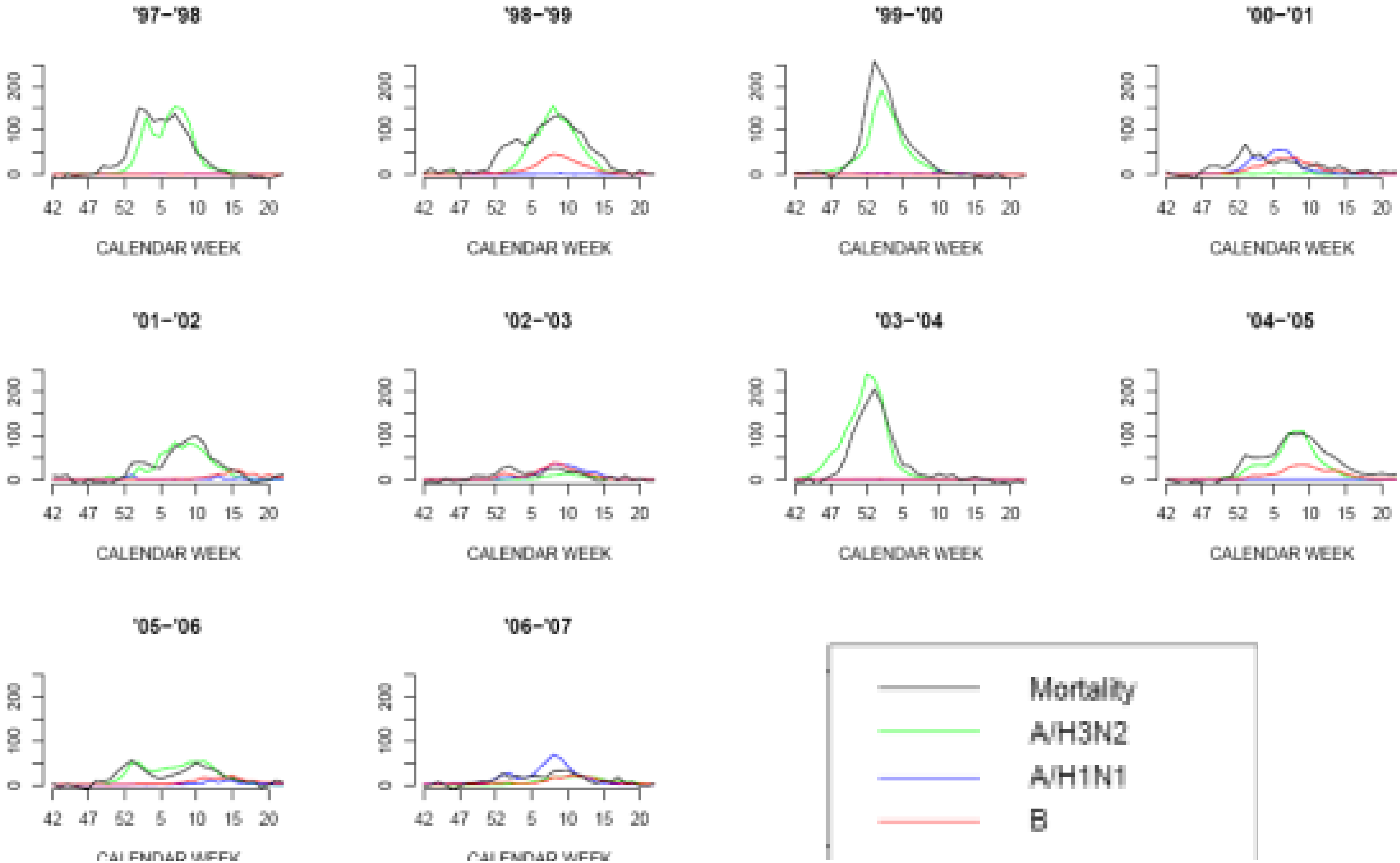
Comparison with excess Pneumonia and Influenza mortality



$$Base(t) = a \cdot \sin\left(\frac{2\pi t}{52.2}\right) + b \cdot \cos\left(\frac{2\pi t}{52.2}\right) + c + d \cdot t + e \cdot t^2 + \ldots$$

- The coefficients are fitted to mortality data during the weeks of low flu circulation.
- Excess mortality is defined as observed mortality – baseline.

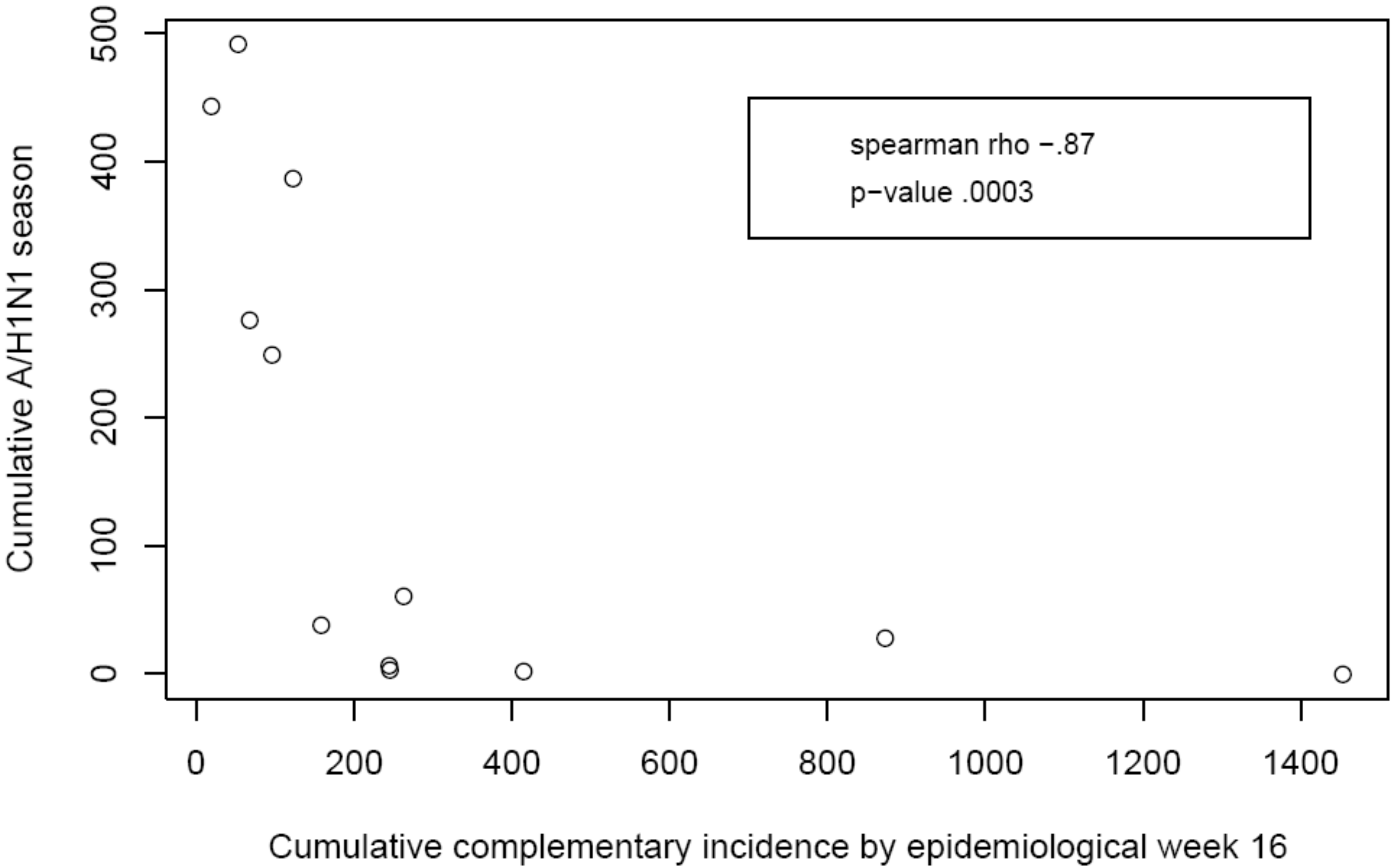
Influenza incidence proxies shifted forward by two weeks vs. excess Pneumonia and Influenza (P&I) mortality



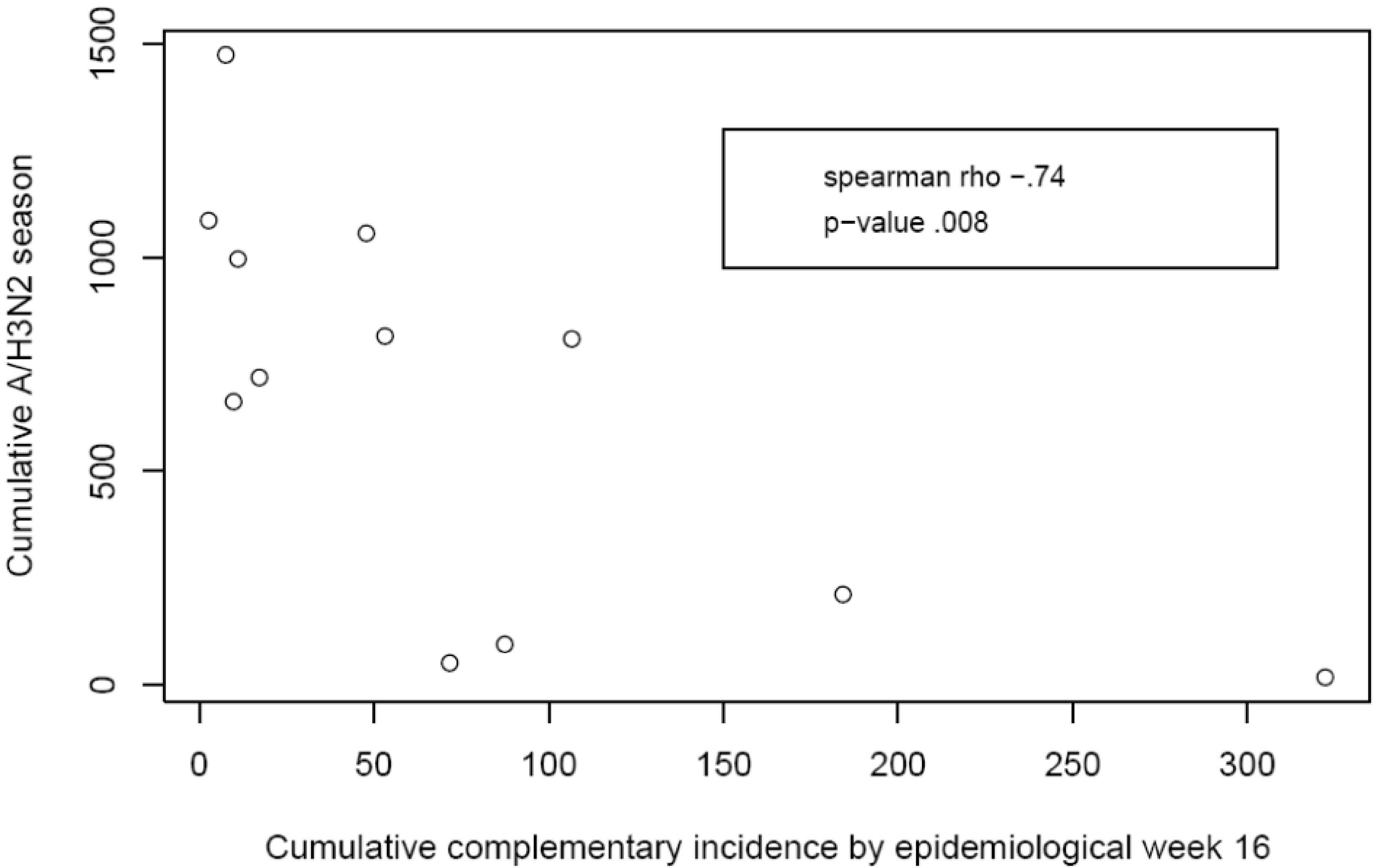
Association between early activity of other strains and total activity of each strain of interest

- For a each strain (which we call the "index strain"), we compare the cumulative incidence of the other two strains combined (the complementary incidence) up to each of several possible calendar weeks (2,3,4, and 5) against the cumulative incidence of the index strain for that entire influenza season.
- We examine the Spearman rank correlation between those pairs of numbers for each choice of index strain and calendar week for the 12 years in the data.
- Negative association was observed for all index strains for each of the four chosen calendar weeks.

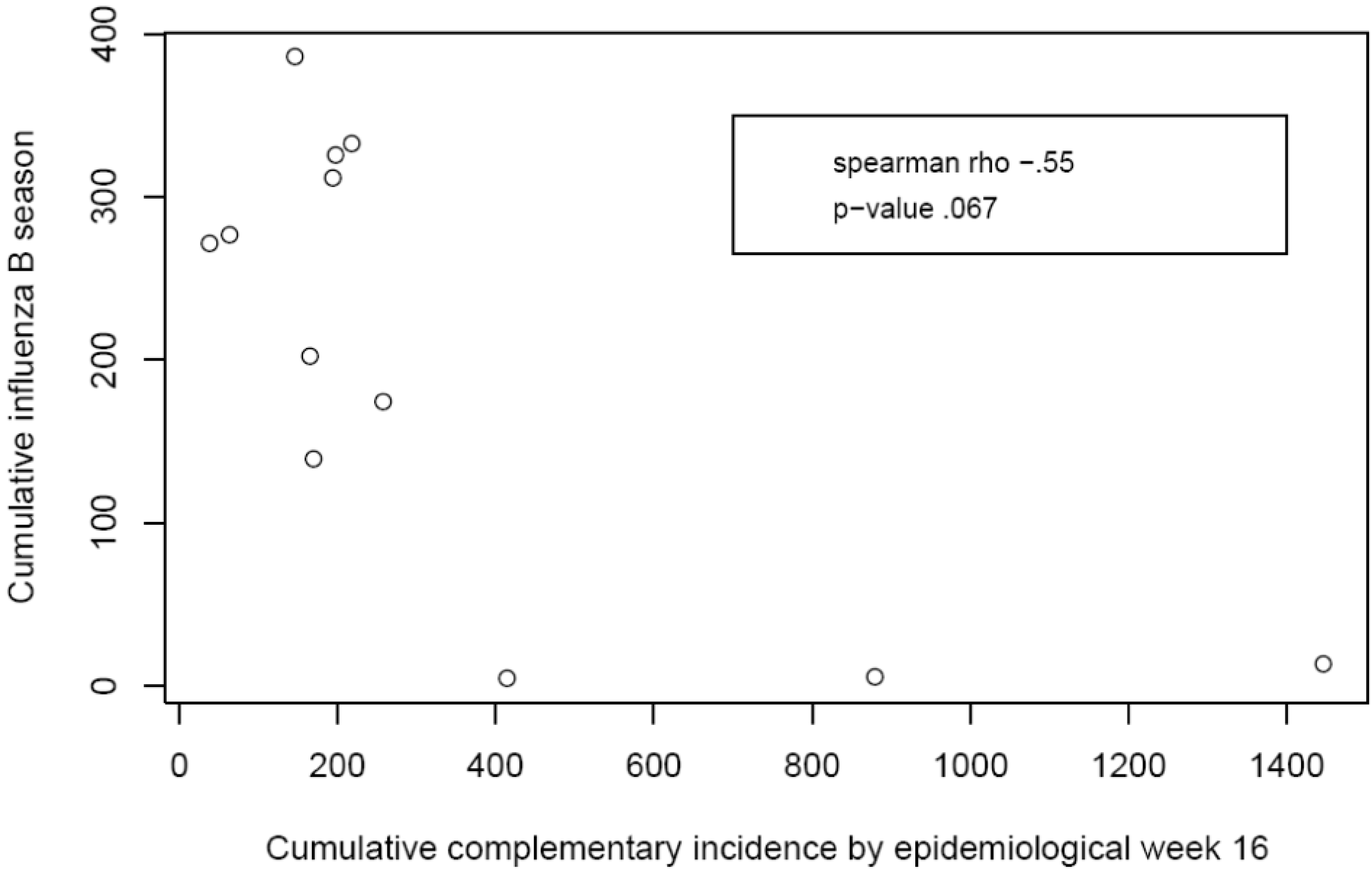
Influenza A/H1N1, calendar week 3 (epidemiological week 16)



Influenza A/H3N2, calendar week 3 (epidemiological week 16)



Influenza B, calendar week 3 (epidemiological week 16)



Potential reasons for the negative correlation

The negative association between strains' incidences may arise from either or both of two mechanisms:

- Early complementary incidence may slow the spread of the index strain.
- Early, rapid spread of the index strain may slow the spread of the complementary strains.

Because A/H3N2 is the only strain that had large, early epidemics and showed a negative and significant correlation between its early incidence and the subsequent incidence of the other strains, the data most strongly support the idea that A/H3N2 incidence interferes with the circulation of other strains.

Prediction method

- We follow influenza incidence in time until either the cumulative incidence of the index strain in the last 5 weeks surpasses a certain threshold h or the cumulative complementary incidence surpasses a certain threshold h_c.
- When either of these conditions is met (stopping week s), the cumulative season for the chosen strain is predicted linearly in terms of its growth rate proxy on week s as well as s itself.
- Prediction accuracy for a choice of thresholds is measured by the residual standard error (RSE) computed from the available US CDC data.

Growth rate predictor and stopping time

$I(t)$ Incidence on week t

X Growth rate predictor

$$X = \frac{I(s) + I(s-1)}{\max(h, I(s) + \ldots + I(s-4))}$$

• Rate of transmission of influenza is affected by seasonal forcing

Larger pool of susceptibles (e.g. novel Fujian H3N2 strain in 2003)

↓

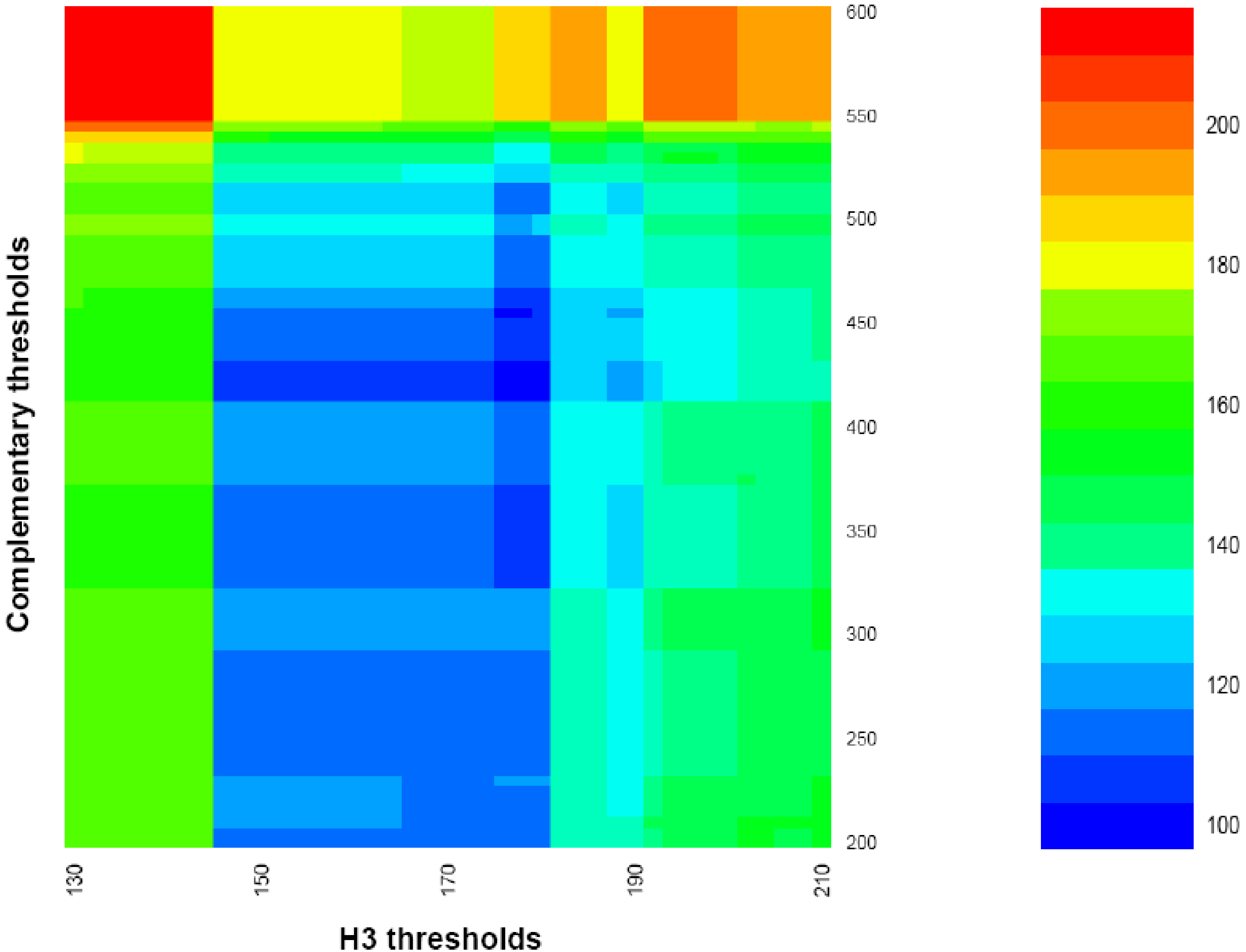
Earlier threshold crossing / Sub-optimal conditions for transmission

↓

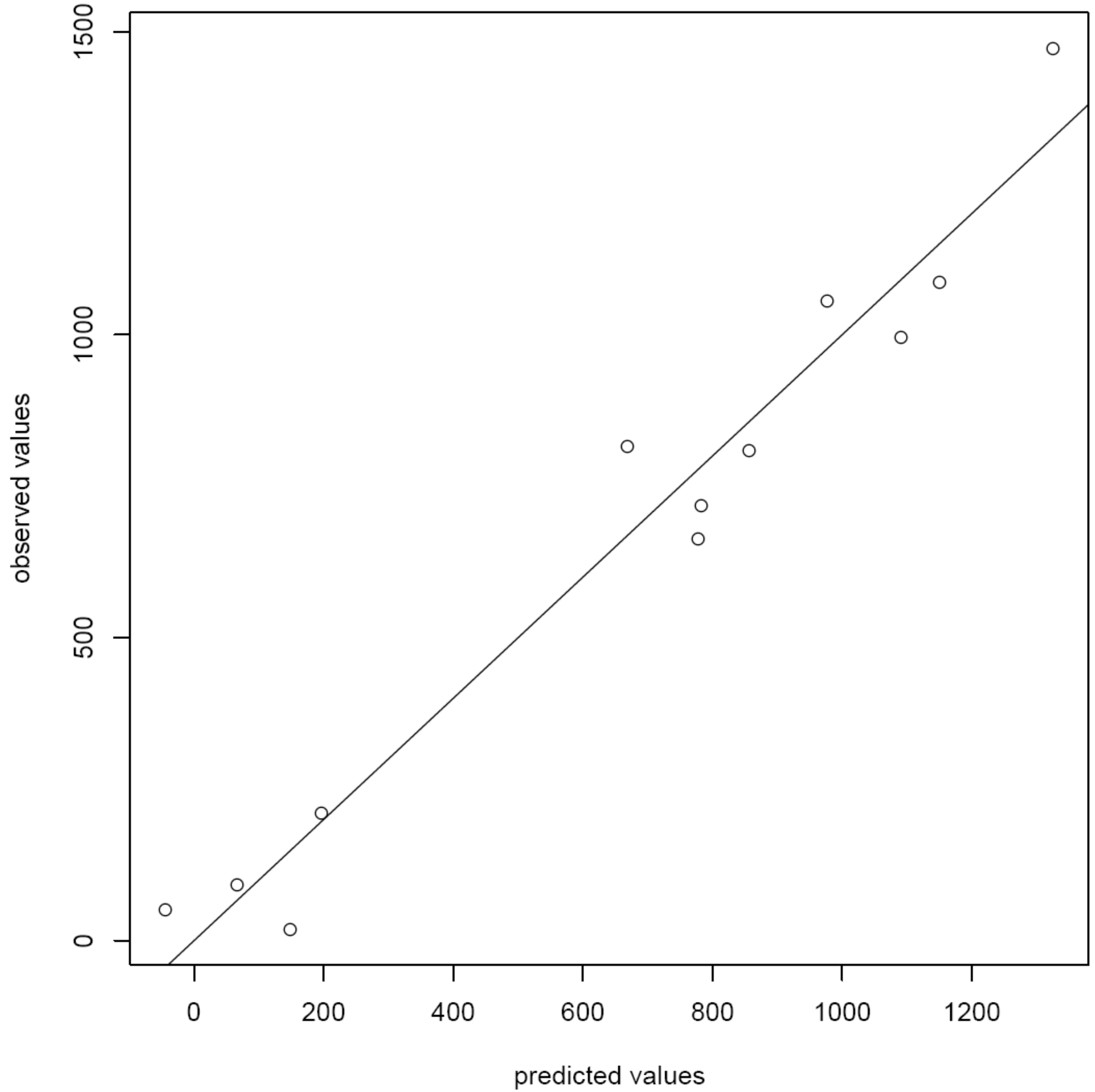
Growth rate doesn't fully reflect on season's potential

• We adjust for seasonality in influenza transmission by adding the stopping time s as an additional covariate in the regression

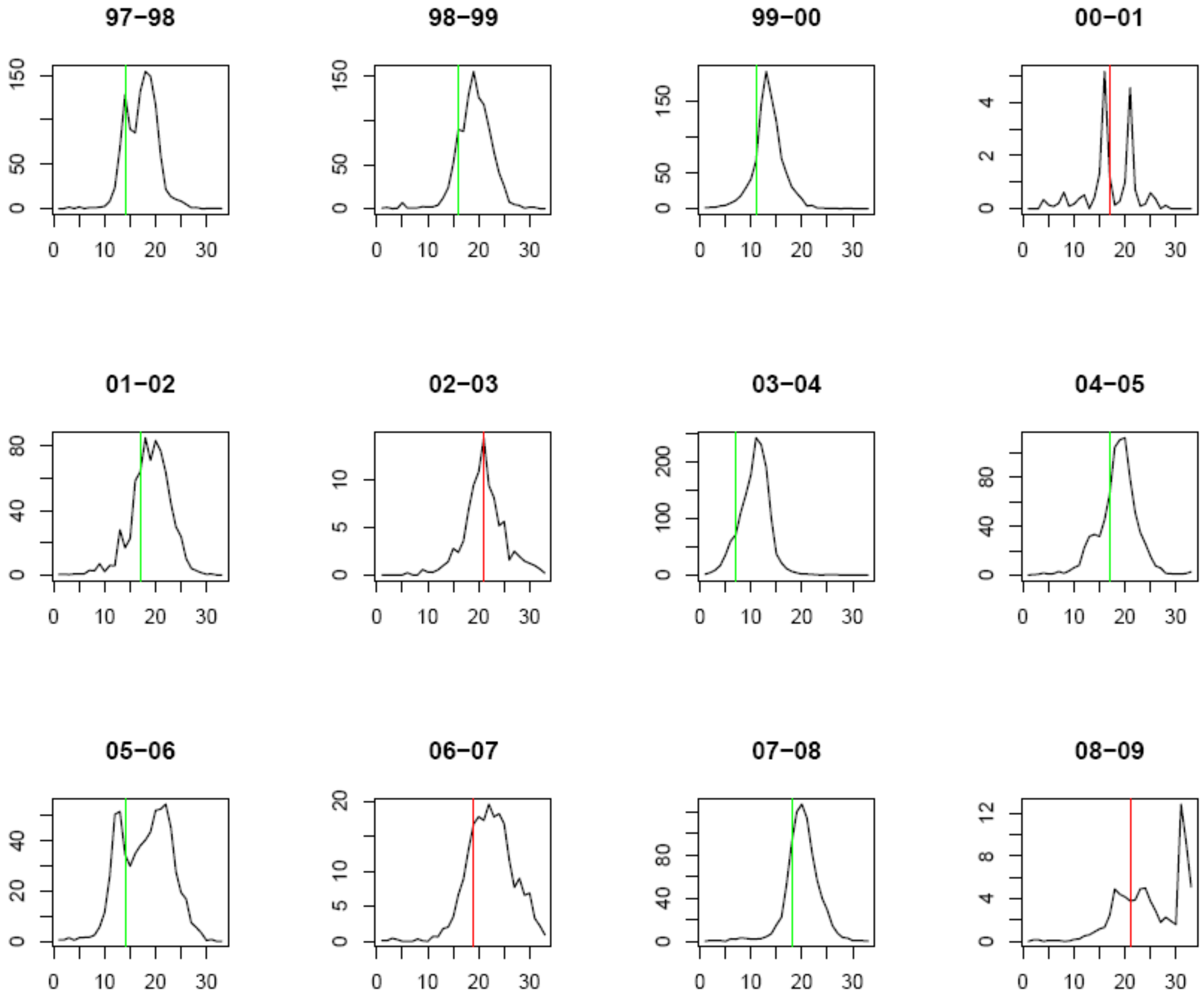
A/H3N2, RSE for prediction for different thresholds



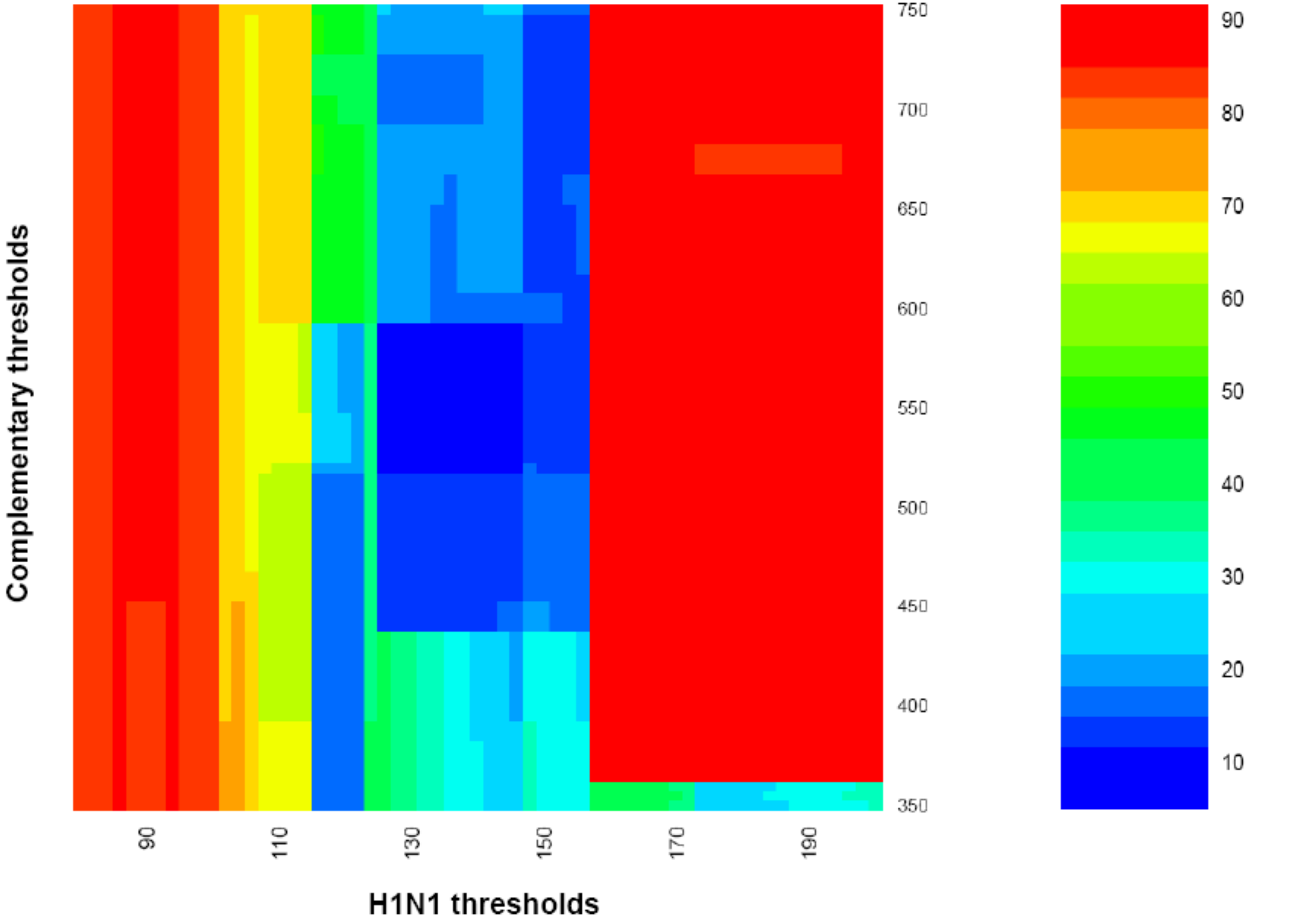
A/H3N2 prediction results



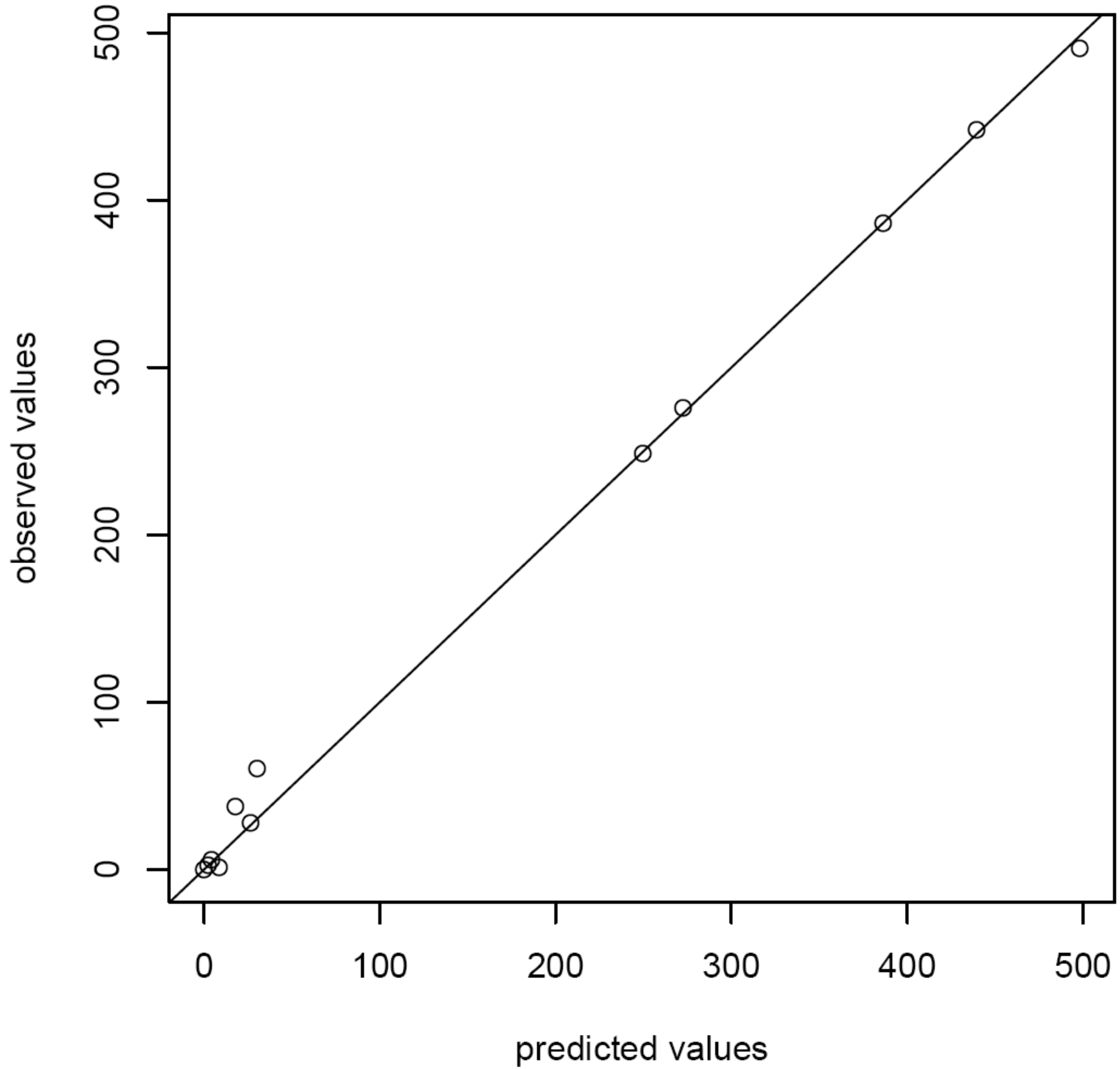
A/H3N2, timing of prediction



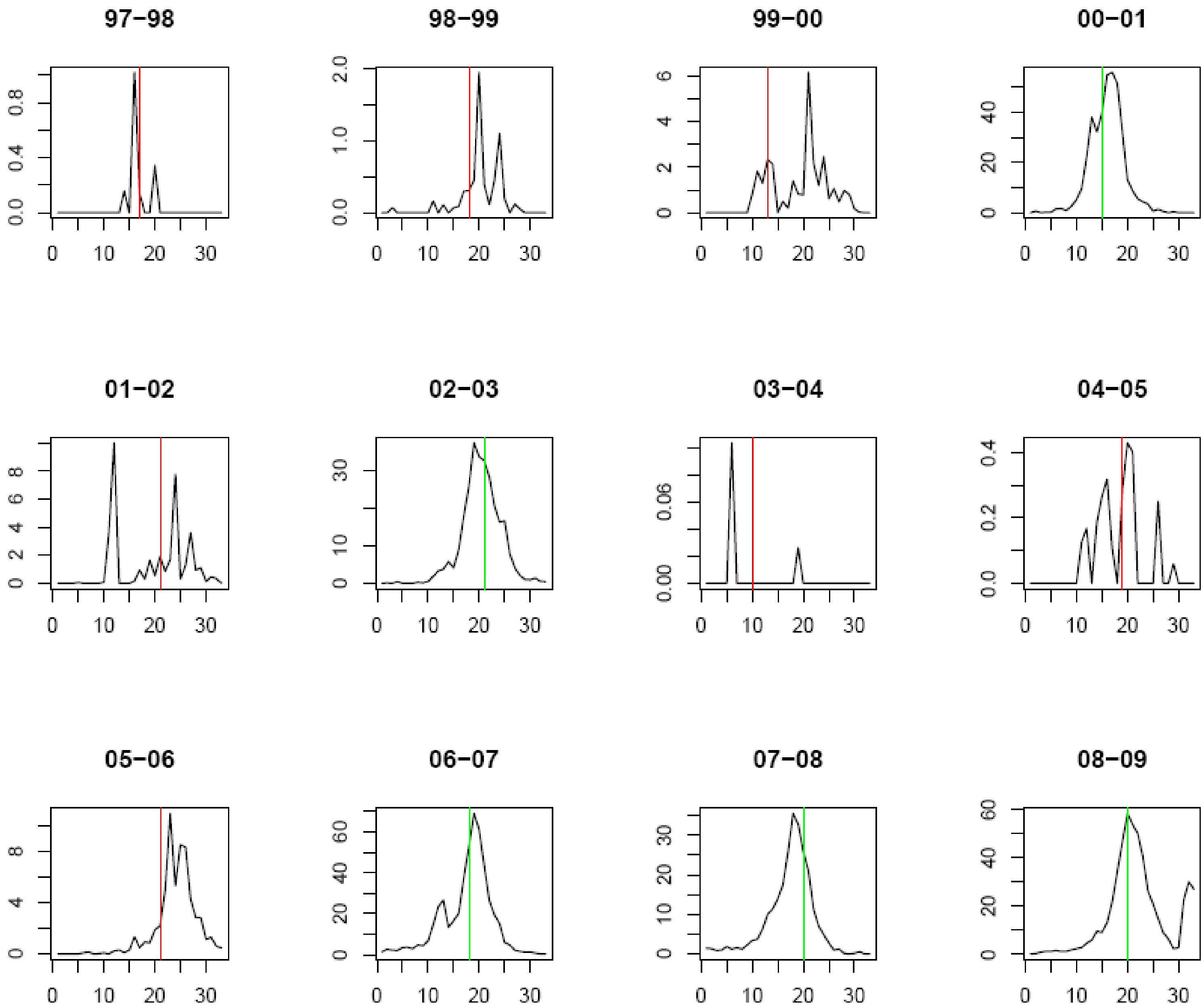
A/H1N1, RSE for prediction for different thresholds



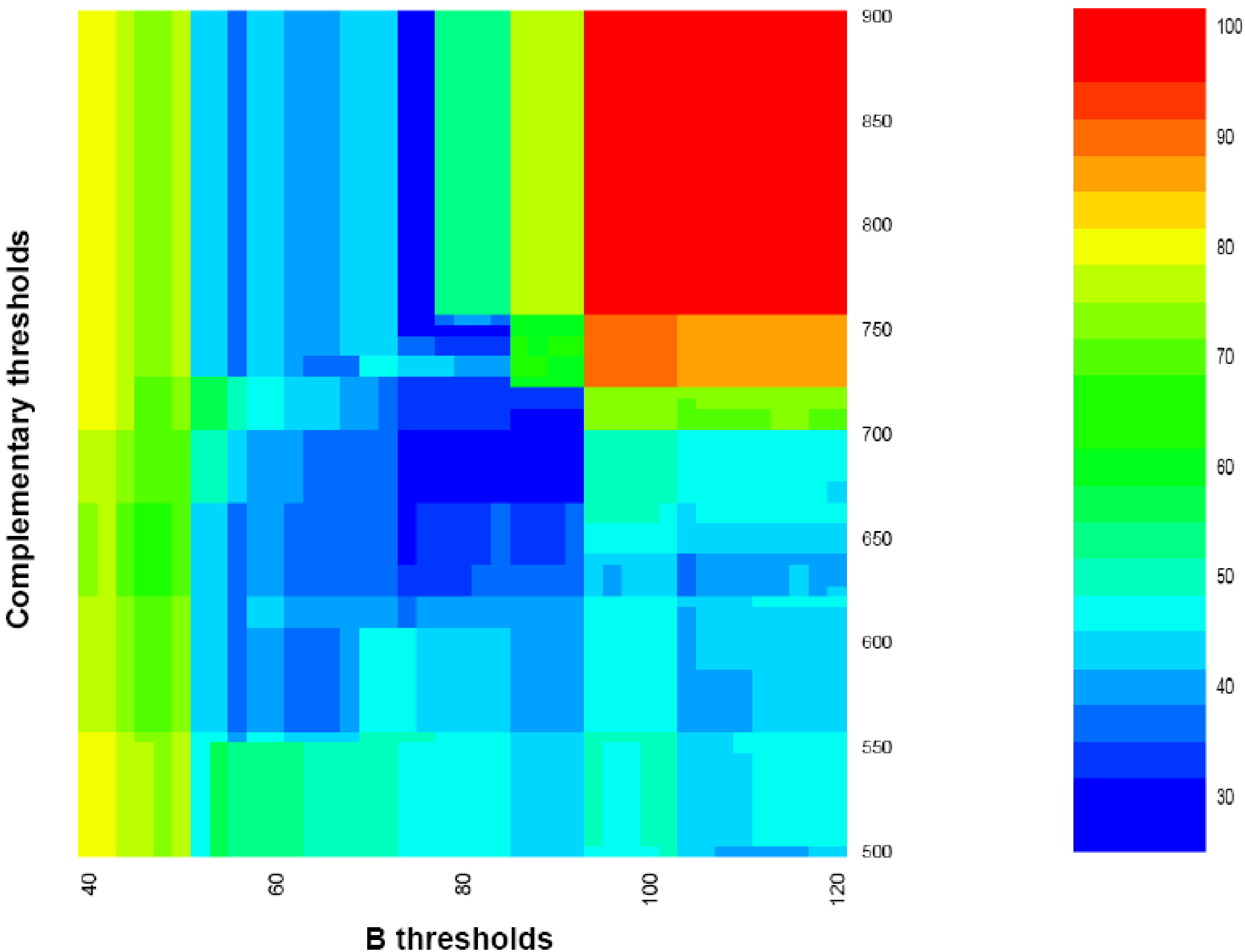
A/H1N1 prediction results



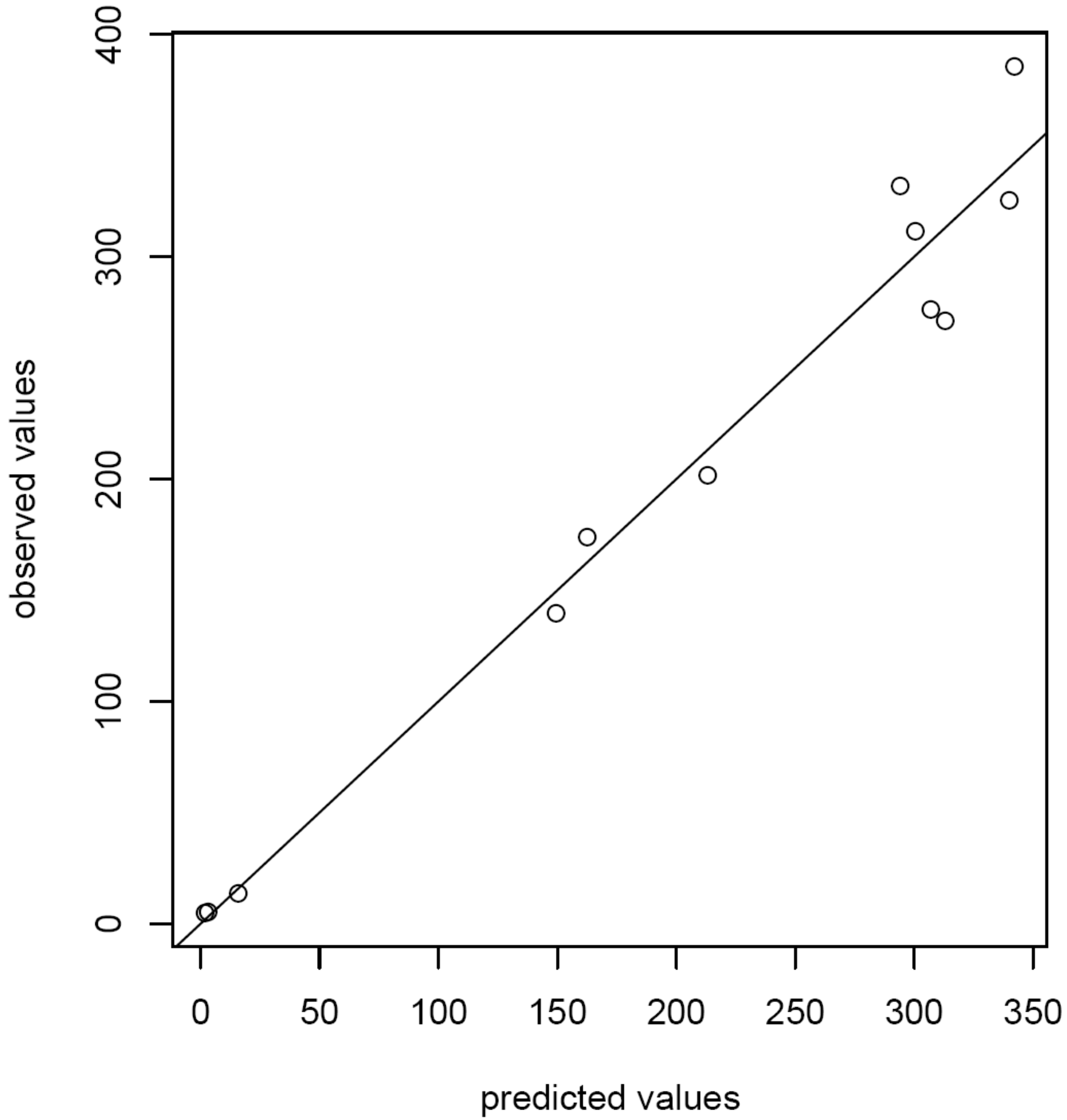
A/H1N1, timing of prediction



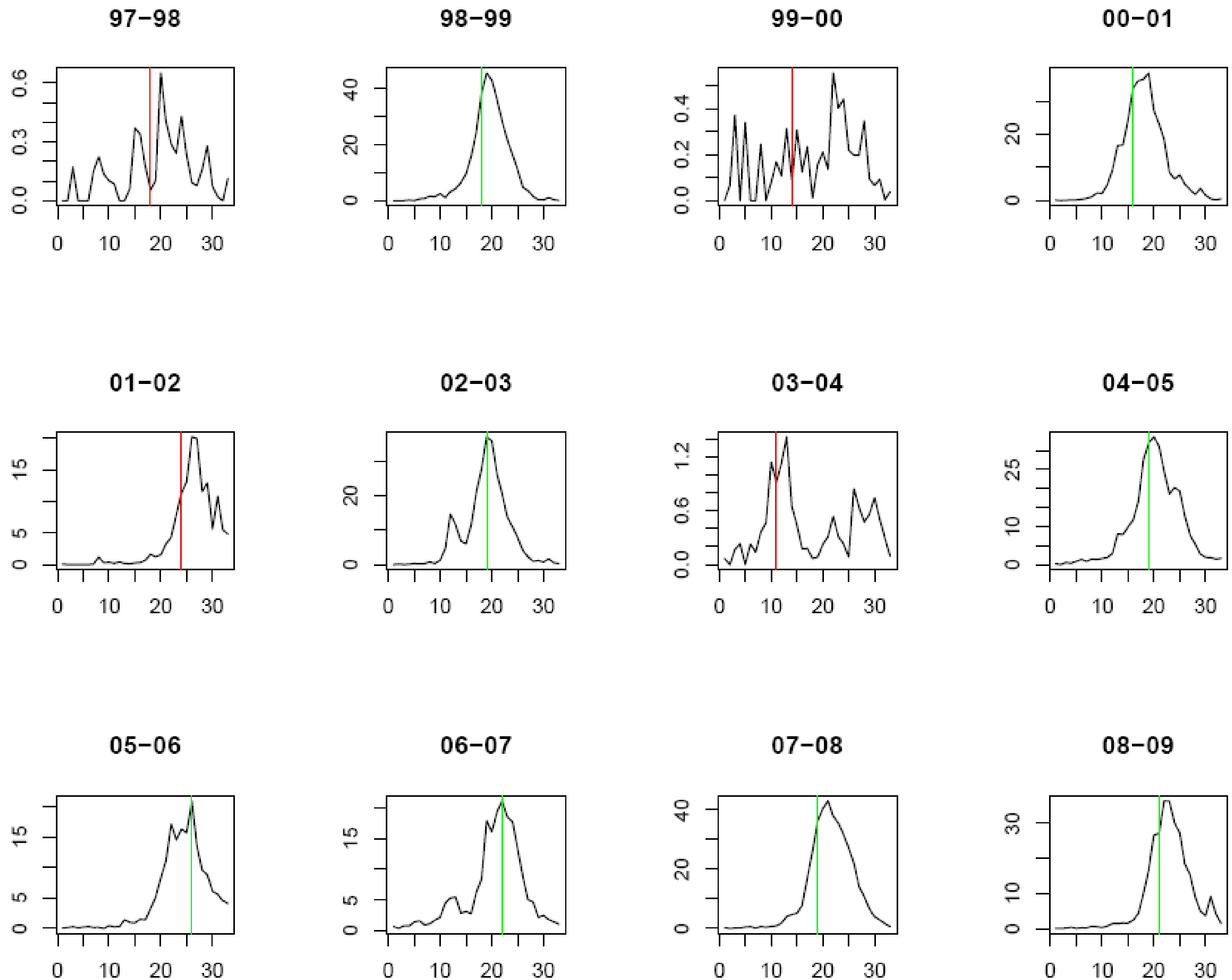
Influenza B, RSE for prediction for different thresholds



Influenza B prediction results



Influenza B, timing of prediction

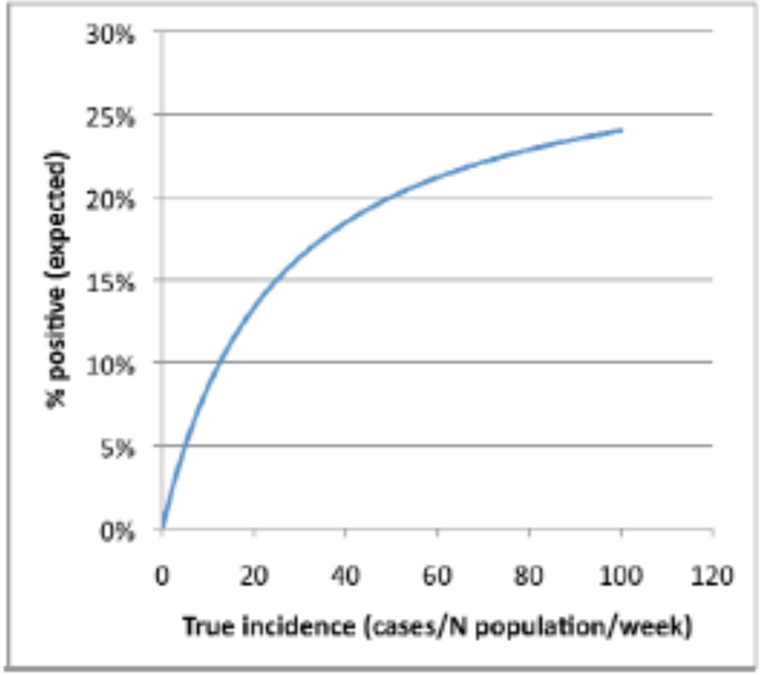


Limitations of current methods for estimation of influenza associated mortality

1. Assume sinusuoidal baseline of non-influenza mortality

2. Assume constant baseline non-flu mortality
   - Post-pneumococcal conjugate vaccine (PCV) introduction, change in shape of baseline

3. Flu measured as % of respiratory specimens testing positive
   - Does not account for increased testing in flu season
   - Not linearly related to incidence



Limitations of current methods (2)

4. Poisson regression assumes flu cases multiply, rather than add to mortality
- If 1000 cases = 1 death, then 2000 cases = 2 deaths: violated by Poisson regression with log link
5. No allowance for change in CFR for novel antigenic variants (e.g. H3N2 Fujian)
6. Recently CDC guidelines: no effort to account for causes of death beyond respiratory & circulatory

Basic model relating incidence and mortality

$M(t)$ Mortality on week t (data for 539 consecutive weeks)

$H3(t), H1(t), B(t)$ Incidence proxies for the three strains

$H3(t) = H3^1(t) + H3^2(t)$ Pre-and-post Fuji A/H3N2 incidence

$Base(t) = Base_1(t) + Base_2(t)$ Pre-and-post PCV annual mortality baselines, modeled by periodic cubic splines

$Trend$ A polynomial in calendar year

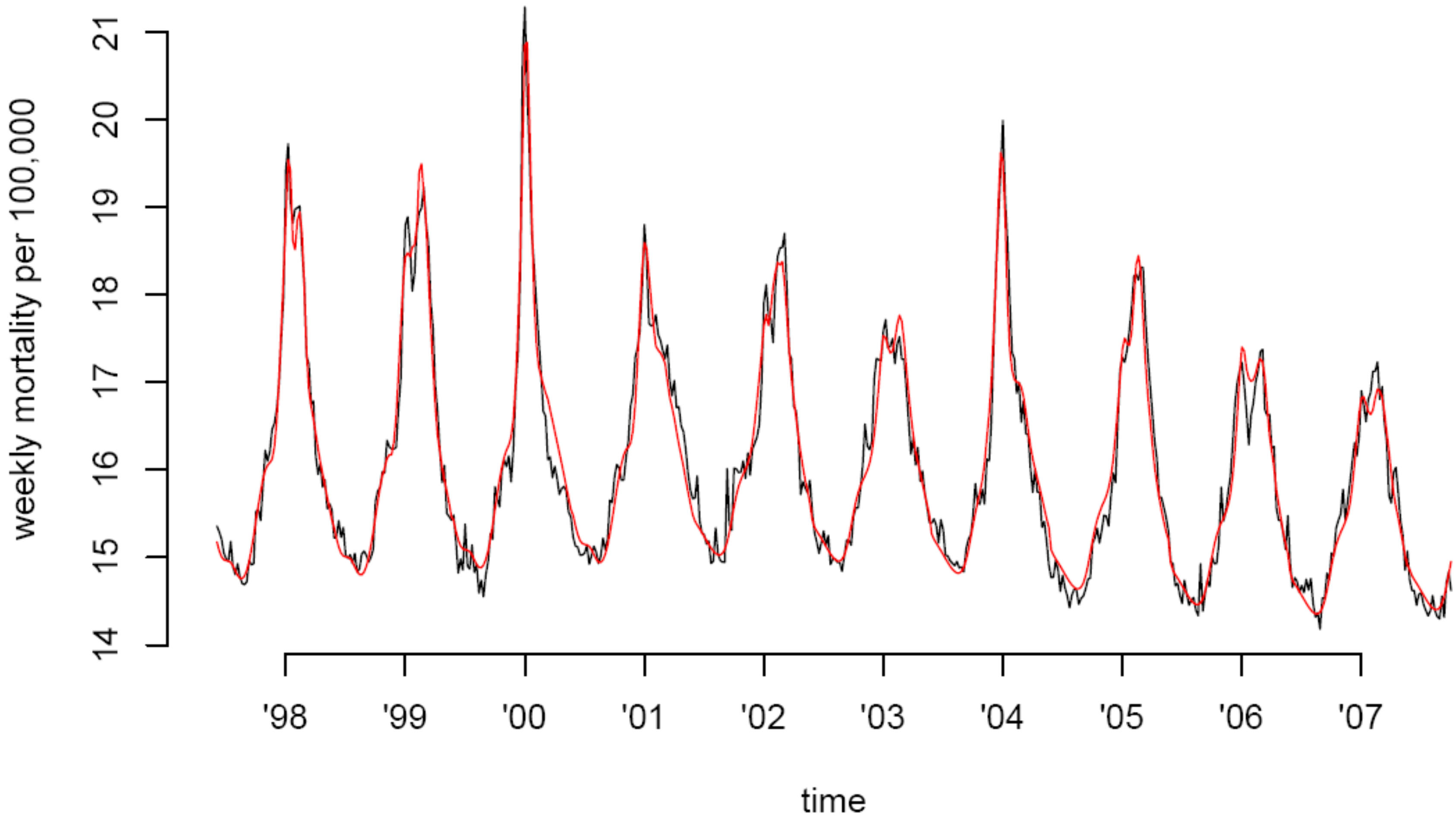
Mortality = Flu Contribution + Trend + Baseline + Noise

$$M(t) = \beta_{H3^1} \cdot S(H3^1(t)) + \beta_{H3^2} \cdot S(H3^2(t)) + \beta_B \cdot S(B(t)) +$$

$$+ Base_1(t) + Base_2(t) + Trend + N(t)$$

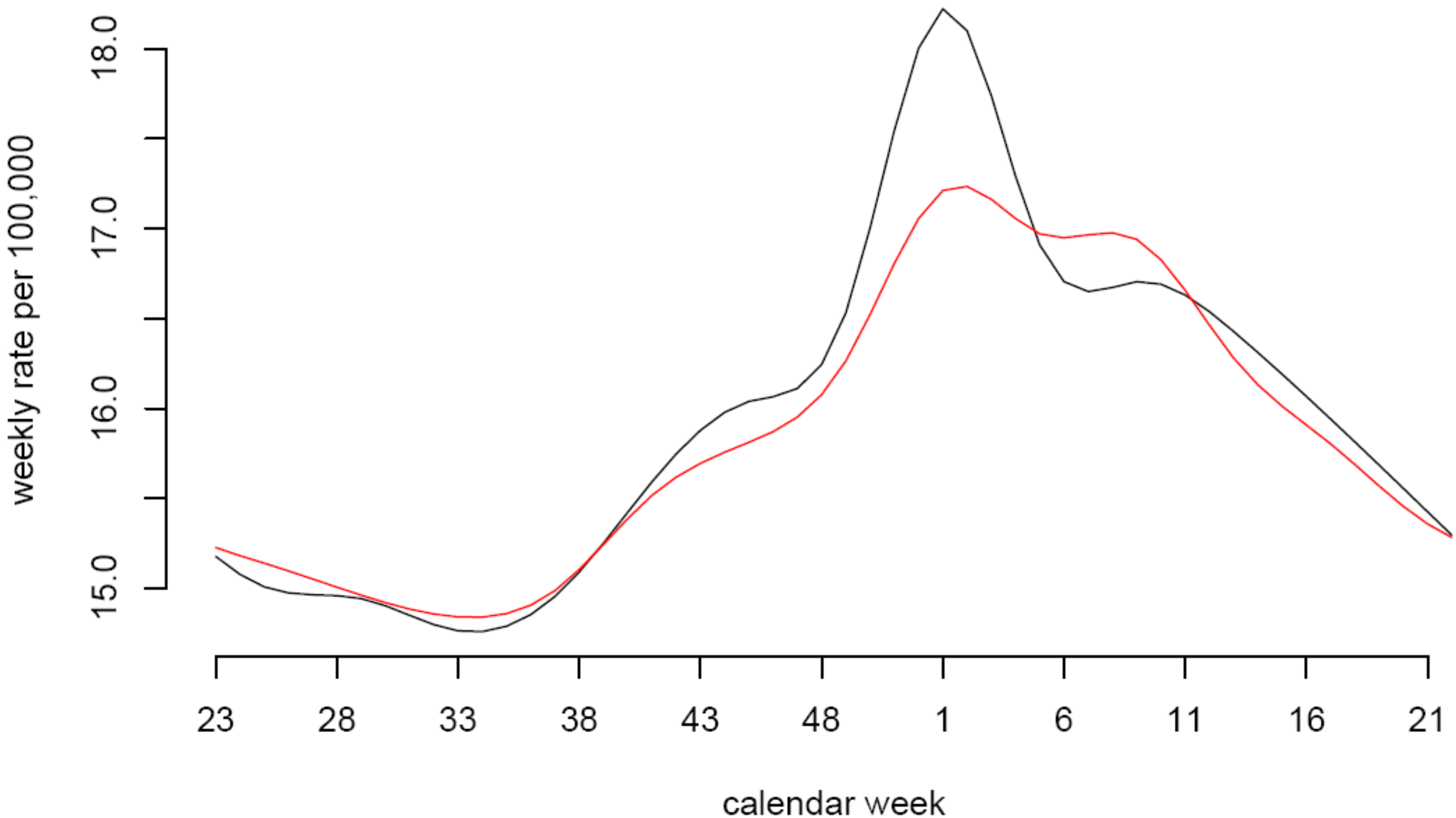
S - forward shift between 1-2 weeks

All cause mortality model fit (1997-2007)



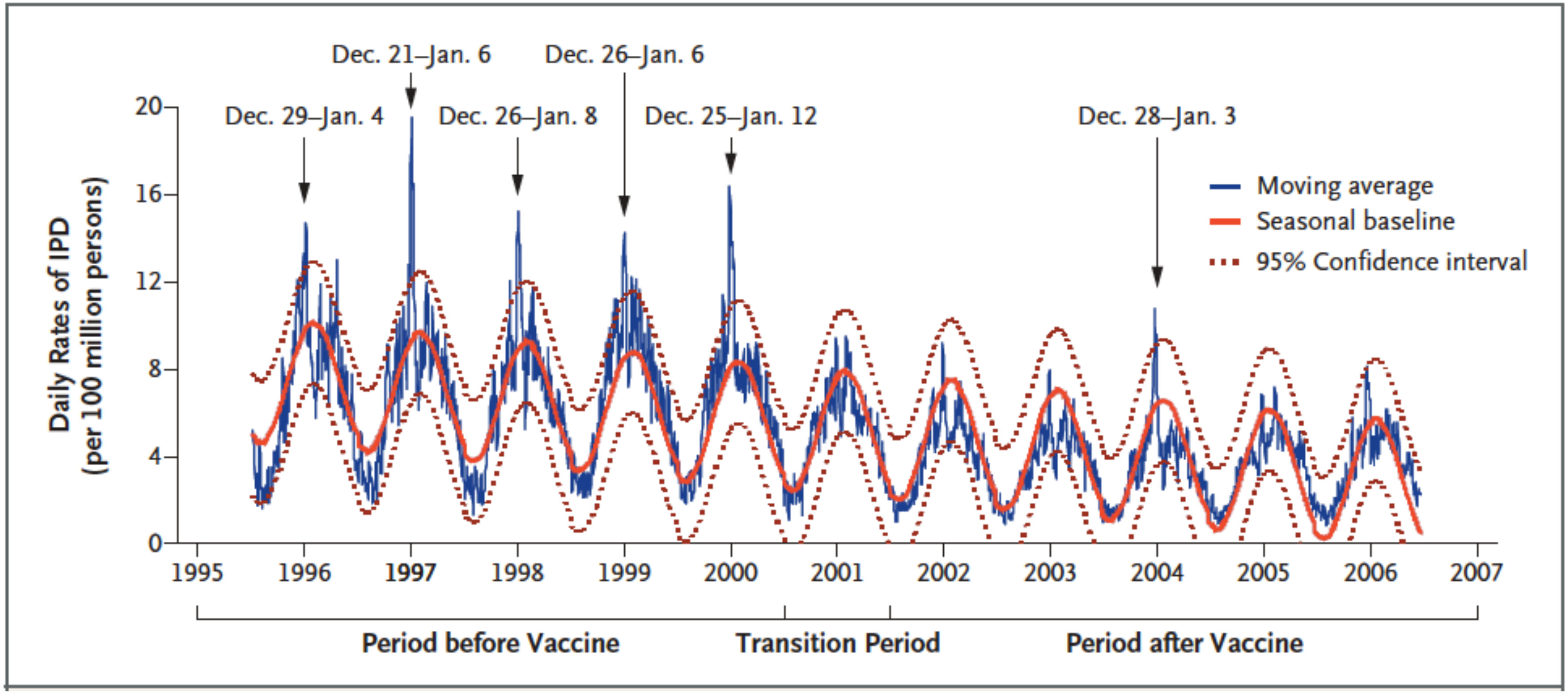
Actual (black) vs. fitted (red) weekly mortality

All cause mortality baseline change



Pre-PCV (black) vs. post-PCV (red) mortality baselines

Similar phenomenon seen for invasive pneumococcal disease



ND Walter et al. *NEJM* 2009

Influenza subtype-specific mortality estimates, 1997-2007

Cause	β^1_{H3}	β^2_{H3}	β_B	R^2	Average rate per 100,000
all cause	15.057 (12.89,17.24)	10.8447 (8.94,12.88)	14.0736 (6.72,21.45)	.9613	11.92 (10.17,13.67)
circulatory	6.0704 (5.04,7.06)	3.7888 (2.87,4.71)	5.5617 (2.07,9.07)	.9777	4.6 (3.79,5.39)
respiratory	5.2167 (4.52,5.9)	3.8455 (3.18,4.49)	1.6425 (-0.81, 4.09)	.9587	3.58 (3.04,4.14)
cancer	1.1516 (0.91,1.4)	0.6165 (0.41,0.83)	1.22 (0.44,1.98)	.8272	0.87 (0.68,1.05)
diabetes	0.3561 (0.27,0.44)	0.2442 (0.17,0.32)	0.6048 (0.34,0.88)	.8932	0.33 (0.26,0.39)
Alzheimer's	0.2783 (0.13,0.42)	0.3380 (0.2,0.47)	1.0908 (0.61,1.57)	.9631	0.41 (0.3,0.52)
renal disease	0.2027 (0.14, 0.26)	0.1838 (0.13,0.24)	0.2821 (0.08,0.49)	.8943	0.19 (0.14,0.24)

Near additivity between all cause and specific cause flu-attributed mortality

Comparison with the current CDC estimates

- Recent CDC methodology (2010) uses circulatory and respiratory (C&R) deaths only in assessing influenza associated mortality, estimating 11.4 annual influenza associated C&R deaths per 100,000 between 1997-2007
- Our annual estimate for the rate of flu contribution to mortality for the same period is 8.2 C&R deaths and 11.9 all cause deaths
- Besides C&R deaths, we exhibit a statistically significant contribution of flu to mortality for diabetes, cancer, Alzheimer's disease, renal disease, and chronic liver disease
- Further work is needed to compare different estimation procedures