Evaluation of Targeted Influenza Vaccination, and possibly Medication Strategies via Population Modeling

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Targeting

- Lloyd-Smith et al. (Nature 2005;438:355-59) argue that targeted interventions are more effective than indiscriminate ones. The difficulties of course lie in identifying targets, and possibly delivering interventions

- We are not the first to advocate vaccinating schoolchildren against influenza, but we deduce this result from observations. That is, our only assumptions are about how to perform the calculations, and our methods are fairly conventional

- So, I'll describe a means of identifying targets. Whenever resources are in short supply, as they often are in Africa, targeting is how to use them most advantageously

- But, by virtue of their disparate generation times, pathogens can evade any host defense. The efficiency of targeting not only uses interventions available today most effectively, but preserves their effectiveness for tomorrow

Pharmaceuticals

Vaccines:

- Once circulating strains are identified, vaccine production requires months, and problems often lead to supply shortages that a pandemic will exacerbate
- An avian H5N1 vaccine has been stockpiled, but this or another virus must mutate or reassort to become transmissible person-to-person
- Efficacy of the stockpiled vaccine for the pandemic strain cannot be known, consequently, but annual efficacy is 30-80% overall
- Ten days to 2 weeks are required to mount protective immune responses

Medications:

- Adamantanes (amantadine, rimantadine) – effective only against influenza A, several toxic effects, rapid emergence of transmissible resistant strains as pathogenic as wild-type – prophylaxis?
- Neuraminidase inhibitors (zanamivir, oseltamivir) – administer w/in 24-72 hrs of onset, little toxicity and resistance is less likely to arise – treatment?

Population Modeling

- Arguably the greatest intellect of the 20th Century admonished us to model as simply as possible, but not more so. Yet contemporary public health policymaking is dominated by individual-based and cohort models, respectively unnecessarily complex for most problems and simplistic for infectious diseases

- Compartmental modeling is consistent with epidemiologists' disposition to group people similar in relevant characteristics. I'm also trained in population biology, so mine usually are cross-classified with demographically-realistic population models. As hypotheses, models are useless unless they can be evaluated. How else would we know whether or not to believe their predictions?

- Population models can be evaluated. IBMs never are, either because their complexity precludes identifying and remedying the cause of inevitable disparities or those who model individuals have a different philosophical perspective (scientists are unusually self-conscious, but we all learn by recognizing patterns in nature, hypothesizing causal explanations, and evaluating our hypotheses)

- Infection occurs at constant rates in cohort models, which consequently lack dynamics. Infection couldn't depend on the number of infectious people, because some of them – key ones for this story – belong to other cohorts. As control measures seek to thwart transmission, models that misrepresent it cannot respond realistically when subjected to interventions

Data Sources

- Other than demographic data, which are readily accessible (but may not be documented in English), a large, prospective, household study conducted during the 1957 pandemic is our only data source. Immunity to pandemic strains is minimal, so age-specific proportions infected – so-called attack "rates" – may be interpreted as forces of infection

- We fit a continuous distribution to compensate for misclassification discovered on reviewing data from surveys following the 1918 pandemic: Over-reporting was observed among younger and older people, and under-reporting among intermediate ages seems likely. This also permits us to choose different age groups

- Whether the log normal or Weibull would be more appropriate for age-specific *activities* than the gamma is future work. For now, this is just a continuous distribution with roughly the right shape

- Statistical distributions also conserve degrees of freedom for estimating the parameters of distributed *preferences*, which the above-mentioned misclassification however precludes. What we really need is a cross-sectional serological survey
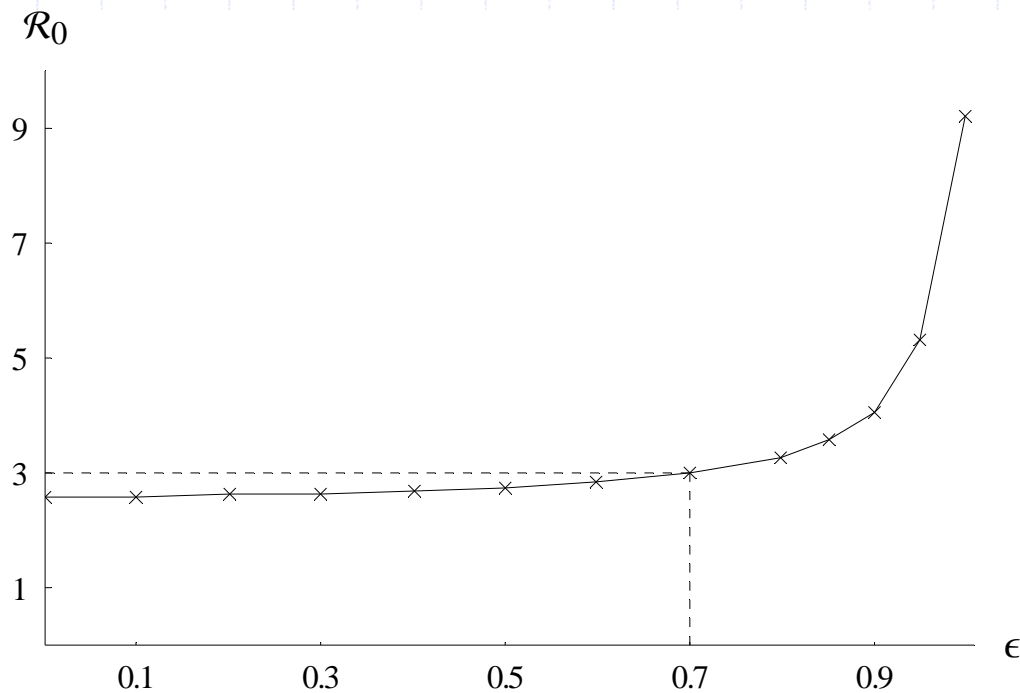
Figures 1

(a)

(b)
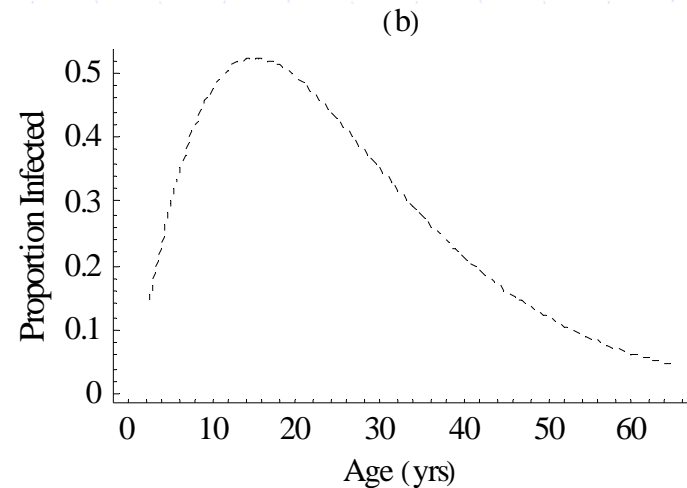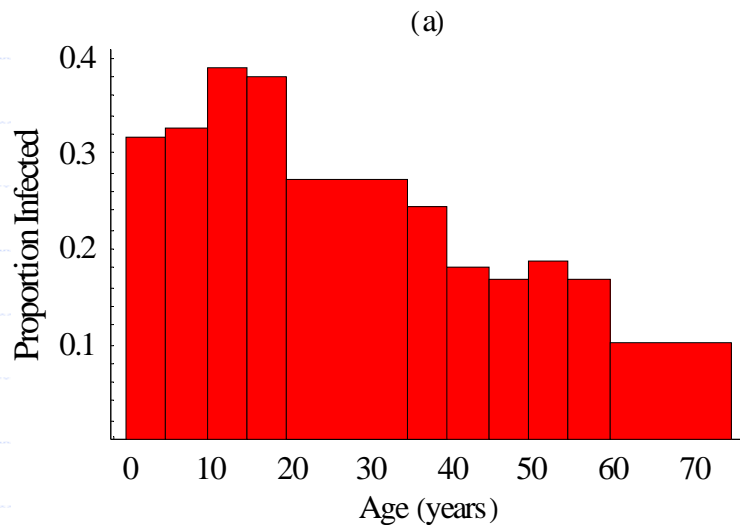
Age-specific proportions infected from a) a prospective study of family contacts (n = 4,155) during the 1957 influenza pandemic (Chin et al. 1960) and b) gamma distribution whose parameters (2.3, 11.4) were fitted via the method of moments
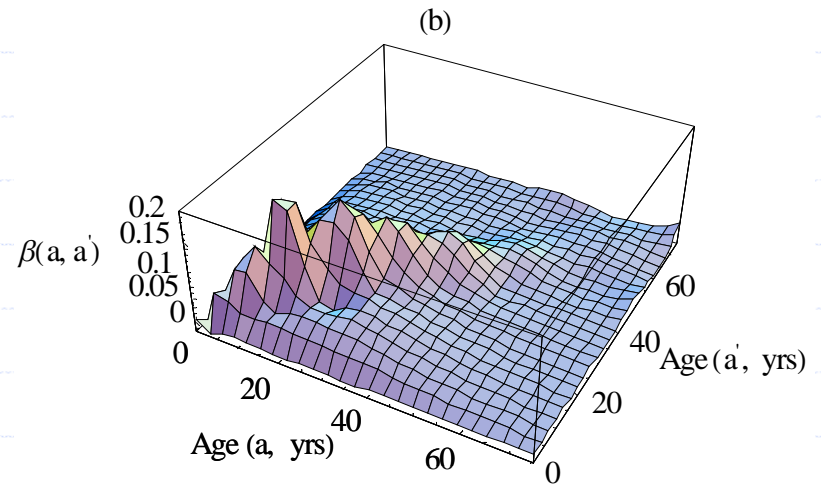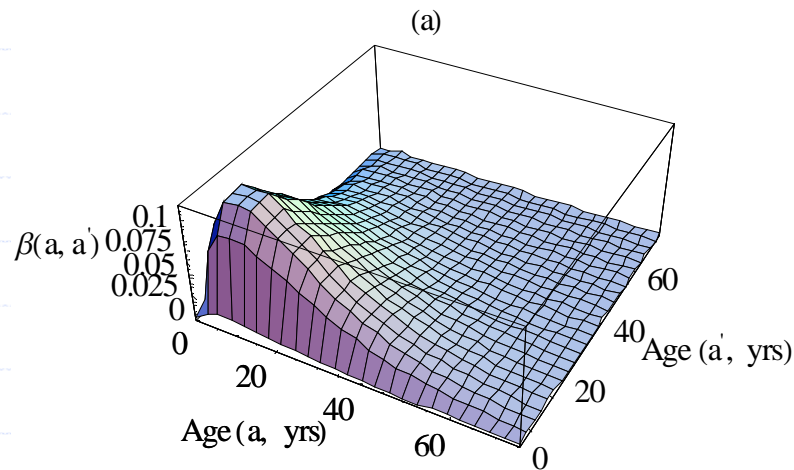
Infection Rates

- Calculated the rates as convex combinations of mixing within and between age groups, $\beta(a,a') = \beta_0[\varepsilon(a)\delta(a,a')b(a)+\{[1-\varepsilon(a)]b(a)[1-\varepsilon(a')]b(a')\}^{1/2}]$, in turn functions of preference and activity, $\varepsilon(a)$ and $b(a)$, where $\delta(a,a')$ is the Kronecker delta (i.e., 1 when $a = a'$ and 0 otherwise)

- Preference is the proportion of contacts with others roughly the same age, activity is the probability of contact during an arbitrary period, and mixing between age groups is the geometric mean of their respective activities

- Misclassification precludes estimating both $b(a)$ and $\varepsilon(a)$, so we choose extreme values via relationship between $\Re_0$ and ε (next slide) and independent estimates of $\Re_0$ for influenza, ≤ 3

Figure 2

Effect of mixing on the reproduction number, $\mathfrak{R}_0$. At the limits, $\varepsilon = 0$ and $\varepsilon = 1$, mixing is indiscriminate (i.e., proportional to activity) and exclusively with others the same age, respectively. In between, it is a convex combination

Figures 3

(a)

(b)

Infection rates, $\beta(a,a')$ corresponding to mixing that is a) proportional to activity alone ($\varepsilon = 0$) and b) also preferential within age groups ($\varepsilon = 0.7$), extreme scenarios defined by independent estimates of $\mathfrak{R} \leq 3$ (figure 2)

Taiwan 2005

Age, a	N(a)	p(a)	$\mu(a)$	$\delta(a)$	$\theta(a)$
<1	195,331	0.478506	0.00365	0.00235	
1-4	949,024	0.477124	0.000296	0.0001	
5-14	3,114,694	0.478899	0.00016	0.00002	
15-24	3,454,774	0.484257	0.000603	0.00003	0.02795
25-34	3,784,046	0.493567	0.001078	0.00004	0.07339
35-44	3,795,282	0.494498	0.002127	0.00008	0.011999
45-54	3,417,131	0.499058	0.004057	0.0002	6.7E-05
55-64	1,843,297	0.507723	0.008563	0.00042	
65-74	1,301,622	0.517849	0.021091	0.00106	
75+	915,182	0.517323	0.055515	0.01499	

$$\frac{\partial V}{\partial a} + \frac{\partial V}{\partial t} = -[\sigma + \mu(a) + o(a) - \iota(a)\{1 - \varphi(a)\}]V(a,t)$$

$$\frac{\partial W}{\partial a} + \frac{\partial W}{\partial t} = \sigma V(a,t) + \omega Z(a,t) - [\alpha v(a) + \lambda(a,t) + \mu(a) + o(a) - \iota(a)\varphi(a)]W(a,t)$$

$$\frac{\partial X}{\partial a} + \frac{\partial X}{\partial t} = \lambda(a,t)W(a,t) - [\gamma + \mu(a) + o(a) - \iota(a)\varphi(a)]X(a,t)$$
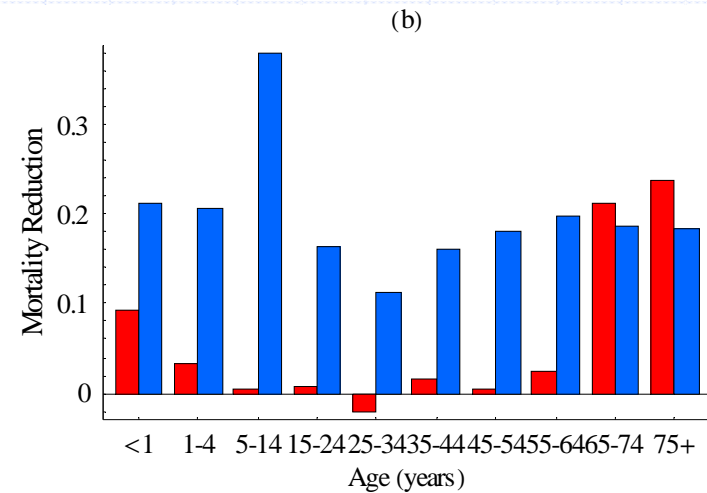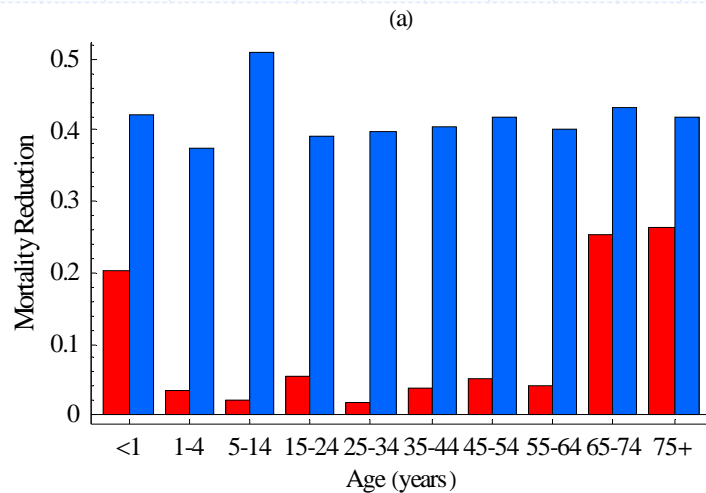
$$\frac{\partial Y}{\partial a} + \frac{\partial Y}{\partial t} = \gamma X(a,t) - [\rho + \delta(a) + \mu(a) + o(a) - \iota(a)\varphi(a)]Y(a,t)$$

$$\frac{\partial Z}{\partial a} + \frac{\partial Z}{\partial t} = \alpha v(a)W(a,t) + \rho Y(a,t) - [\omega + \mu(a) + o(a) - \iota(a)\{1 - \varphi(a)\}]Z(a,t)$$

$$V(0,t) = \int_0^\infty \theta(a)p(a)Z(a,t)da \quad W(0,t) = \int_0^\infty \theta(a)p(a)S(a,t)da$$

NB: ignore, for the present, migration and passively-acquired maternal antibodies, not because they are unimportant, but because we lack information
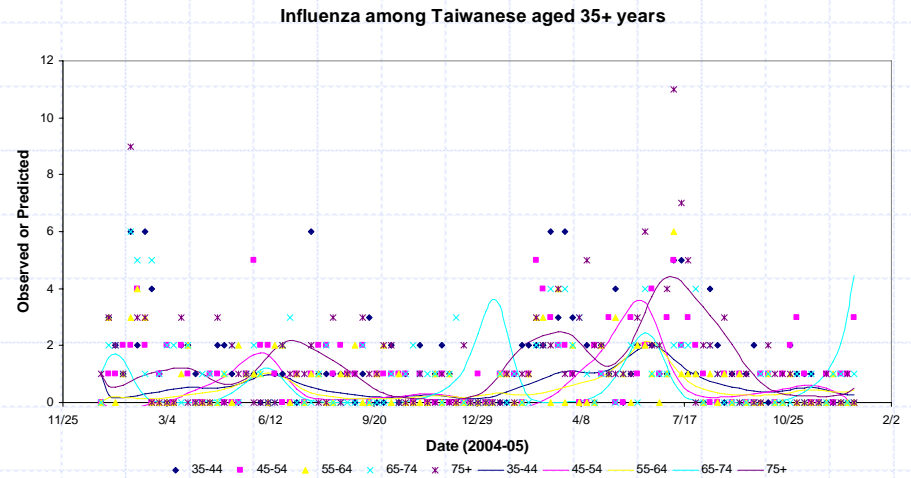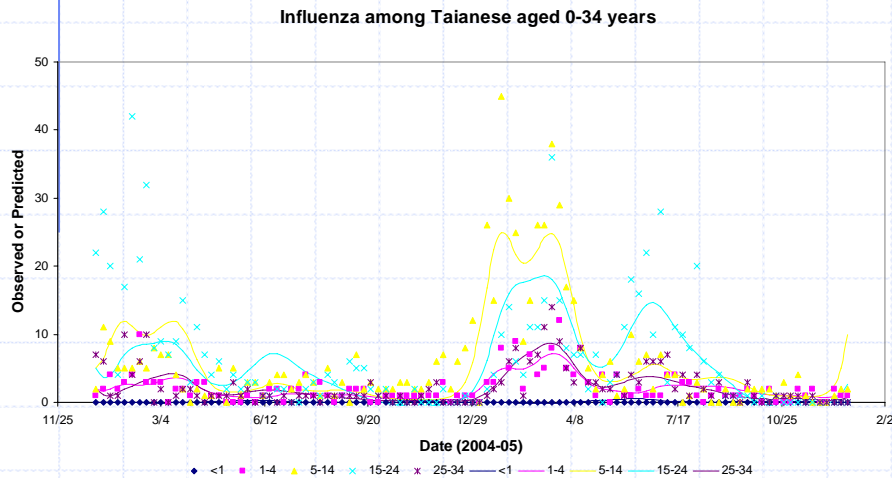
Figures 4

(a) (b)

Proportionate mortality reductions evident in stochastic simulations of the two vaccination strategies (infants and elderly adults, red bars; schoolchildren, blue bars) given the infection rates illustrated in figures 3a and b
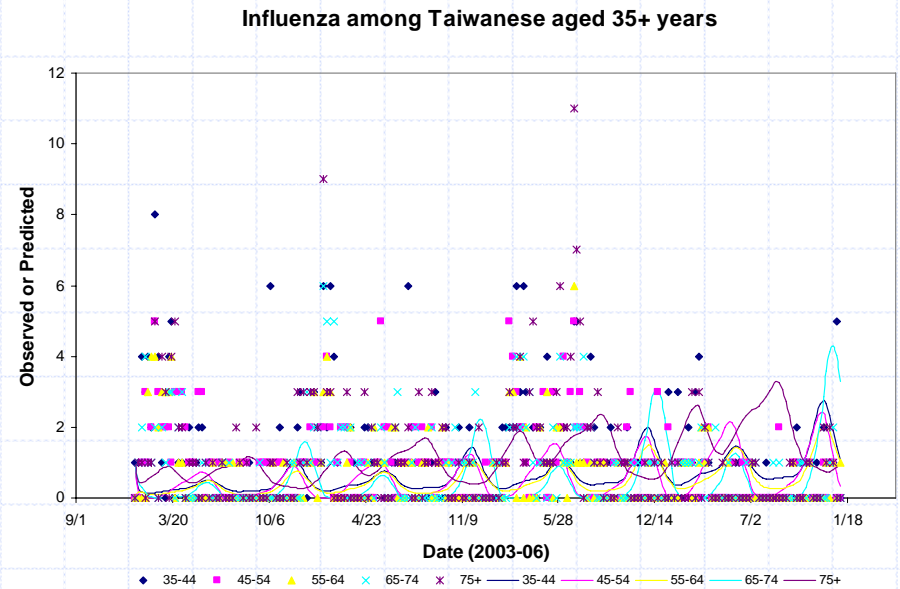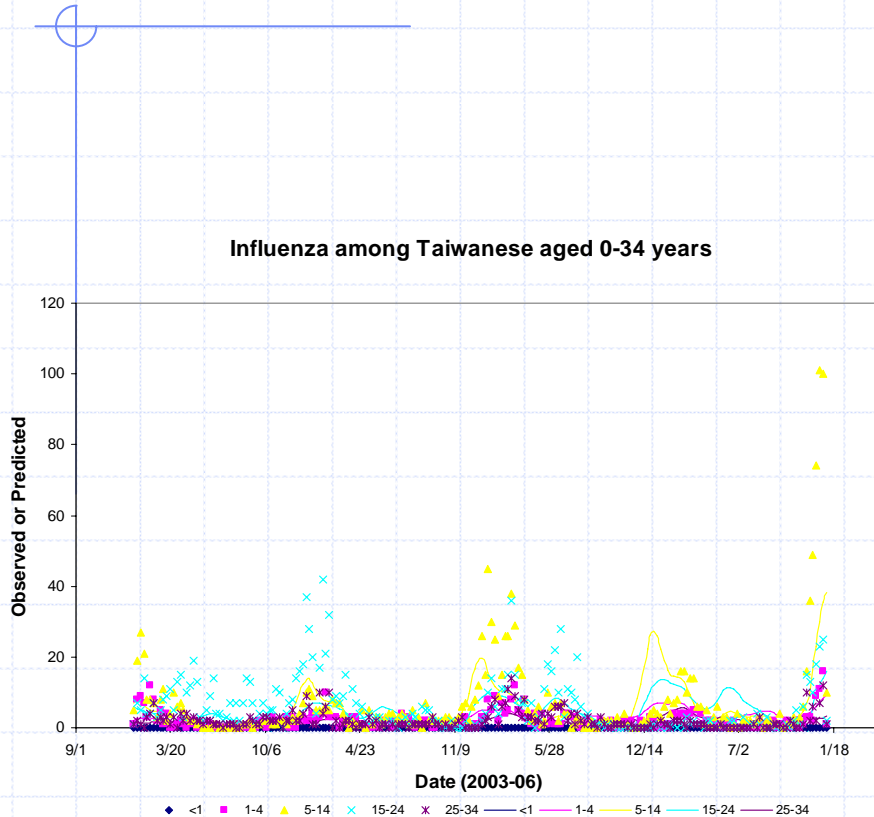
Figure 5
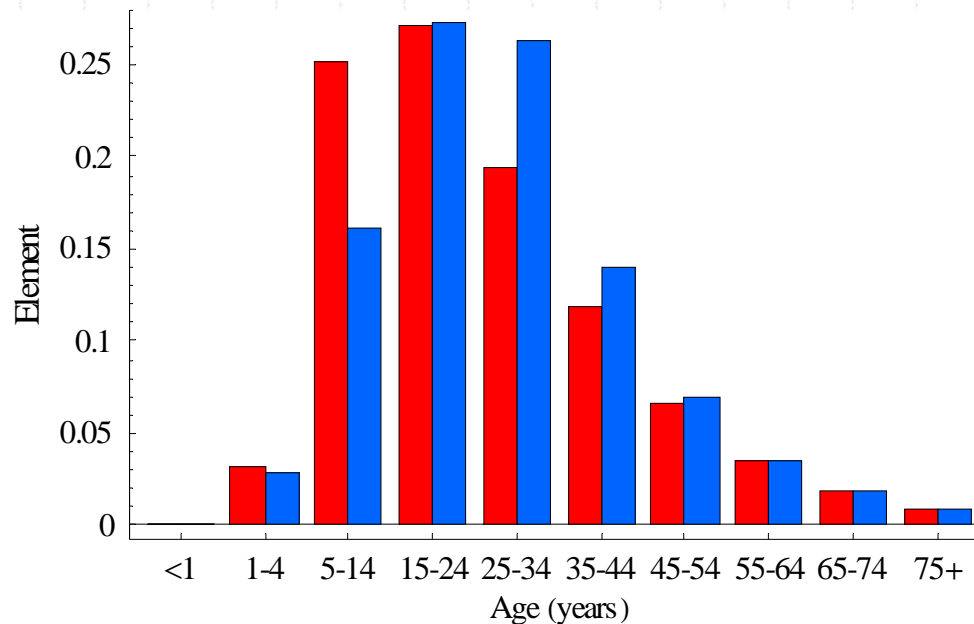
Normalized age-specific contributions to $\Re_0$ given $\varepsilon = 0$ or 0.7 (red and blue bars, respectively). Increasing preference shifts contributions to older ages, concomitantly reducing the indirect effects of vaccinating schoolchildren (cf. figures 4a and b)

Specific Case Definition, National Health Insurance Claims, 2 yrs

Influenza among Taianese aged 0-34 years

Influenza among Taiwanese aged 35+ years

Specific Case Definition, National Health Insurance Claims, 4 yrs

Influenza among Taiwanese aged 0-34 years

Influenza among Taiwanese aged 35+ years

Laboratory Surveillance

Influenza in Taiwan

Influenza and RSV in Taiwan

Targeted Vaccination

6/26/2007
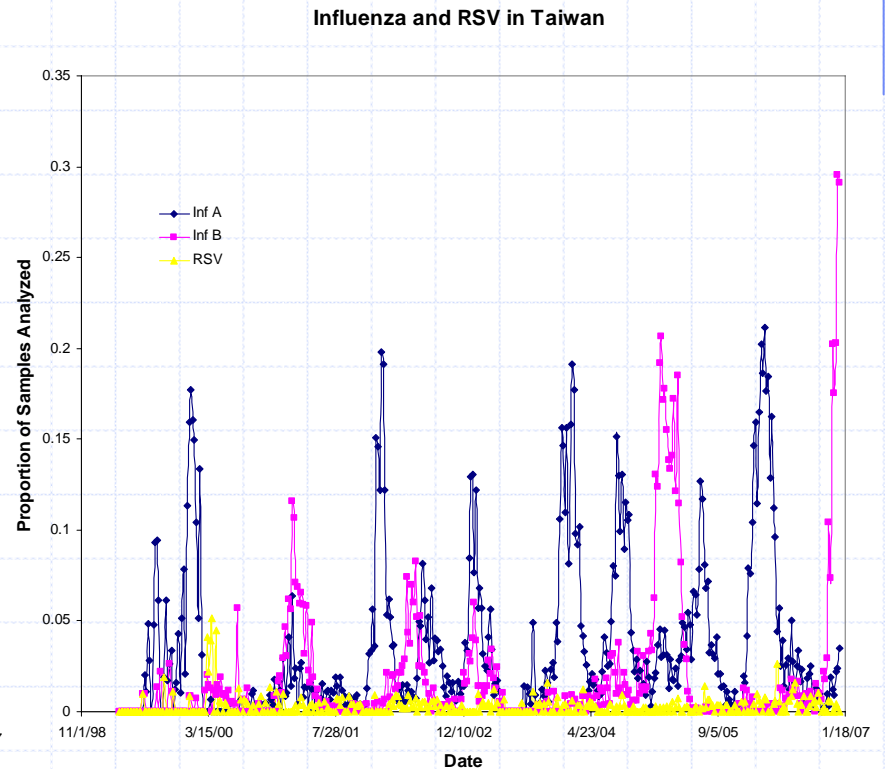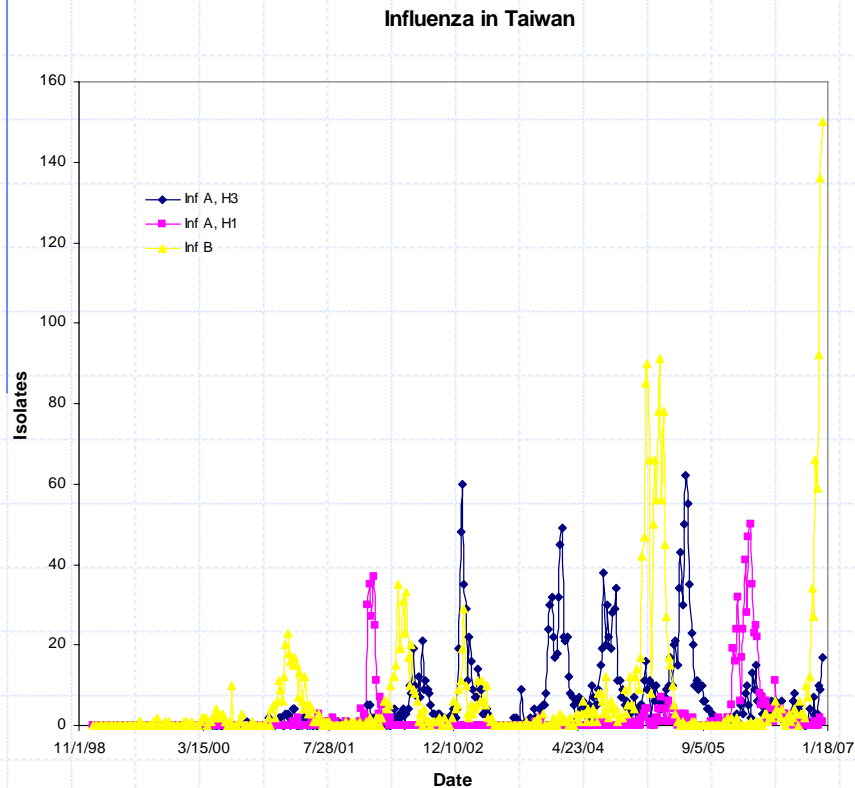
Plans

- The Taiwanese government would like us to determine the impact of their laboratory's projected vaccine production

- If insufficient, they will either subsidize private sector production or contract with foreign manufacturers

- We've also modeled anti-viral medications to evaluate control via prophylaxis or treatment while minimizing the risk of resistance

Evolution of Resistance

- While working on efficient vaccination strategies, we realized that efficient medication strategies would minimize opportunities for resistance to evolve. So, I'll conclude by describing a model with which we plan to explore strategies to attain this dual objective

- As transmissible mutants have arisen, we believe modelers should be more concerned about the planned widespread prophylaxis with relatively few available anti-viral medications, which – insofar as there have historically been multiple waves – could be disastrous

- Lipsitch et al. (PloS Med 2007;4:111-21) is innovative, but biologically unrealistic in one respect we believe important. And the authors claim results with age-structured and unstructured versions are similar, meaning they didn't try various allocation strategies

- As pathogens can evade any host defense by virtue of their disparate generation times, this is part of a more general research program I've begun with academic colleagues

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Vaccines:

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Another Influenza Model
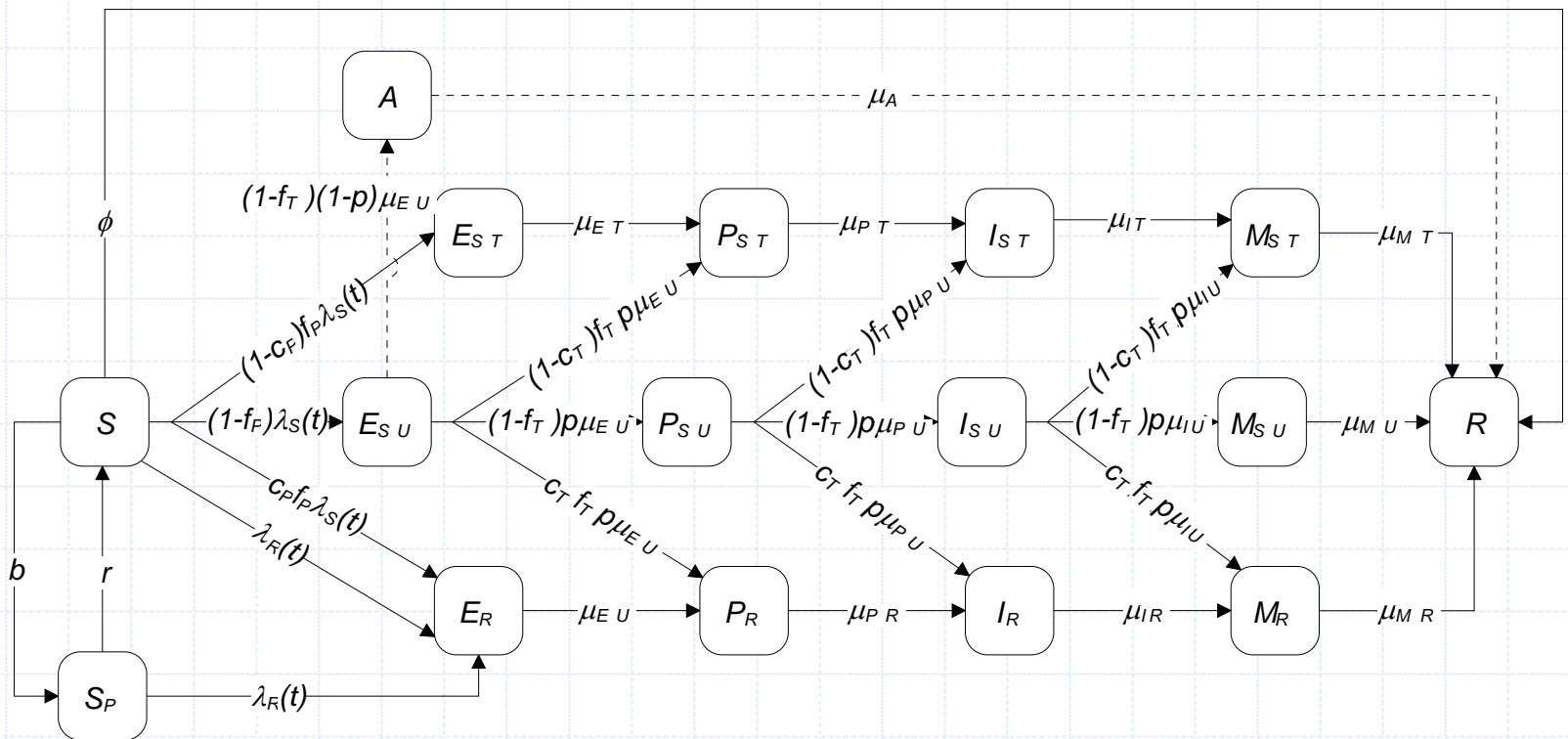
Medication Strategies

- We developed a model including prophylaxis and medication post-exposure and at various stages during illness

- Susceptible people (S) begin/end prophylaxis at rates b and r, a fraction f_p receives medication post-exposure, among whom a fraction c_p develops resistance (respectively E_{ST} and E_R). A fraction 1-p does not develop symptoms (A), but among the complement, f_{ci} receive medication during stage i and c_{ti} develop resistance. The remaining states are prodrome (P), acute illness (I, during which treatment is still beneficial, and M) and recovered (R)

- With this model, we expect to be able to demonstrate that timely treatment of schoolchildren would reduce the duration and number who must be treated (i.e., have the greatest impact and minimize the risk of resistance evolving). Of course, those most vulnerable to complications also must be treated

- In contrast, prophylaxis would not only be relatively inefficient, but reduce any fitness disadvantage associated with resistance, facilitating the spread of resistant relative to wild-type strains

Colleagues

- Jim Alexander
- Jen-Hsiang Chuang
- Zhilan Feng
- Denis Taneri
- Bill Thompson
- Peet Tüll
- Jianhong Wu

Targeted Vaccination