Incidence prediction in seasonal H3N2 influenza: incorporating evolution into population dynamics

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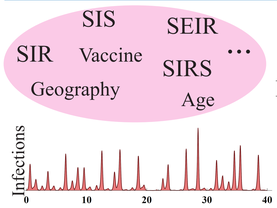
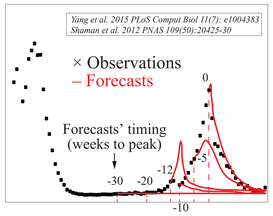
ABSTRACT

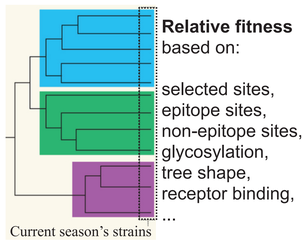
Inter-pandemic or seasonal influenza exacts an enormous annual burden in terms of global human health and economic impact to society. Incidence prediction ahead of season remains a challenge largely because of the virus' antigenic evolution. We propose here a forecasting approach that incorporates evolutionary change into an epidemiological model, and remains sufficiently parsimonious for parameter estimation based on retrospective surveillance. The proposed models link amino-acid sequences of hemagglutinin epitopes with a transmission model for seasonal H3N2 influenza, also informed by H1N1 levels. With a monthly time series of H3N2 incidence in the United States over 10 years, we demonstrate the feasibility of prediction ahead of season and present a forecast for the upcoming 2016/2017 season.

INTRODUCTION: current scope of influenza forecast



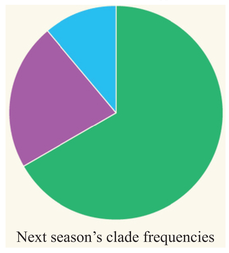
Epidemiological forecasts within season
(lead time of weeks)



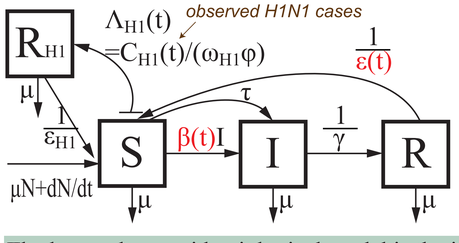


Purely Evolutionary forecasts

Bush et al. 1999 Science 286(5446):1921-25
Koelle et al. 2014 Nature 507:47-8
Lukzsa et al. 2014 Nature 507:57-61
Neher et al. 2014 eLife 3:e03568



METHODS: Model for Seasonal H3N2 with H1N1



- **Transmission**: $\beta(t)=e^{(\sum_6 \omega_i s_i(t)+\omega_\beta D(t))}(d\Gamma/dt)$
  seasonality *Gamma noise*
- **Immunity loss**: $\varepsilon(t)=\varepsilon_0 e^{\omega_\varepsilon D(t)}$
- **Evolution**: $D(t)=\sum_{t':t'<t}(\overline{D_{t't}}e^{-\theta(t-t')})$

The key and our epidemiological model is the introduction of an evolutionary index **D(t)** computed exclusively from genetic sequences that can influence only transmission **β(t)**, only loss of immunity **ε(t)**, or both.

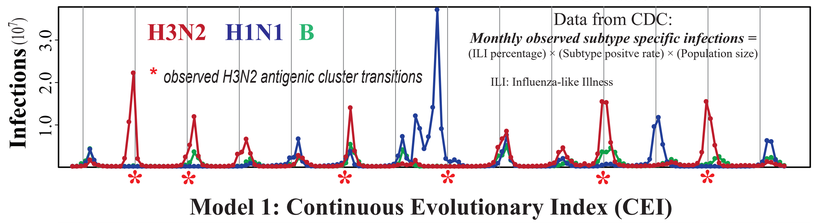
D(t) quantifies the H3N2 evolutionary change for each month relative to the 'recent' past. $\overline{D_{t't}}$ corresponds to the average hamming distance for epitope sites between month t and season t', where sequences in the US were subsampled from all available ones in the GISAID EpiFlu database.

$$dS/dt = \mu N+dN/dt - \Lambda_{H1}(t) + R_{H1}/\varepsilon_{H1} - \beta(t)S\{I/N\}^{\alpha} + R/\varepsilon(t) - \tau - \mu S$$
$$dI/dt = \beta(t)S\{I/N\}^{\alpha} - I/\gamma + \tau - \mu I$$
$$dR/dt = I/\gamma - R/\varepsilon(t) - \mu R$$
$$dR_{H1}/dt = \Lambda_{H1}(t) - R_{H1}/\varepsilon_{H1} - \mu R_{H1}$$

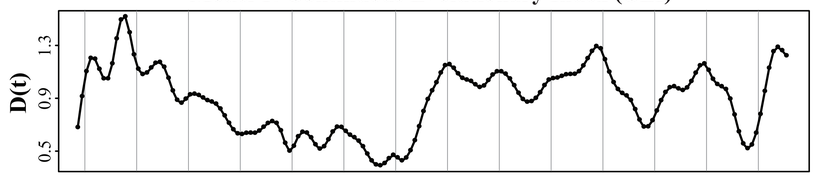
Parameters were optimized using maximum likelihood iterating filtering (MIF) implemented in the R package "pomp". We drew cases from a normal distribution: $C(t) = \text{normal}(\varphi I(t), \rho I(t))$, where φ is the reporting rate and ρ is the reporting error. The likelihood function is $L(t) = \text{normal}(C(t), \varphi I(t), \rho I(t))$.

RESULTS: model selection, comparison and fitting

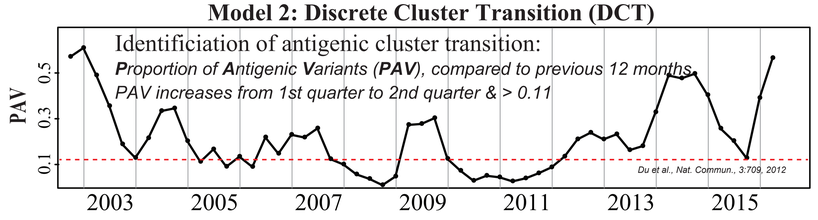
DATA: Seasonal Influenza Infections in United States



Model 1: Continuous Evolutionary Index (CEI)



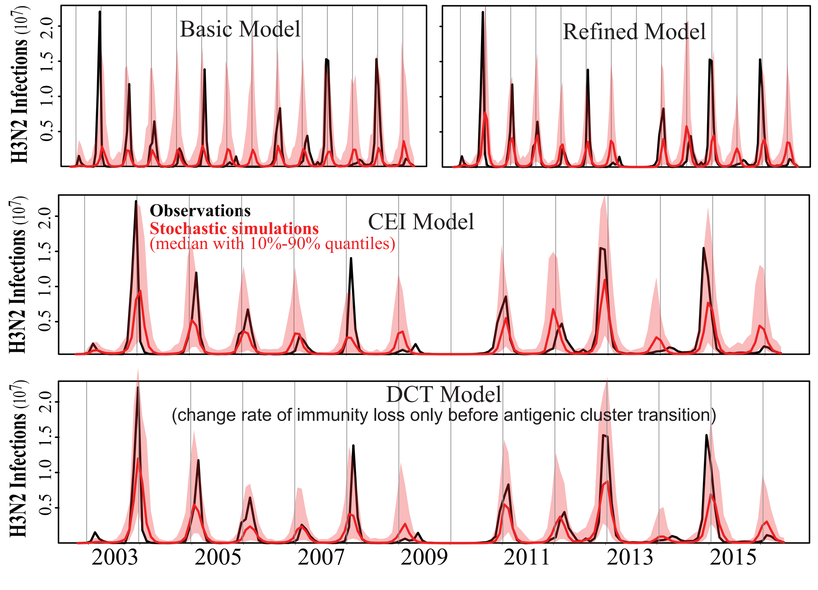
Model 2: Discrete Cluster Transition (DCT)



Model Comparison

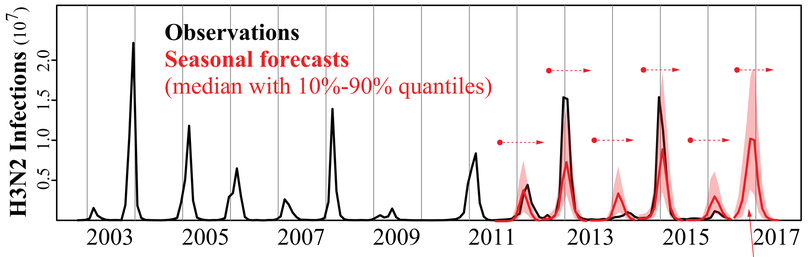
Models	Epidemiology H1N1	Epidemiology $\alpha \neq 1$ ρ_{winter} & ρ_{summer}	Evolution Immunity loss $\omega_\varepsilon \neq 0$	Evolution Transmission $\omega_\beta \neq 0$	Number Parameters	AIC
Basic	×	×	×	×	14	4493
Basic-H1	√	×	×	×	17	4478
Refined	√	√	×	×	19	4471
Immunity loss/Transmission	√	√	√	√	22	4450
Transmission	√	√	×	√	21	4458
Immunity loss (CEI)	√	√	√	×	21	4448
Immunity loss (DCT)	√	√	√	×	20	4445

Model Simulation



RESULTS: Out-of-fit forecasts based on DCT model

The cluster model was trained using data until the end of a given season (June 30th), and predictions were made for the next season. During the prediction window (one season), the average monthly H1N1 levels from the training dataset were used, as well as a prediction of when a antigenic cluster transition occurs (based on PAV). When a cluster transition is predicted, a quauntity similar to D(t) is used in this model to modify the immunity loss rate.

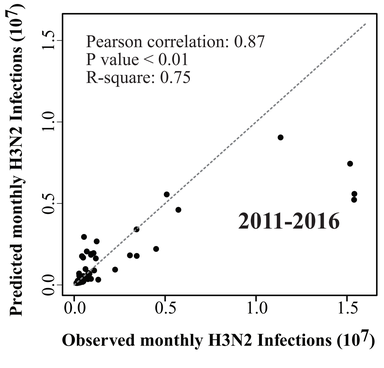


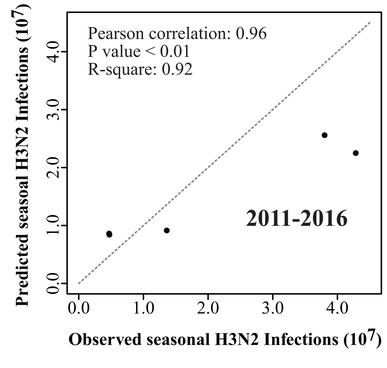
Incidence Level (High/Low*) Forecasts for Seasonal H3N2 Infections

Seasons	Observed	% High (1000 simulations)	Forecasts (>50%: high)
2011/2012	Low	16.9	Low
2012/2013	High	99.6	High
2013/2014	Low	3.2	Low
2014/2015	High	99.7	High
2015/2016	Low	5.0	Low
2016/2017	High#	100.0	High

** compared to average seasonal H3N2 infections from the training dataset*
 # based on current CDC reports, not known at the time when this work was done

Real time forecast





CONCLUSION & DISCUSSION

- Our findings support the feasibility of proposed approches. Extensions and applications to other places and other (sub)types are underway.
- They also underscore the strong effect of H3N2 evolution on its own transmission dynamics and those of other (sub)types. A low fitness of H3N2 may also provide an early warning for the emergence of other (sub)types.
- Our analyses also emphasize the importance of surveillance and sequencing efforts during the summer season, when influenza activity is low but is important for antigenic variants' identification and for incidence prediction in the following season.

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