A Perspective on Multiple Waves of Influenza Pandemics

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Flu pandemics

Flu pandemics occur when different strains of the flu virus, from different animals (especially humans, pigs, chickens and ducks) get mixed together and these strains are relatively unaffected by immunity from older strains.

These novel strains are spread rapidly and can infect very large numbers of people.
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The most recent pandemics occurred in 1918 (Spanish flu), 1957 (Asian flu), 1968 (Hong Kong flu), 2009 (swine flu, pH1N1).

Flu pandemics typically come in waves.
pH1N1 positive tests

US Incidence Data

First Wave

Second Wave

Week of 2009

17 20 23 26 29 32 35 38 41 44 47
Question

What mechanism causes there to be multiple waves during flu pandemics?
The mechanisms

1. Seasonal contact rate (periodic transmission rate)
2. All sources of variability in contacts (behavior changes) and transmissibility (time-dependent transmission rate)
3. Population heterogeneity
4. Virus mutation and delayed susceptibility
5. Waning immunity
The mechanisms

1. Seasonal contact rate (periodic transmission rate)

2. Population heterogeneity

5. Waning immunity
The mechanisms

2. All sources of variability in contacts (behavior changes) and transmissibility (time-dependent transmission rate)

4. Virus mutation and delayed susceptibility
Mathematical modeling of epidemics (SEIR model)

$S$ susceptible, not yet infected
$E$ infected, cannot infect others (exposed)
$I$ infected, can infect others
$R$ recovered, cannot become infected again

\[
\begin{align*}
\frac{dS}{dt} &= -\beta IS \\
\frac{dE}{dt} &= \beta IS - \alpha E \\
\frac{dl}{dt} &= \alpha E - \nu l \\
\frac{dR}{dt} &= \nu l
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Model parameter values: $\alpha = 1$, $\nu = 1/3$.
All others selected so that $R_0 \in [1.2, 2.25]$. 
Mechanism 2: Time-dependent transmission rate

Additional model assumption

The transmission rate captures all sources of variability of the contact rate between susceptible and infected individuals and the virus transmissibility.

Inverse problem for SEIR system

Given infection data there is a new method to extract the $\beta(t)$ that will reconstruct the data. (Pollicott, Wang, Weiss 2012)

We use the explicit inversion formula to determine $\beta(t)$ given the 2009-2010 infection data. $\beta(t)$ depends on $\beta(0)$. 
Mechanism 2: Time-dependent transmission rate

- Generates the two waves.
- Transmission rate does not decrease over the summer.
Mechanism 2: Time-dependent transmission rate

- Generates the two waves.
- Transmission rate does not decrease over the summer.
- No insight into what causes the change in transmission rate.
- Explicit formula depends on $\beta(0)$ - hard to estimate.
Mechanism 4: Virus mutation and delayed susceptibility

Influenza virus diversity

The genetic diversity of the influenza virus increased significantly during the pandemic.

Additional model assumptions

The increase in genetic diversity results in strains with higher transmissibility in the human population.
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Some individuals who were not susceptible to the virus during the first wave become susceptible when new strains with greater transmissibility emerge.
Mechanism 4: Modeling with genetic diversity

Genetic diversity function - normalize and interpolate the monthly genetic diversity data.

Assume: individuals become susceptible at a rate proportional to the genetic diversity.

\[ \frac{dS}{dt} = -\beta IS + \gamma d(t)N \]
\[ \frac{dE}{dt} = \beta IS - \alpha E \]
\[ \frac{dl}{dt} = \alpha E - \nu l \]
\[ \frac{dR}{dt} = \nu l \]
\[ \frac{dN}{dt} = -\gamma d(t)N \]
Mechanism 4: Virus mutation and delayed susceptibility

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- Generates the two waves.
- Who is in the $N$ class?
One verses two waves

Some countries only had one wave of 2009 pH1N1 - China.

When the first cases of H1N1 started appearing in the US, China instituted strong border control.
One versus two waves

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When the first cases of H1N1 started appearing in the US, China instituted strong border control.

Question

What would the H1N1 profile in the US have been if the US instituted border control? Could there have been only one wave?

Border control by reducing I(0).
One verses two waves

Genetic diversity model

- Strong control - one wave, lower maximum prevalence, earlier peak, same attack rate.
Conclusions

- All 5 mechanisms generate a second wave - most likely some combination created the two waves.
- New mechanisms - time-dependent transmission rate and virus genetic diversity.
- Strong border control would result in one wave, but has little effect on the attack rate (total number infected).
- Earlier vaccination would significantly decrease the attack rate and can eliminate the second wave of infections.
