# Seasonal influenza in New Zealand

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# Drift and shift

- Globally, influenza causes three to five million cases of severe illness per year, resulting in up to half a million deaths.
- **Antigenic drift:** mutations cause small changes in surface antigens generating a variety of strains. The population has partial immunity due to previous exposure. The dominant strains cause an epidemic.
- **Antigenic shift:** re-assortment, e.g. haemagglutinin from an avian strain introduced to genome of human influenza, produces a virus with novel surface antigens. Everybody is susceptible and a pandemic may happen.

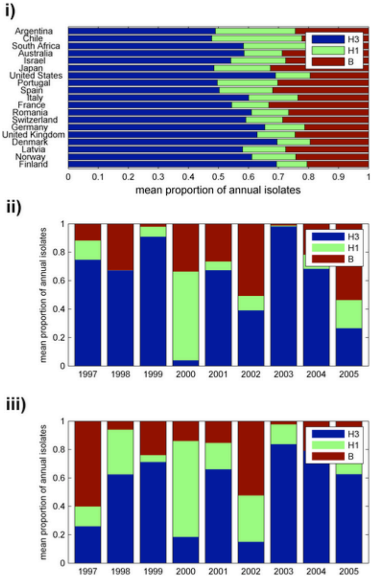
# Pandemic influenza

- **1889: Russian flu (H2N2?)** kills around 1 million.
- **1918: Spanish flu (H1N1)** kills up to 40 million.
- **1957: Asian flu (H2N2)** kills up to 4 million.
- **1968: Hong Kong flu (H3N2)** kills around 700 thousand.
- **1989: UK flu epidemic** kills 29 thousand.

* HA: Haemagglutinin. NA: Neuraminidase.

- **2003: SARS** kills 774.

# Seasonal influenza




## Annual influenza epidemics

- **H3: Influenza A (H3N2).** Appeared in 1968 and displaced H2N2.
- **H1: Influenza A (H1N1).** Caused 1918 pandemic. Reappeared in a 1977 but did not displace H3N2.
- **B: Influenza B.** Only infects humans. Two distinct ‘lines’ in circulation, *Victoria* (mainly in Asia) and *Yamagata* (worldwide).

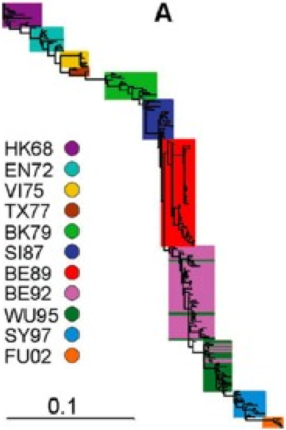
Figures from Finkelman *et al.* 2007.

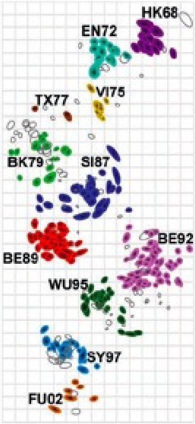
# Why the seasonal pattern?

Picture: Lance Jennings

- Influenza spreads from a tropical reservoir in (birds?) and humans (not B?). (Finkelman, others)
- Increased crowding in winter and increased transmission due to temperature, humidity, less sunlight, etc. (Cannell *et al.* 2008, others)
- Transmission dynamics and/or virus evolution generate periodic behaviour. (Dushoff *et al.* 2004, Recker *et al.* 2007, others)

# Between-season drift



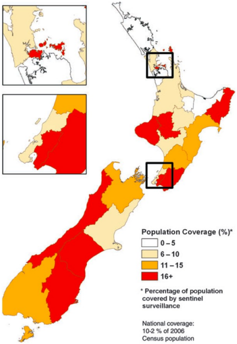




- Phylogenetic tree of the HA1 nucleotide sequences.

  Figures from Smith *et al.* 2004.

- Antigenic map of influenza A (H3N2) virus from 1968 to 2003.

# New Zealand sentinel GP surveillance

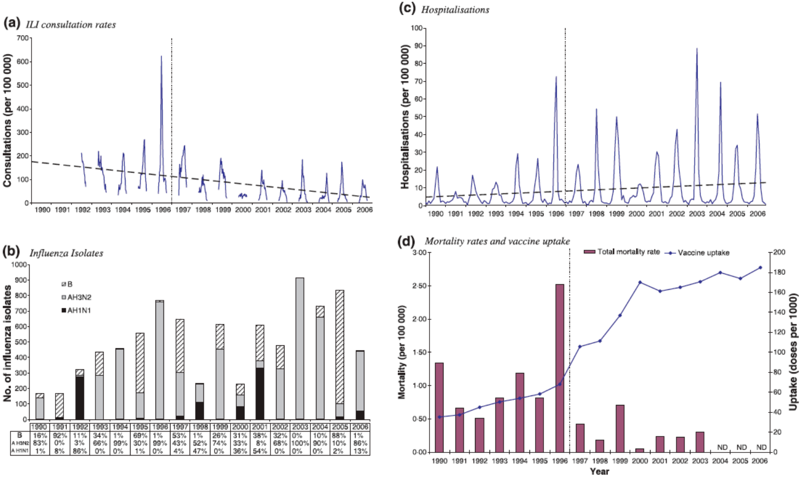



- Figure from Huang *et al.* 2008. Influenza and Other Respiratory Viruses 2:139-45.

- Operated by ESR* as part of the WHO global programme for influenza surveillance.
- Sentinel practices record the daily number of consultations for ILI (influenza like illness) from May to September, plus some data.
- Respiratory samples from patients with ILI are sent to a laboratory for identification (3 per week).
- Results to WHO Flunet.

*Institute of Environmental Science and Research

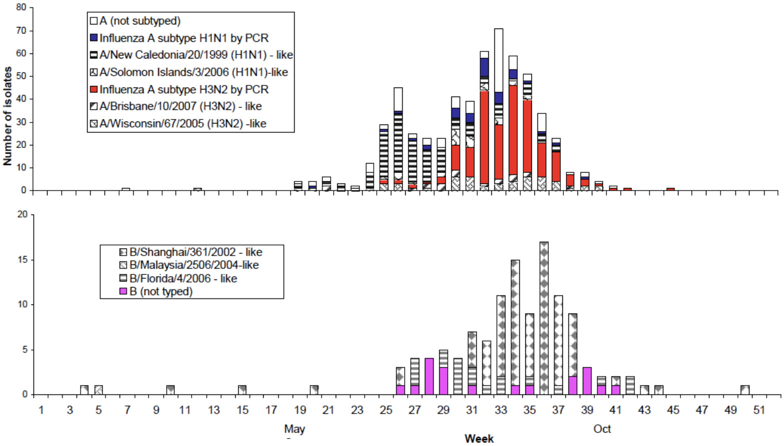
# New Zealand data 1990 - 2006




| | 1990 | 1991 | 1992 | 1993 | 1994 | 1995 | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| B | 16% | 92% | 11% | 34% | 1% | 69% | 1% | 53% | 1% | 26% | 31% | 38% | 32% | 0% | 10% | 88% | 1% |
| A H3N2 | 83% | 0% | 3% | 66% | 99% | 30% | 99% | 43% | 52% | 74% | 33% | 8% | 68% | 100% | 90% | 10% | 86% |
| A H1N1 | 1% | 8% | 86% | 0% | 0% | 1% | 0% | 4% | 47% | 0% | 36% | 54% | 0% | 0% | 0% | 2% | 13% |

- Figures from Huang *et al.* 2008.

# New Zealand data - 2007




- 646 samples: 31% H1N1, 44% H3N2, 25% B.

Figure from Lopez & Huang 2007.

# A New Zealand model

- A three-strain epidemic model to guide vaccination policy.
- The proportion of the population infectious:

$$\frac{\mathrm{d}y_S}{\mathrm{d}t} = \mathcal{R}_0 x_S y_S - y_S$$

  where $S \in \Omega = \{H1, H3, B\}$.
- The function $x_S(t) = 1 - u_S + (1 - \mathcal{P})(u_S - z_S)$, for some $0 \leqslant \mathcal{P} \leqslant 1$, is the *relative susceptibility* of the population. A proportion $z_S$ is specifically protected, and a proportion $u_S$ is non-specifically protected.

  Assumptions
  - Neglect virus evolution within season.
  - No cross-subtype protection between seasons.
  - No cross-type protection within seasons.

# Within-season immunity - H1N1

- The proportion of the population *specifically protected*:

$$\frac{\mathrm{d}z_{H1}}{\mathrm{d}t} = \mathcal{R}_0 y_{H1} \left(1 - z_{H1}\right)$$

- The proportion of the population protected:

$$\frac{\mathrm{d}u_{H1}}{\mathrm{d}t} = \mathcal{R}_0 \left(y_{H1} + y_{H3}\right)\left(1 - u_{H1}\right) \qquad u_{H1}(0) = z_{H1}(0)$$

$$u_{H1}(t) = 1 - \frac{\left(1 - z_{H1}(t)\right)\left(1 - z_{H3}(t)\right)}{1 - z_{H3}(0)}$$

- The relative susceptibility of the population is

$$x_{H1}(t) = \left(1 - z_{H1}(t)\right)\left(1 - \mathcal{P} + \mathcal{P}\frac{1 - z_{H3}(t)}{1 - z_{H3}(0)}\right)$$

# What is $\mathcal{P}$?

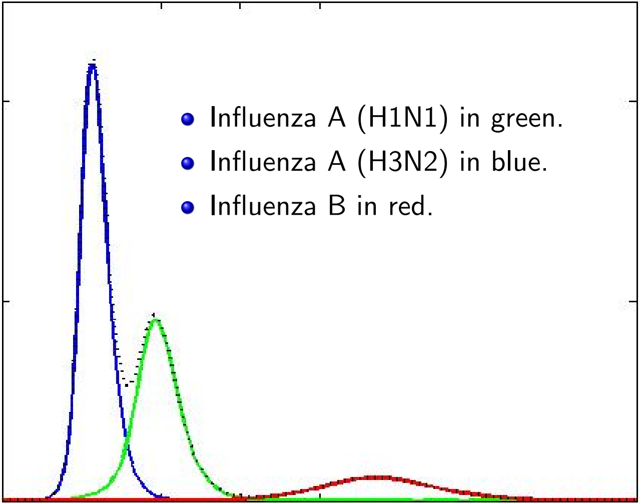
- It appears that there is no cross-immunity among subtypes - although the evidence is somewhat conflicting. (Andreasen 2003).
- Transient nonspecific immunity is paramount in the generation of such dynamics, and in limiting diversity within subtypes - although other mechanisms that induce nonspecific inter-strain competition (...) may also contribute. ... A number of studies support the existence of short-lived nonspecific within-subtype and between-subtype immune responses (Ferguson *et al.* 2003).
- Some degree of generalized immunity or ecological interference may be needed to account for these interannual subtype patterns (Koelle *et al.* 2006).

# What is $\mathcal{R}_0$?

- While the estimated $\mathcal{R}_0$ remains obscure, epidemiologists have directly measured its father, secondary attack rates, for more than 5 decades. For a highly infectious virus, secondary attack rates for influenza are surprisingly low. (Cannell *et al.* 2008).

- Andreasen (2003) $\mathcal{R}_0 \simeq 3 - 10$.
- Boni *et al.* (2004) $1.2 < \mathcal{R}_0 < 6$.
- Dushoff *et al.* (2004) $9.6 < \mathcal{R}_0 < 10.4$ and sinusoidal.
- Ferguson *et al.* (2003) $\mathcal{R}_0 = 5$.
- Gog & Grenfell (2002) $\mathcal{R}_0 \leqslant 5$.
- Gog *et al.* (2003) $\mathcal{R}_0 = 20$.
- Koelle *et al.* (2006) $\mathcal{R}_0 = 5$.
- Minayev & Ferguson (2008) $\mathcal{R}_0 = 2$.
- Recker *et al.* (2007) $\mathcal{R}_0 \simeq 4$.

# Within-season profile



- Influenza A (H1N1) in green.
- Influenza A (H3N2) in blue.
- Influenza B in red.

# The final size equation

- The proportion of the population infected with variant $S$ in the season is $\mathcal{Z}_S = z_S(\infty) - z_S(0)$, where

$$\mathcal{R}_0 m_S \mathcal{Z}_S + \log\left(1 - \frac{\mathcal{Z}_S}{1 - z_S(0)}\right) = 0$$

  and

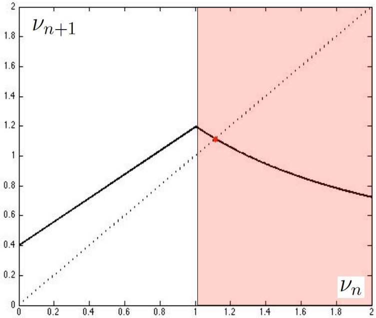
$$m_S = \frac{1}{\mathcal{Z}_S} \int_{z_S(0)}^{z_S(\infty)} \frac{x_S(t)}{1 - z_S(t)} \, \mathrm{d}z_S(t)$$

- For influenza A (H1N1): (and similarly for H3N2)

$$m_{H1} = 1 - \mathcal{P} + \frac{\mathcal{P}}{\mathcal{Z}_{H1}} \int_{z_{H1}(0)}^{z_{H1}(\infty)} \frac{1 - z_{H3}(t)}{1 - z_{H3}(0)} \, \mathrm{d}z_{H1}(t)$$

- For influenza B, $m_B = 1$ (assuming no interaction with A).

# Between seasons - influenza B




- Fixed point has 11% of population infected with influenza B.

- Immunity to influenza B lasts on average 4.8 years. Define $\mu_B = (1-b)\,d_B$.
- *Effective* $\mathcal{R}_0$. Let

$$\nu_n = \mathcal{R}_0\,(1 - z_B(0))$$

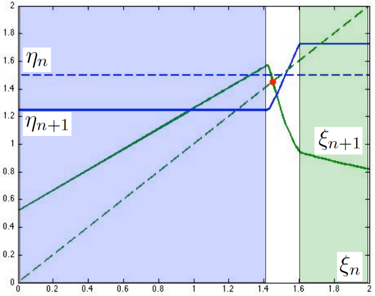
at the start of year $n$. Then

$$\nu_{n+1} = (1-\mu_B)\,\mathcal{R}_0 + \mu_B \Phi(\nu_n)$$

with $\Phi(\nu) = -\mathcal{W}\left(-\nu e^{-\nu}\right)$ and $y = \mathcal{W}(x)$ if $ye^y = x$.

(Lambert W-function. Ma & Earn 2006)

# Between seasons - influenza A




- Green is $\xi$ (H1N1).
- Blue is $\eta$ (H3N2).
- The fixed point is <u>unstable</u> with $\mathcal{R}_0 = 2$.

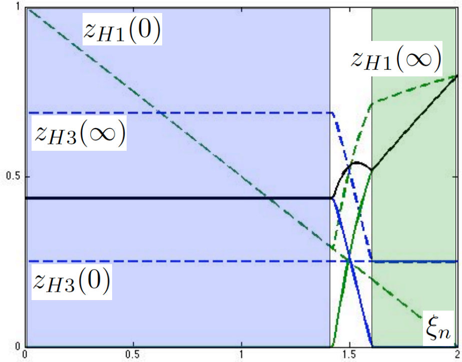
- Immunity to H1N1 lasts 3.5 years, and to H3N2 1.7 years.
- *Effective* $\mathcal{R}_0$. Let

$$\xi_n = \mathcal{R}_0 \left(1 - z_{H1}(0)\right)$$
$$\eta_n = \mathcal{R}_0 \left(1 - z_{H3}(0)\right)$$

at the start of year *n*. Then

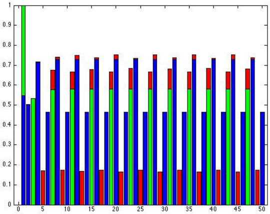
$$\xi_{n+1} = (1 - \mu_{H1})\, \mathcal{R}_0 + \frac{\mu_{H1}}{m_{H1}} \Phi\left(m_{H1}\xi_n\right)$$
$$\eta_{n+1} = (1 - \mu_{H3})\, \mathcal{R}_0 + \frac{\mu_{H3}}{m_{H3}} \Phi\left(m_{H3}\eta_n\right)$$

# Within seasons - influenza A

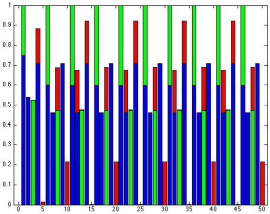



- Epidemic size as a function of *effective* $\mathcal{R}_0$.
  $\xi_n = \mathcal{R}_0\,(1 - z_{H1}(0))$

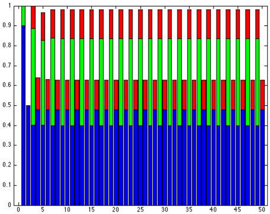
# Repeated epidemics



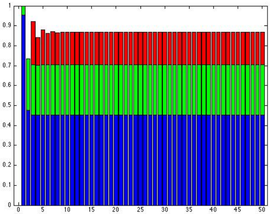
$\mathcal{R}_0 = 1.5$ period 4



$\mathcal{R}_0 = 2.0$ period 10



$\mathcal{R}_0 = 3.0$ period 2

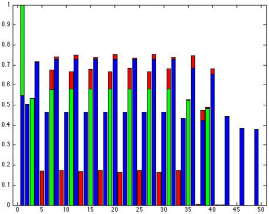


$\mathcal{R}_0 = 4.0$ period 1

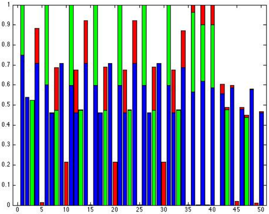
# Vaccination

- The WHO make twice-yearly recommendations on vaccine formulation:
  - in February for the next Northern Hemisphere winter;
  - in September for the next Southern Hemisphere winter.
- The Australian Influenza Vaccine Committee meets in October, with representatives from New Zealand and South Africa.
- New Zealand adopts the AIVC recommendation. In 2007 this was:
  - an A/Solomon Island/3/2006 (H1N1) - like strain;
  - an A/Brisbane/10/2007 (H3N2) - like strain;
  - a B/Florida/4/2006 - like strain.
- Free influenza vaccination has been available to those 65+ since 1997, and other risk groups since 1999.

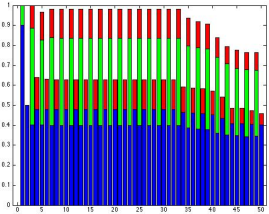
# Repeated epidemics with vaccination



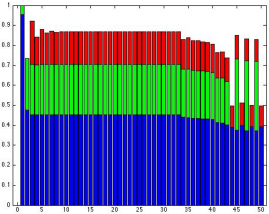
$\mathcal{R}_0 = 1.5$



$\mathcal{R}_0 = 2.0$

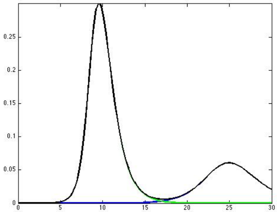


$\mathcal{R}_0 = 3.0$

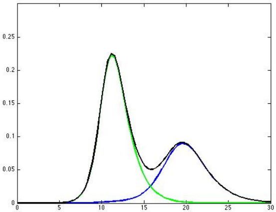


$\mathcal{R}_0 = 4.0$

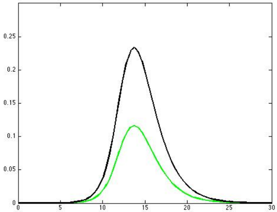
# Within season epidemics: effect of prior exposure



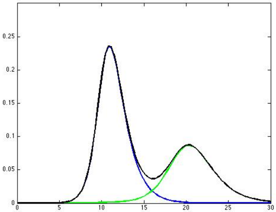

$z_{H1}(0) = 0.05$




$z_{H1}(0) = 0.15$



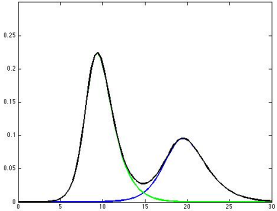

$z_{H1}(0) = 0.25$



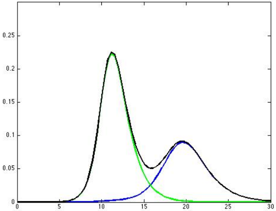

$z_{H1}(0) = 0.35$

- $z_{H3}(0) = 0.25$
- $y_{H1}(0) = 10^{-6}$
- $y_{H3}(0) = 10^{-6}$

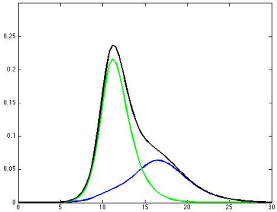
# Within season epidemics: effect of initial infection



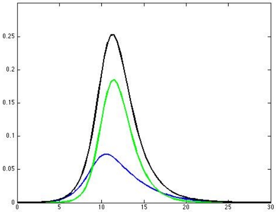

$y_{H1}(0) = 10y_{H3}(0)$




$y_{H3}(0) = y_{H1}(0)$




$y_{H3}(0) = 10y_{H1}(0)$




$y_{H3}(0) = 100y_{H1}(0)$

- $z_{H1}(0) = 0.15$
- $z_{H3}(0) = 0.25$
- min $y_S(0) = 10^{-6}$

# The two-strain toy model

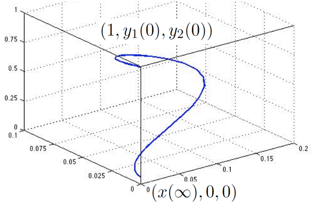
- The proportion not infected this year

$$\frac{\mathrm{d}x}{\mathrm{d}t} = -\mathcal{R}_0 x\,(y_1 + y_2)$$

- Assume complete cross-immunity, $\mathcal{P} = 1$.
- Proportion immune to strain 1 is $x_1(t) = x_1(0)x(t)$.

$$\frac{\mathrm{d}y_1}{\mathrm{d}t} = x_1(0)\mathcal{R}_0 x y_1 - y_1$$
$$\frac{\mathrm{d}y_2}{\mathrm{d}t} = x_2(0)\mathcal{R}_0 x y_2 - y_2$$

New joint work with Viggo Andreasen.

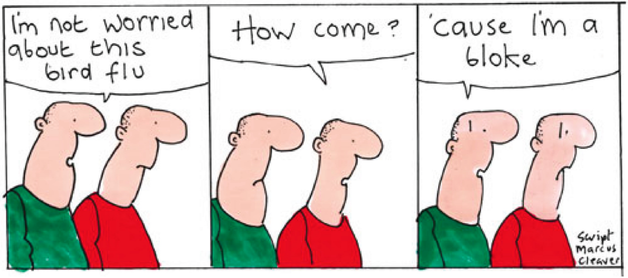



- Given $\mathcal{R}_0$, $x_1(0)$ and $x_2(0)$, we have a map $(y_1(0), y_2(0)) \rightarrow x(\infty)$.
- Epidemic peaks are at

$$\phi = \frac{y_2}{y_1} = -\frac{x_1(0)\mathcal{R}_0 x - 1}{x_2(0)\mathcal{R}_0 x - 1}$$

# Future work

- Use information from the toy model to refine the final size equation.
- Tune the model parameters (using data!).
- Extend to a three age-group model.
- Make sensible pronouncements on the vaccination policy.




** Thanks to Sue Huang and Mathew Peacey (ESR), Lance Jennings (Canterbury DHB) and Viggo Andreasen (RUC).

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# The end


- Thanks to the organisers for inviting me, and to DIMACS and ECDC for funding.