

Disease modeling – a versatile tool in combating emerging infections



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Disease modeling

- Mathematical modeling of infectious disease
 - Using mathematics to describe and predict the spread of infectious diseases.
 - Computer simulations.
 - Analogies
 - Physics: Motion of planets
 - Atmospheric sciences: Weather forecast
 - Aeronautic engineering: Aerodynamics of planes
 - Mechanical engineering: Thermodynamics of engines
 - Chemical engineering: Chemical reactions in reactors
 - Electrical engineering: Integrated circuits
 - Telecommunications: Operations of network servers

Pandemic influenza

- Recent spread of H5N1 avian influenza has heightened concern that the next influenza pandemic may be imminent
- Human-to-human transmission appears to be possible but inefficient. Mutations or reassortment may overcome this hurdle.
- No existing immunity among humans. Similar to the 1918 pandemic.
- Vaccine production cannot start until the pandemic strain has been isolated. It is almost impossible to predict the pandemic strain in advance. So vaccines will unlikely be available during the first 4 to 6 months of the pandemic.

Using math modeling to advise pandemic preparedness

- Learning from the past
 - How transmissible was the 1918 pandemic influenza?
- Predicting the future
 - Containment: Can we contain the pandemic virus at the source?
 - Travel restriction: Can we avoid or slow down a global pandemic by restricting international travel?
 - Mitigation: What are the effectiveness of quarantine, isolation, and large-scale antiviral intervention in slowing down the pandemic in modern populations?
 - Resource optimization: Optimally adjust the dose of pre-pandemic vaccines to maximize herd immunity.
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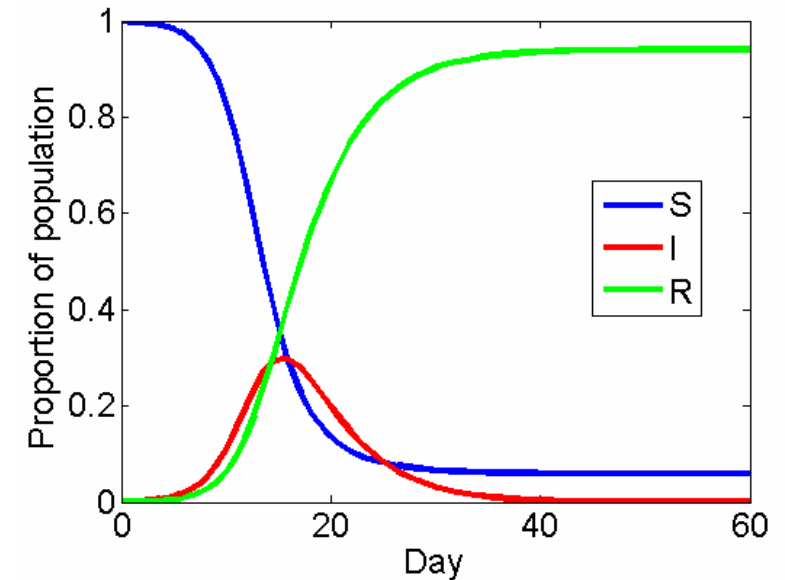
The simplest epidemic model

- The SIR (Susceptible-Infected-Recovered) model

Susceptible: $\frac{dS}{dt} = - \underbrace{\beta S \frac{I}{N}}_{\text{Number of new infection}},$
Change in the number of susceptibles

Infected: $\frac{dI}{dt} = \underbrace{\beta S \frac{I}{N}}_{\text{Number of new infection}} - \underbrace{\mu I}_{\text{Number of recovery}},$
Change in the number of infecteds

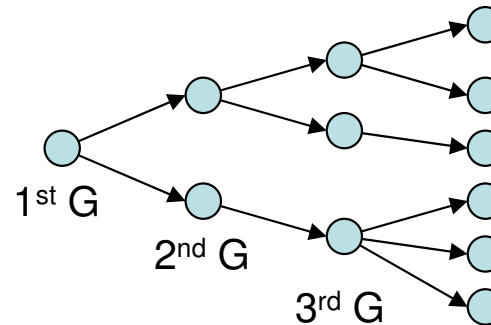
Recovered: $\frac{dR}{dt} = \underbrace{\mu I}_{\text{Number of recovery}}.$
Change in the number of recovereds



Essential epidemiological parameters

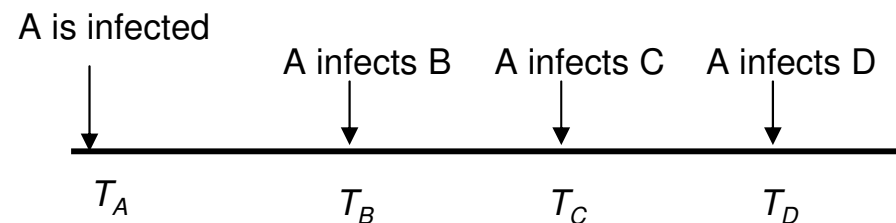
- Basic reproductive number R_0 ($= \beta/\mu$ in the SIR model)
 - The average number of secondary cases generated by a primary case in a completely susceptible population

The number of infections increases exponentially during the early phase



- Generation time (serial interval) T_g
 - The average time between infection (onset of symptoms) of the infector and infections (onset of symptoms) of his infectees

$$T_g = \frac{(T_B - T_A) + (T_C - T_A) + (T_D - T_A)}{3}$$



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Transmissibility of 1918 pandemic influenza

Mills CE, Robins JM, Lipsitch M (2004) Transmissibility of 1918 pandemic influenza. *Nature* 432: 904-906

Data: Pneumonia & Influenza Mortality death curves for 45 US cities

Model: Deterministic SEIR model

Results: R_0 , reproductive number

Median $R_0 = 2.9$

Interquartile range of $R_0 = (2.4, 3.3)$

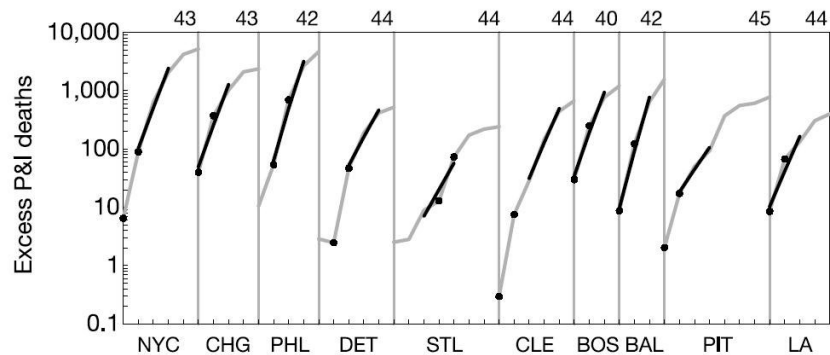


Figure 1 Graph of the logarithm of excess P&I deaths in 1918 for the ten most populous cities in the US. Curves from each city are separated by vertical bars for clarity, with the week number listed above each peak. Curves are shown from left to right, in order of decreasing population size: New York City (NYC), Chicago (CHG), Philadelphia (PHL), Detroit (DET), St Louis (STL), Cleveland (CLE), Boston (BOS), Baltimore (BAL), Pittsburgh (PIT) and Los Angeles (LA). Raw data are shown as grey lines. Black lines indicate model fits for the initial R estimates. Black dots indicate the weeks used for the extreme R estimates.

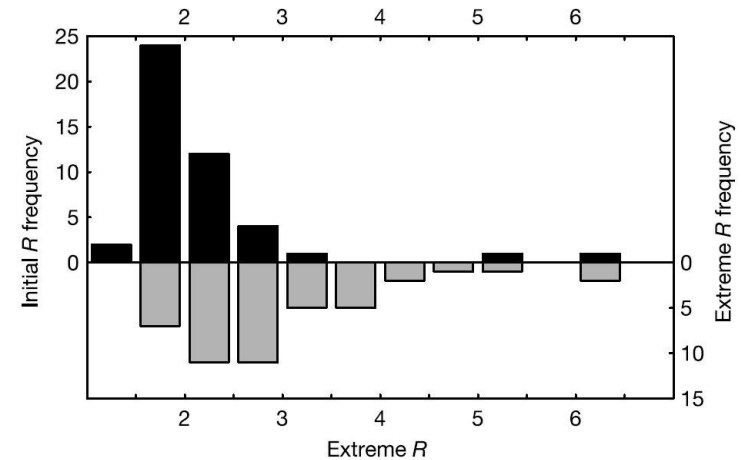


Figure 2 Histogram of initial and extreme estimated R values for 45 cities during the 1918 influenza pandemic. Dark bars show initial R estimates, grey bars show extreme R estimates.

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Delaying international spread of pandemic influenza

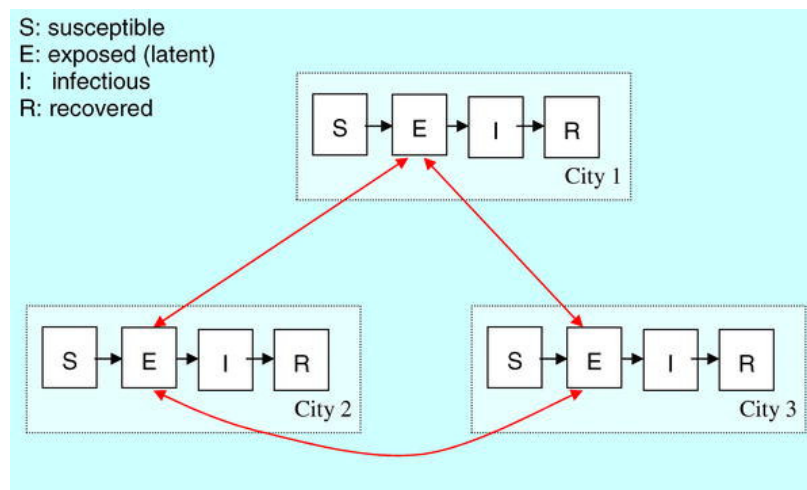
Cooper BS, Pitman RJ, Edmunds WJ, Gay NJ (2006) Delaying the international spread of pandemic influenza. *PLoS Med* 3: e212

Data:

Number of seats on flights between 105 cities from International Air Transport Association
City sizes from the United Nations urban agglomeration data

Model:

Stochastic SEIR meta-population model

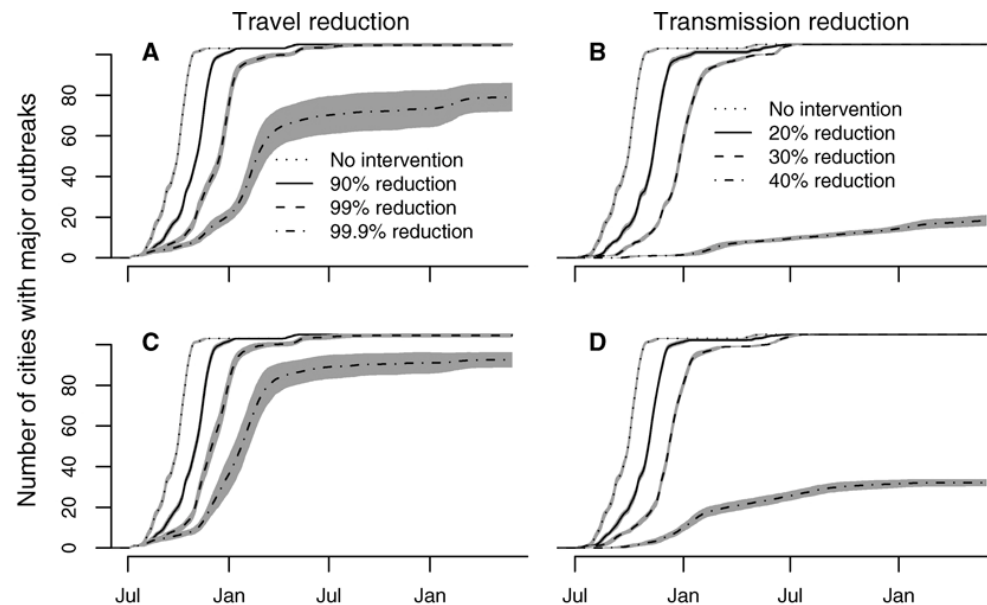


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Results:

Intervention imposed after one case (A and B) and 100 cases (C and D)



Conclusion:

Travel restriction has limited effectiveness in slowing down the pandemic

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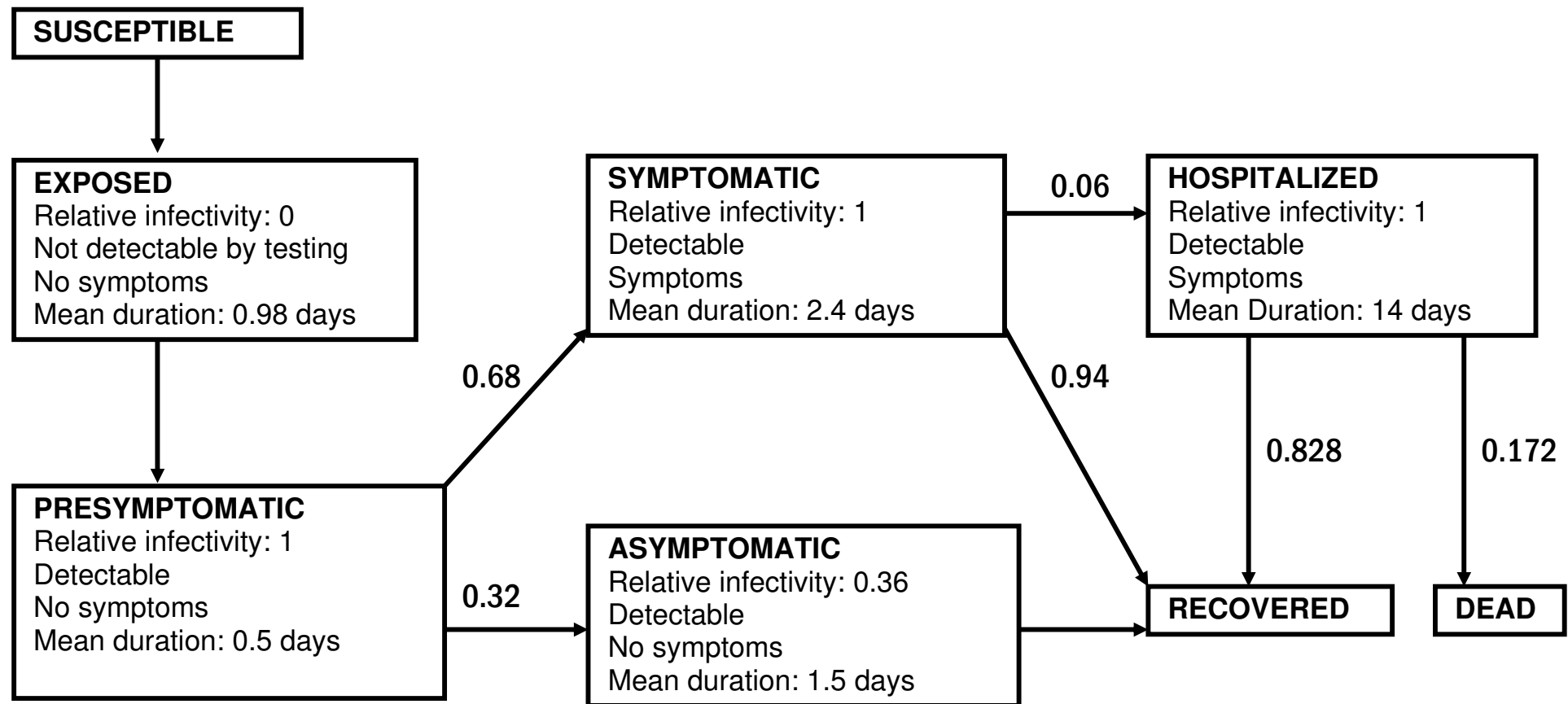
Factors that Make an Influenza Pandemic Difficult to Mitigate

- The pandemic strain cannot be predicted with high accuracy
 - Well-matched vaccines are unlikely to be available in advance
- Short generation time (about 3 days)
 - Mitigation must operate efficiently at this time-scale
- Symptom-based diagnosis is unlikely to be specific during the early phase
 - Symptom-based strategies will be disruptive
- Potentially high proportion (10% to 25%) of asymptomatic infection. Transmissions may occur before the onset of symptoms
 - Non-symptomatic transmissions limit the efficacy of symptom-based strategies
- High volume of international travel
 - Travel restriction is unlikely to prevent importations effectively

Wu JT, Riley S, Fraser C, Leung GM (2006) Reducing the impact of the next influenza pandemic using household-based public health interventions. *PLoS Med* 3: e361.

Natural History of Influenza

Wu JT, Riley S, Fraser C, Leung GM (2006) Reducing the impact of the next influenza pandemic using household-based public health interventions. *PLoS Med* 3: e361.



Transmission Network For Influenza

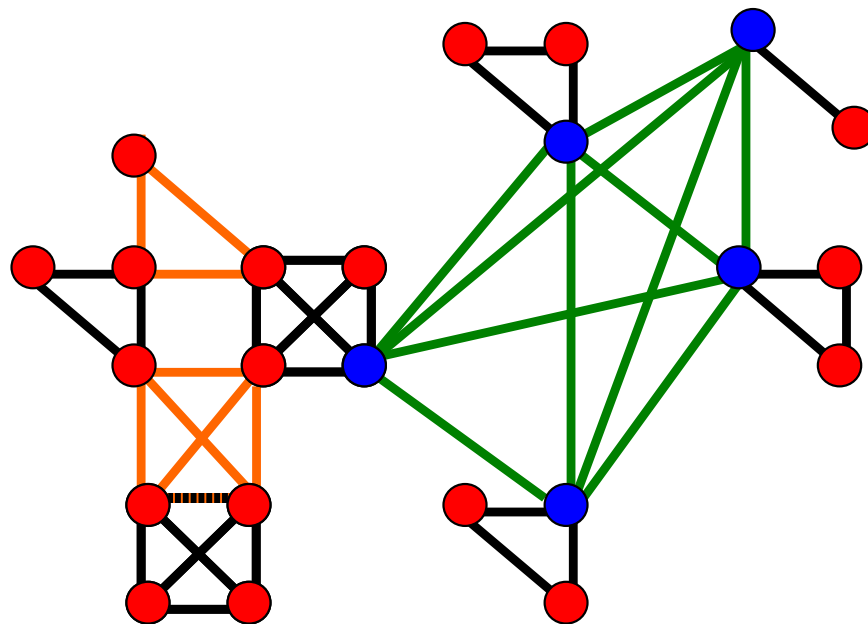
Wu JT, Riley S, Fraser C, Leung GM (2006) Reducing the impact of the next influenza pandemic using household-based public health interventions. *PLoS Med* 3: e361.

Model the population as a network: Each *node* represents an individual and each *edge* represents a social interaction that is relevant to influenza transmission.

We assume 3 types of social interactions for transmissions:

Traceable: (i) Household; (ii) Peer-group;

Untraceable: (iii) Community

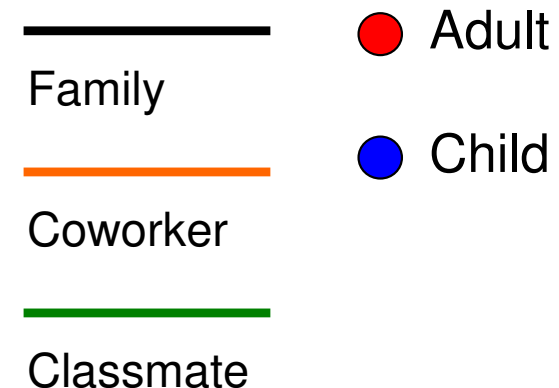


Hong Kong:

% children = 19.44

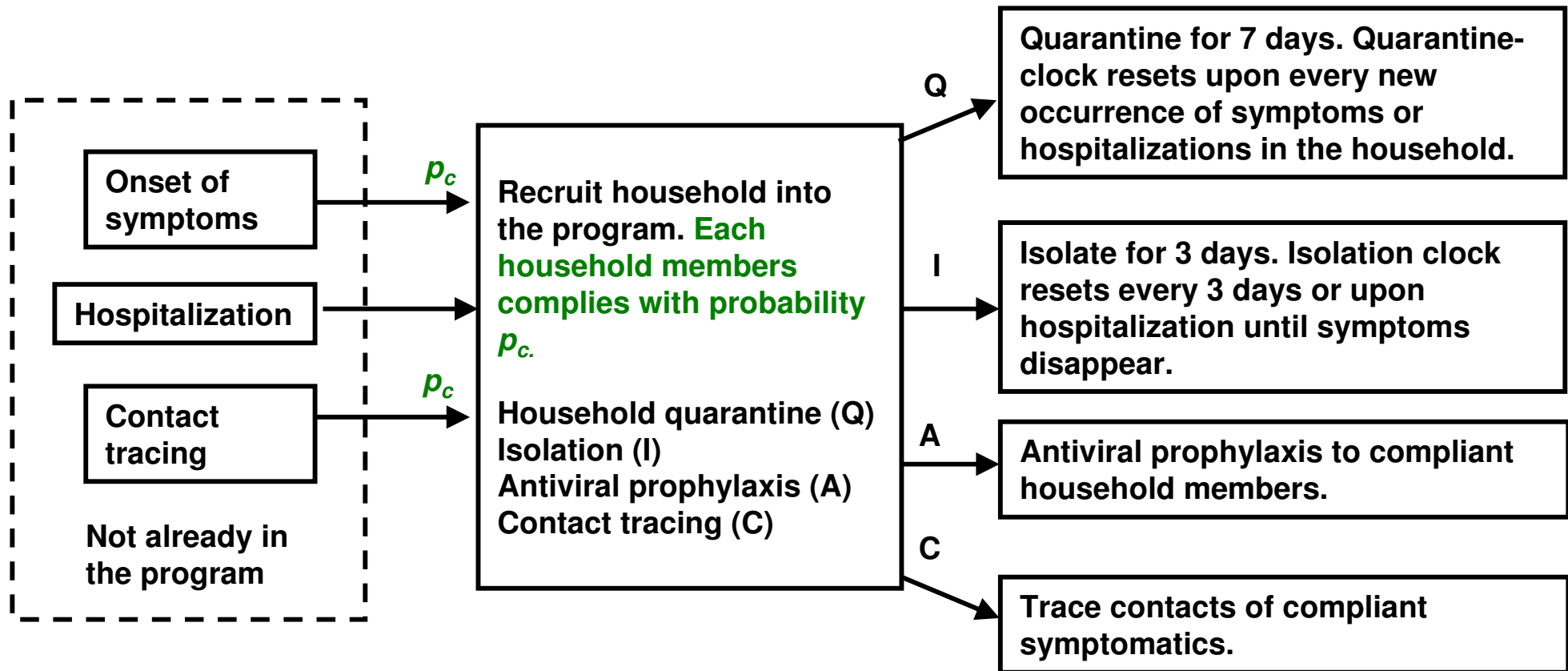
Avg class size = 40

Avg size of household = 2.9



Basic Ideas of a City-wide Household-Based Intervention Program

Wu JT, Riley S, Fraser C, Leung GM (2006) Reducing the impact of the next influenza pandemic using household-based public health interventions. *PLoS Med* 3: e361.

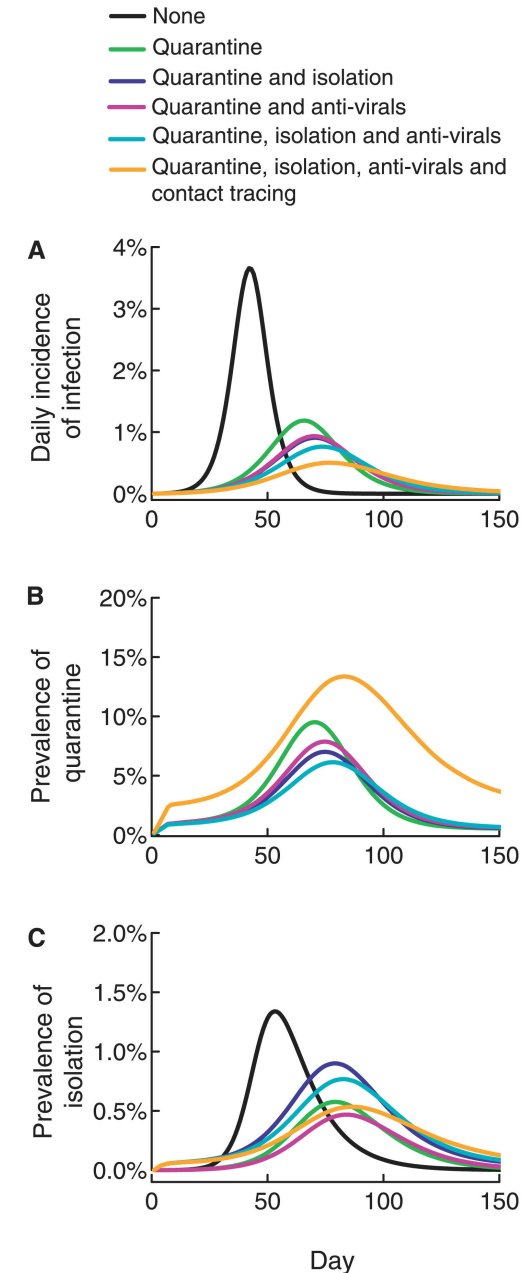


Base Case Results

Wu JT, Riley S, Fraser C, Leung GM (2006) Reducing the impact of the next influenza pandemic using household-based public health interventions. *PLoS Med* 3: e361.

- Main intervention parameters
 - 50% quarantine compliance (QC)
 - 75% decrease in peer-group infectivity if QC
 - 100% decrease in community infectivity if QC
 - 50% voluntary isolation
 - 69% decrease in susceptibility by Tamiflu
 - 30% decrease in infectivity by Tamiflu

Strategy	Infection Attack Rate	Peak Prevalence of Quarantine	Peak Prevalence of Isolation	Doses of Anti-virals Per Capita
None	74%	-	1.4%	0.9
Q	50%	9.8%	0.6%	0.6
QI	44%	7.3%	0.9%	1.2
QA	44%	8.2%	0.5%	3.9
QIA	41%	6.4%	0.8%	3.9
QIAC	35%	14%	0.6%	9.9



Implications on mitigation strategies

Wu JT, Riley S, Fraser C, Leung GM (2006) Reducing the impact of the next influenza pandemic using household-based public health interventions. *PLoS Med* 3: e361.

- Even with only moderate compliance (50%), city-wide household-based public health interventions can
 - Slow down the outbreak until effective vaccines become available
 - Decrease peak infection incidence with realistic level of quarantine to avoid breakdowns of health systems and other systems crucial for normal operations of the city (e.g. police enforcement, utilities services, transportation, etc)
- However, resource and logistic requirements (e.g. isolation facilities, antiviral stockpile) are substantial
- Compliance is pivotal \Rightarrow Promote compliance
 - Proactive measure, e.g. increase public awareness to instill compliance
 - Reactive measure e.g. incorporate antiviral prophylaxis into intervention
- Current biotechnology research focus on vaccines and antivirals. But testing can make a significant impact too.
- Contact tracing coupled with rapid and accurate testing may be a practical enhancement (during the early and late phase of the pandemic)

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Pre-pandemic Influenza Vaccines (as of June 2007)

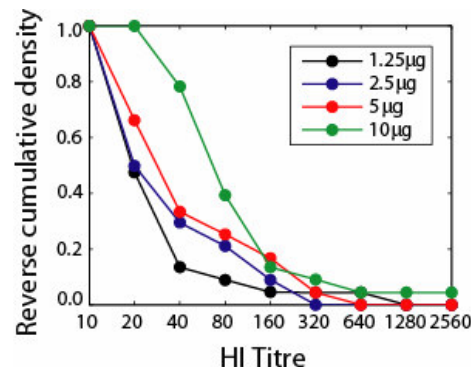
- Data available for three candidate vaccines
 - 2 Adjuvant inactivated whole-viron vaccines
 - Lin (1.25 μg – 10 μg)
 - Bresson (7.5 μg – 30 μg)
 - 1 non-adjuvated split-viron vaccine
 - Treanor (7.5 μg – 90 μg)
- The US Pandemic Plan already commits to 20 million doses of pre-pandemic vaccines.
- Maximum tested dose is typically the smallest dose that meets the vaccine license requirement (based on serological response, e.g. HI titers).
- What is the optimal use of pre-pandemic vaccination?
 - Transmission limiting strategies (e.g. vaccinate children first) vs. morbidity / mortality limiting strategies (vaccinate the elderly first)

Optimizing the dose of pre-pandemic vaccines

Riley S, Wu JT, Leung GM (2007) Optimizing the dose of pre-pandemic influenza vaccines. *PLoS Med* 4: e218

- Dose, d – The amount of antigen contained in a vaccine.

Lin vaccine trial results

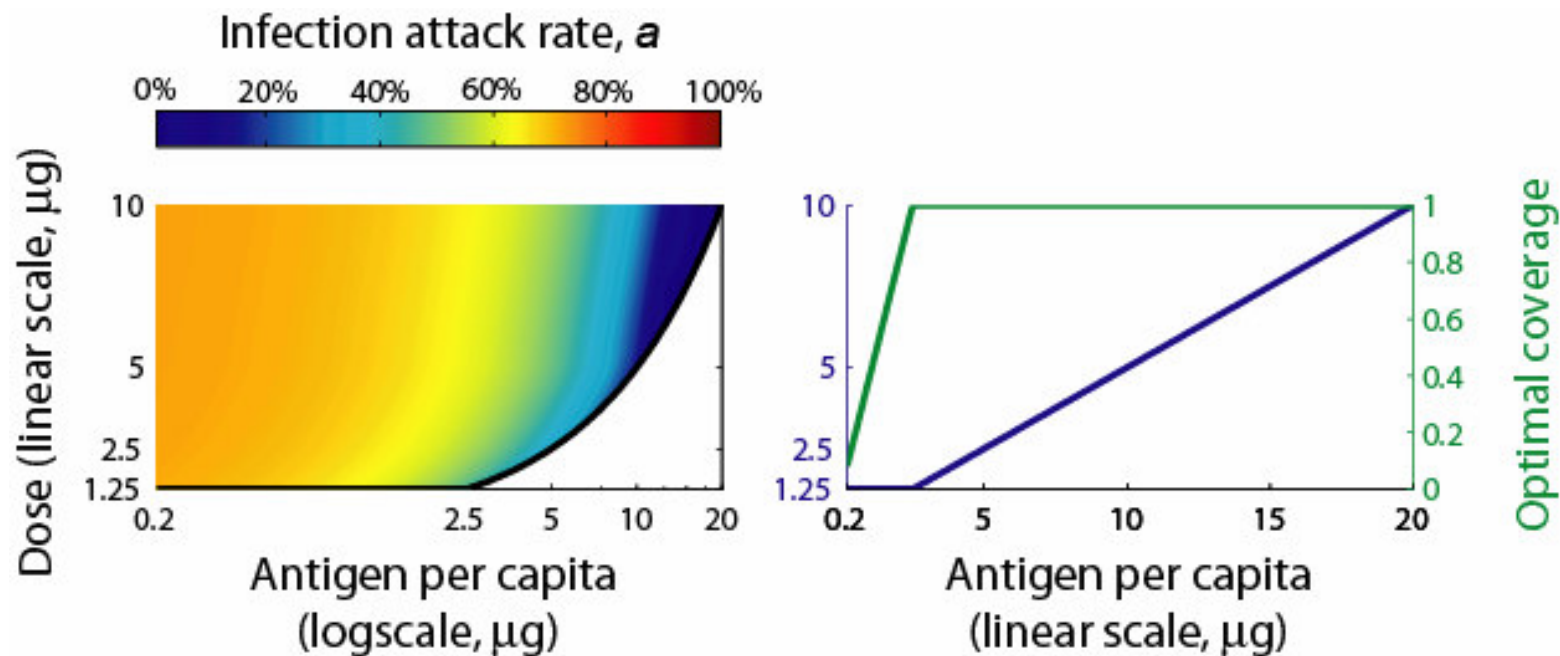


- Coverage, $c(d) = S/d$ – Proportion of population vaccinated
- All or some of vaccine stockpiles may be used to reduce the infection attack rate (IAR).
- Hypothesis
 - Doses other than the maximum tested dose may achieve a lower IAR because higher coverage may lead to greater population-level protection even with reduced individual-level vaccine efficacy.

Optimal dose versus maximum tested dose

Riley S, Wu JT, Leung GM (2007) Optimizing the dose of pre-pandemic influenza vaccines. *PLoS Med* 4: e218

- Results for the Lin vaccine. Results are qualitatively the same for all three vaccines.



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- 20 million vaccines at max tested dose for the 300 million individuals in the US
- 2-tiered dosing – Give max tested dose to the 9 million health-care workers (HCW) in the US while optimizing the remaining vaccine stockpile

Vaccine	Protection data used to calibrate model ¹	Response type within immune states ²	Δ Attack rate ³	
			Single uniform dose	2-tiered dosing ⁴ (HCW plus optimized dose)
Lin [5]	HK strain from Ref [14]	Leaky	8.9%	4.8%
		All-or-nothing	11.6%	6.3%
	Pre-1968 strain from Ref [14]	Leaky	9.0%	4.8%
		All-or-nothing	11.8%	6.4%
	Field data from Ref [15]	Leaky	16.7%	8.8%
		All-or-nothing	19.2%	10.4%

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