Mathematical Epidemiology and the Modeling of SARS

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Why Mathematical Epidemiology（數理流行病學）Now?
Emerging and re-emerging infectious diseases

- Cleaner environment (polio小兒麻痺: emerge in Europe in 19th century, first major outbreak in US in 1916)
- Re-emerging diseases (TB肺結核: co-infection with HIV)
- More and Faster Globalization 全球化 (HIV 1959? SARS 2003, WNV西尼羅病毒)
- Modern advances in science and technology on understanding of infectious diseases (Molecular biology分子生物學: Is 1918 Influenza (流感) epidemic due **to a strain of swine flu? Origin of HIV?)**

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Definition of Epidemiology (流行病學)

- Traditional Definition: The study of communicable diseases (傳染病) which is temporarily prevalent in a community.
- Modern Definition (after 1950): The study of all health-related states or phenomena prevalent in a community and their control. (Also include non-infectious diseases such as cancer 癌症, gout 痛風, obesity 肥胖, etc.)

DEFINITION OF MATHEMATICAL EPIDEMIOLOGY (數理流行病學)

"The application of mathematics* to the study of infectious disease epidemiology"

數學在傳染病流行病學上之應用

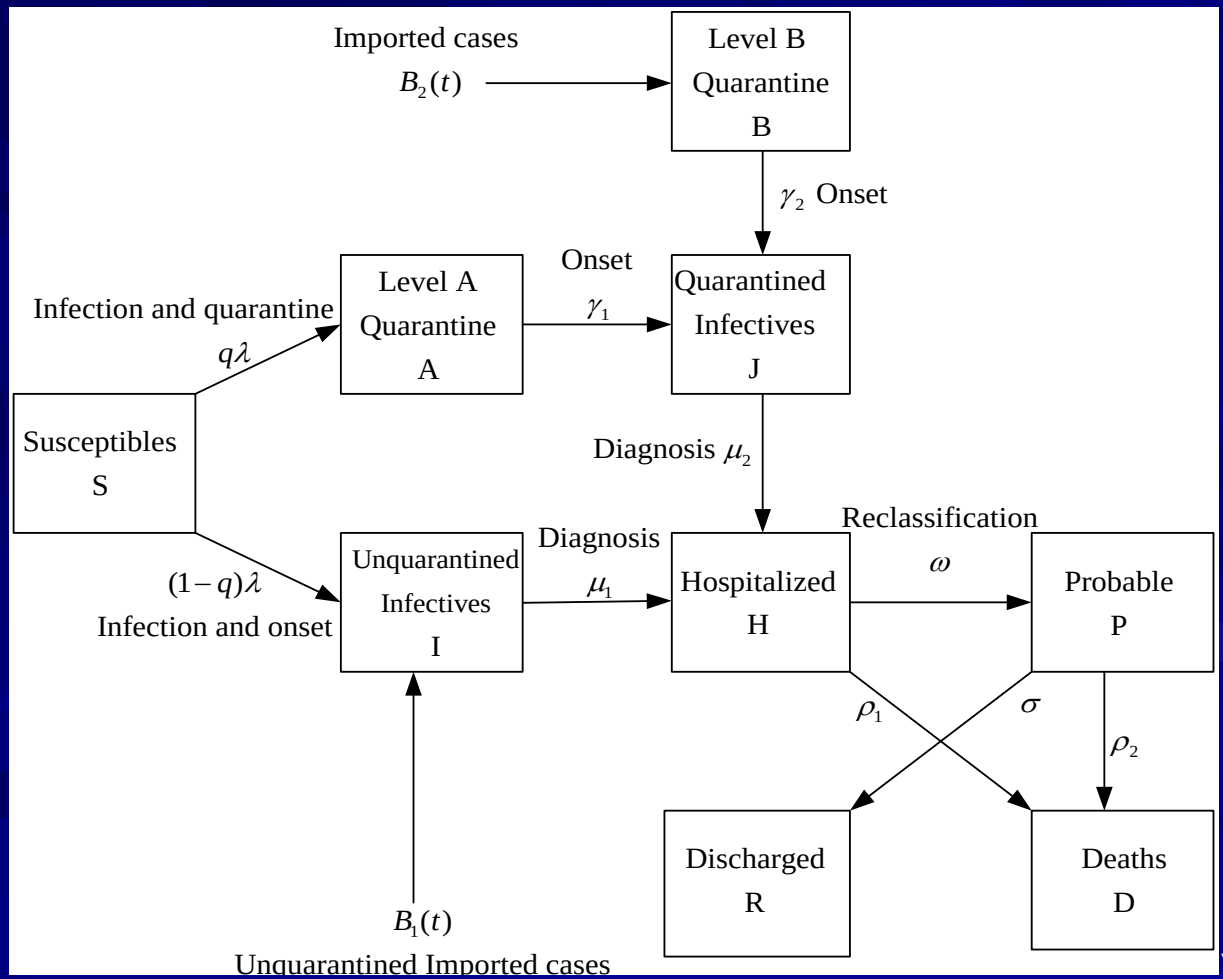
-*Infectious Diseases of Humans*, by Anderson and May, 1991

*Includes but not limited to statistics

Recent Modelings of SARS Outbreak

- Quarantine and intervention measures for SARS (with King, Ho, Chen, Hsu, *et al*., EID, 2005)
- Model of quarantine and intervention measures (with S.-B. Hsu, revised for *SIAP*)
- Infection age-dependent integro-differential equations model for SARS (with G. Webb *et al*., in progress)
- Genes associated with susceptibility to SARS (with Ho, Hsu Schmitz, Chen, *et al*., in progress)

A SARS Model with Intervention Measures and Public Response to Severity of an Outbreak (Hsieh, King, Chen, Ho, Hsu, and Wu)



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Model with "Severity-dependent" Infection Rate due to public/social response to severity of outbreak

$$
\begin{aligned}
S_{n+1} &= A S_n - \lambda \\
A_{n+1} &= A_n - \gamma_1 A_n + q\lambda \\
B_{n+1} &= B_n - \gamma_2 B_n + B_2(n) \\
J_{n+1} &= J_n - \mu_2 J_n + \gamma_1 A_n + \gamma_2 B_n \\
I_{n+1} &= I_n - \mu_1 I_n + (1-q)\lambda + B_1(n) \\
H_{n+1} &= H_n - \omega H_n - \rho_1 H_n + \mu_1 I_n + \mu_2 J_n \\
P_{n+1} &= P_n - \rho_2 P_n - \sigma P_n + \omega H_n \\
D_{n+1} &= D_n + \rho_1 H_n + \rho_2 P_n \\
R_{n+1} &= R_n + \sigma P_n
\end{aligned}
$$

with

$$
\begin{aligned}
\lambda &= \frac{\beta I_n}{1 + a(P_n + R_n + D_n)} \times \frac{S_n}{S_n + I_n} \\
&\approx \frac{\beta I_n}{1 + a(P_n + R_n + D_n)} \\
&\approx [1 - a(P_n + R_n + D_n)]\beta I_n
\end{aligned}
$$

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Estimation Method

The three-stage least squares (3SLS) procedure involves the application of generalized least squares estimation to a system of equations, each of which has first been estimated using two-stage least squares (2SLS) . The 3SLS procedure can be shown to yield more efficient parameter estimates than does 2SLS because it takes into account of the cross-equation correlation.

Reference: R. S. Pindyck, D. L. Rubinfeld, *Econometric Models and Economic Forecasts* (McGraw-Hill, 1997)

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Table. Model parameter estimates

Parameter	Estimated value	95%CI	p-value
Initial infection rate	**β =0.429**	**(0.363-0.495)**	**<0.0001***
Severity-dependent constant	**a=0.0013**	**(0.0006-0.0020)**	**0.0030****
Daily quarantine rate	**q=0.0277**	**(0.0124-0.0430)**	**0.0003#**
Removal rate for Level A quarantine	γ_1=0.1037	(0.0595-0.1479)	<0.0001
Removal rate for Level B quarantine	γ_2=0.3218	(0.2387-0.4049)	<0.0001
Admission rate for non-quarantined	μ_1=0.3791	(0.3418-0.4165)	<0.0001
Admission rate for quarantined cases	μ_2=0.4206	(0.3152-0.5260)	<0.0001
Classification rate as probable case	ω=0.1166	(0.1012-0.1321)	<0.0001
Fatality rate of cases other than probable	ρ_1=0.0139	(0.0090-0.0189)	<0.0001
Fatality rate of probable cases	ρ_2=0.0080	(0.0050-0.0109)	<0.0001
Discharge rate of probable cases	σ =0.0617	(0.0567-0.0667)	<0.0001

*p-value of 1- μ 1+ β
**p-value of a β
#p-value of *q* β

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Efficiency of quarantine

- Cumulative quarantine rate:

  24/480=5%

- Mean quarantine rate (averaged percentage of infected but asymptomatic persons who were actually quarantined on that day):

  q=2.77%

SARS case fatality rate

WHO definition: for Taiwan
85 cumulative deaths/480 cumulative cases=17.7%

Average case fatality ratio over the time period 2/25-6/25 of a probable SARS case conditional on outcomes of only death or recovery :

$$\frac{\rho_2}{\rho_2+\sigma}=\frac{0.0080}{0.0080+0.0617}=0.114=11.4\%$$

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Table. Impact of Level A quarantine with various theoretical scenarios on the numbers of SARS cases and SARS fatality as compared with the estimated effective quarantine rate q=0.0277 (+ denotes additional cases, - denotes reduction in cases).

	Increase when q=0.00	Reduction when q=0.2	Reduction when q=0.6	Reduction when q=1
SARS Cases	+42(10%)	-179(44%)	-309(76%)	-327(80%)
Deaths	+8(10%)	-39(49%)	-58(73%)	-64(81%)

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Table. Impact of Level B quarantine of imported cases under various theoretical scenarios on the numbers of SARS cases and SARS fatality.

	SARS cases	Deaths
If one un-quarantined imported case after 4/28 had been quarantined	-2(0.5%)	-1(1.3%)
If all 16 un-quarantined imported cases had been quarantined	-91(22%)	-19(24%)
If one imported case quarantined before 4/28 had not been quarantined	+5(1.2%)	+1(1.3%)
If one imported case quarantined after 4/28 had not been quarantined	+1(0.3%)	0(0)
If both quarantined imported cases had not been quarantined	+7(1.7%)	+1(1.3%)
If no one was quarantined in either Level A or B quarantine	+49(11%)	+9(11%)

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Table 6. The effect of the change in the infection rate β [1-a(Pn+Rn+Dn)] on the numbers of SARS cases and SARS fatality compared to a=0.0013. The percentage increase or reduction from theoretical numbers of cases or death using model are given in parenthesis.

	No public response (a=0.00)	Slight decrease in public response (a=0.0006)	Slight increase in public response (a=0.0020)
SARS cases	+13015	+291(67%)	-103(24%)
Deaths	+1415	+55(65%)	-20(24%)

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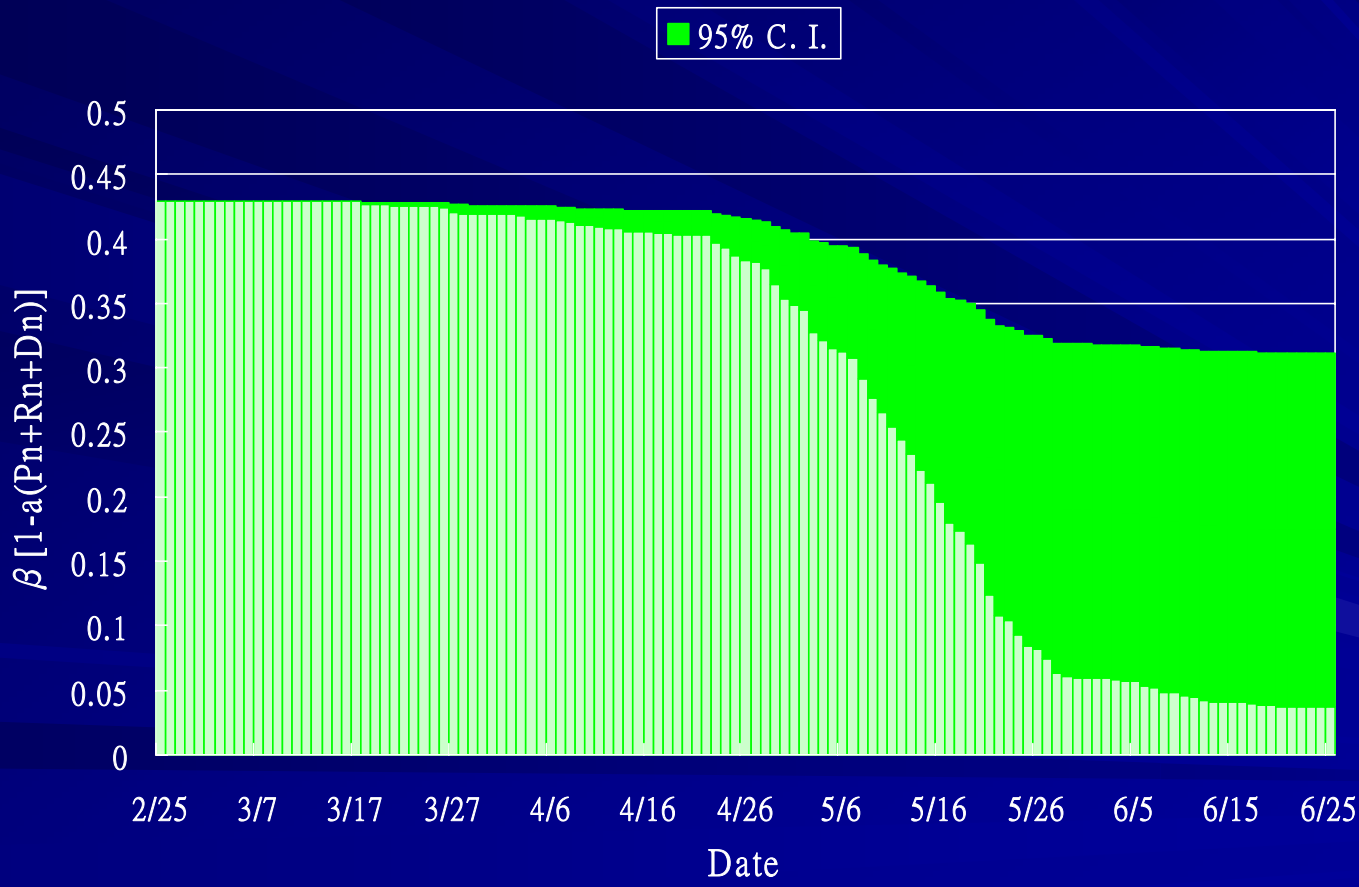
Fig. 3B. Temporal change in severity-dependent infection rate $\beta[1-a(P_n+R_n+D_n)]$ during 2/25-6/25. (a=0.0013, β=0.429)



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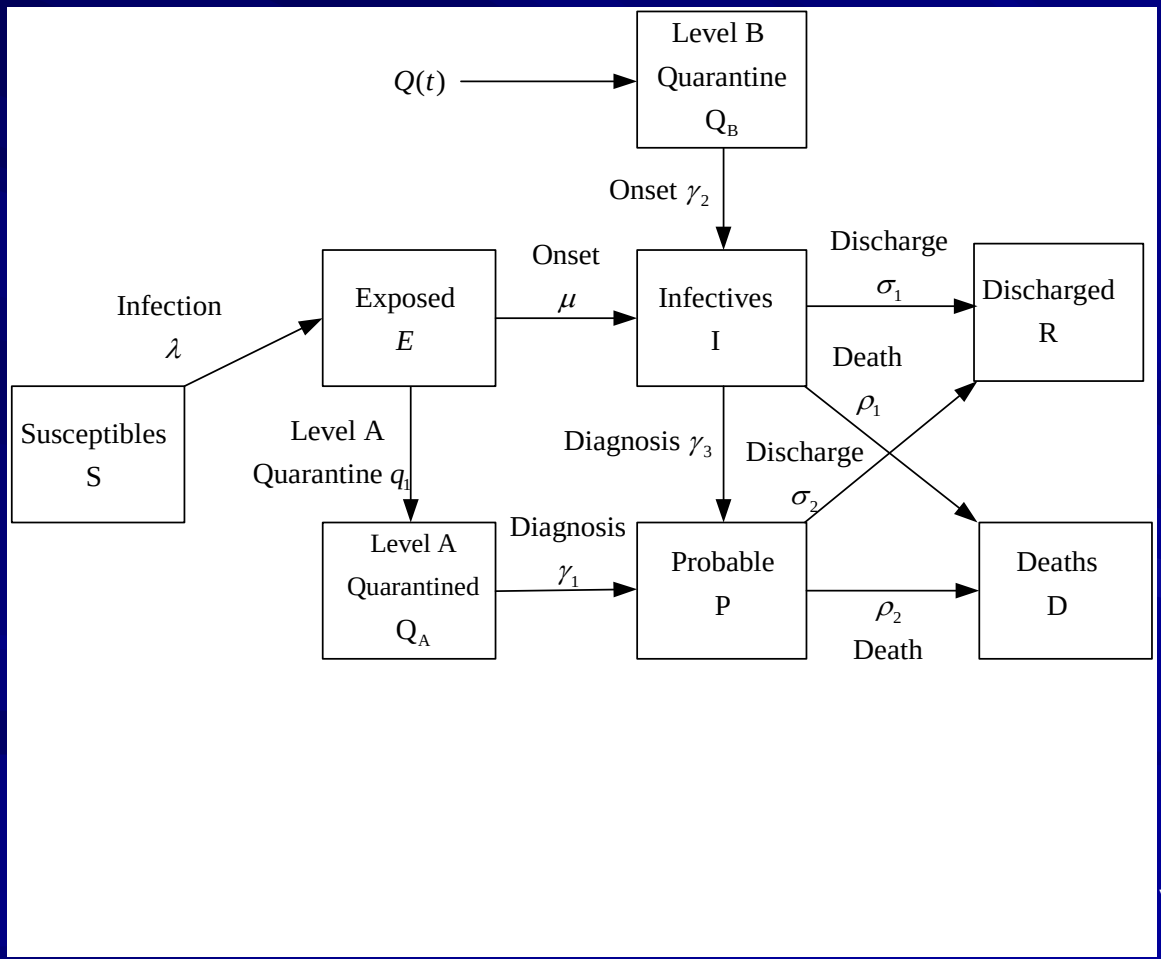
Conclusions

- Both Level A and Level B quarantine in Taiwan contributed to reduction in infections and deaths, but were not as effective as social response/public campaign to reduce infections.
- Level A quarantine had more impact than Level B quarantine. But timeliness of quarantine is an important factor.
- Quarantine needs to be combined with other measures including public campaign to reduce infections.

A SARS ODE Model with Intervention Measures and Public Response to Severity of an Outbreak (with S. B. Hsu)



Basic Reproduction Number
R_0 (傳染基數)

Definition: The number of secondary infections produced by an infective newcomer (index case) in a disease-free population.

$R_0 < 1$ means the disease will fade away eventually. Otherwise the disease will persist in the population. (e.g., Anderson and May 1991)

Also known as: Net reproductive value (R. A. Fisher 1930, *Genetic Theory of Natural Selection*), basic reproductive rate (MacDonald 1952, 1957, *Epidemiology and Control of Malaria*).

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Model Equations

$$
\begin{aligned}
S^{'} &= -\lambda(S,E,I,Q_A,Q_B,P,R,D)S \\
E^{'} &= \lambda(S,E,I,Q_A,Q_B,P,R,D)S - \mu E - q_1 E \\
Q_A^{'} &= q_1 E - \gamma_1 Q_A \\
Q_B^{'} &= Q(t) - \gamma_2 Q_B \\
I^{'} &= \mu E + \gamma_2 Q_B - (\sigma_1 + \rho_1 + \gamma_3) I \\
P^{'} &= \gamma_1 Q_A + \gamma_3 I - (\sigma_2 + \rho_2) P \\
R^{'} &= \sigma_1 I + \sigma_2 P \\
D^{'} &= \rho_1 I + \rho_2 P,
\end{aligned}
$$

with incidence of infection with quarantine:

$$
\begin{aligned}
\lambda(S,E,I,Q_A,Q_B,P,R,D) = &\frac{c\beta}{1+a(P+R+D)} \\
&\times \frac{I + \alpha_A Q_A + \alpha_B Q_B + \alpha_P P}{S + E + I + \alpha_A Q_A + \alpha_B Q_B + \alpha_P P}.
\end{aligned}
$$

Model without Quarantine

$$
\begin{aligned}
S^{'} &= -\lambda(S,E,I,P,D)S \\
E^{'} &= \lambda(S,E,I,P,D)S - \mu E \\
I^{'} &= \mu E - (\sigma_1 + \rho_1 + \gamma_3) I \\
P^{'} &= \gamma_3 I - (\sigma_2 + \rho_2) P \\
R^{'} &= \sigma_1 I + \sigma_2 P \\
D^{'} &= \rho_1 I + \rho_2 P,
\end{aligned}
$$

where $\lambda(S,E,I,P,R,D) = \beta[\frac{c}{1+a(P+R+D)}]\frac{I+\alpha_P P}{S+E+I+\alpha_P P}$.
The Disease-Free Equilibrium (DFE) is $(S^*, 0, 0, 0, R^*, D^*)$ with $S^* + R^* + D^* = S_0 + I_0$, the initial populations. An endemic equilibrium is $(0, 0, 0, 0, R^{\#}, D^{\#})$ with $R^{\#} + D^{\#} = S_0 + I_0$.

Basic Reproduction Number

The basic reproduction number R_0 for the case without quarantine (using method proposed by van den Driessche and Watmough, 2002):

$$R_0 = \frac{\beta c}{(\sigma_1 + \rho_1 + \gamma_3)[1 + a(R^* + D^*)]} + \frac{\beta c \alpha_P \gamma_3}{(\sigma_1 + \rho_1 + \gamma_3)[1 + a(R^* + D^*)](\sigma_2 + \rho_2)}$$

For the model with quarantine, the effective basic reproduction number with quarantine R_Q is:

$$R_Q = \beta \frac{c}{[1 + a(R^* + D^*)]} \{ \frac{\mu}{(\sigma_1 + \rho_1 + \gamma_3)[\mu + q_1]} + \frac{\alpha_A q_1}{\gamma_1 [\mu + q_1]} \} + \frac{c\beta}{[1 + a(R^* + D^*]} \frac{\alpha_P}{(\sigma_2 + \rho_2)} \{ \frac{\gamma_3}{(\sigma_1 + \rho_1 + \gamma_3)} \frac{\mu}{[\mu + q_1]} + \frac{q_1}{\mu + q_1} \}$$

For the limiting system:

$$\begin{aligned}
S^{'} &= -\frac{\beta(I+\alpha_A Q_A)}{S+E+I+\alpha_A Q_A} S \frac{c}{1+a(D_\infty+R_\infty)}, \\
E^{'} &= \frac{\beta(I+\alpha_A Q_A)}{S+E+I+\alpha_A Q_A} S \frac{c}{1+a(D_\infty+R_\infty)} - (\mu+q_1)E, \\
Q_A^{'} &= q_1 E - \gamma_1 Q_A, \\
I^{'} &= \mu E - \widetilde{q} I.
\end{aligned}$$

Let $\widehat{\beta} = \dfrac{\beta c}{1+a(D_\infty^*+R_\infty^*)}$, we have the following theorem.

Lemma 0.11. *If $W_1(t) \to \infty$ as $t \to \infty$, then we have $W_2(t) \to \widetilde{W_2} < \infty$, $Z_3 = \dfrac{W_3}{W_1} \to 0$, and $S(t) \to S_\infty > 0$.*

We now have the main theorem:

Theorem 0.12. *Let $\widetilde{\beta} = \dfrac{\beta c}{1+aN}$.*

1. *If $W_1(t) \to \infty$ as $t \to \infty$ and $\widetilde{\beta} < A_2$ and E_0, E_{23}^* are unstable, then $S(t) \to S_\infty > 0$;*
2. *If $W_1(t) \to 0$ as $t \to \infty$ and $\widetilde{\beta} > A_2$ and one of the two equilibria E_0, E_{23}^* is stable, then $S(t) \to 0$ as $t \to \infty$;*
3. *The bistable case occurs when $\widetilde{q} < \widetilde{\beta} < A_2$, or $(\mu+q_1)(1+\dfrac{W_2^*}{1+\alpha_A W_3^3}) < \widetilde{\beta} < A_2$.*

Proof.

1. **If not, $S(t) \to 0$ as $t \to \infty$, i.e., $S_\infty^* = 0$. Consider the limiting system above where we have**

$$\widehat{\beta} = \frac{\beta c}{1+a(D_\infty^*+R_\infty^*)} = \frac{\beta c}{1+aN} = \widetilde{\beta} < A_2.$$

   It follows that $\lim\limits_{t\to\infty} W_1(t) = +\infty$ (assuming the convergence is global) $\Longrightarrow S(t) \to S_\infty > 0$. Hence we have a contradiction.

2. **If not, assume $S(t) \to S_\infty^* > 0$. Then $S_\infty^* + D_\infty^* + R_\infty^* = N$. Consequently,**

$$\widehat{\beta} = \frac{\beta c}{1+a(D_\infty^*+R_\infty^*)} > \frac{\beta C}{1+a(S_\infty^*+D_\infty^*+R_\infty^*)} = \frac{\beta C}{1+aN} = \widetilde{\beta} > A_2$$

   and $\lim\limits_{t\to\infty} S(t) = S_\infty = 0$, again a contradiction.

□

Remark : It can be shown that the local stability condition for the effective reproduction number with quarantine $R_Q < 1$ is equivalent to the condition in (1) of Theorem 0.12, namely $\widetilde{\beta} = \dfrac{\beta c}{1+a(S_\infty^*+D_\infty^*+R_\infty^*)} < A_2$.

Concluding Remarks

1. Model without quarantine but with behavior change due to public response to the severity of the disease: If $\beta c > \sigma_1 + \rho_1 + \gamma_3$, the epidemic would persist without public response. If the magnitude of public response as measured by the parameter a is sufficiently large so that $R_0 < 1$, the reduction of infections will be large enough to drive the epidemic down to disease-free state.

2. Model with both quarantine and behavior change: The effective reproduction number with quarantine R_Q gives local stability of DFE when $R_Q < 1$. However there are ranges of the parameters which would lead to bistable steady states. In such cases, we conjecture that there is a saddle point with 2-dimensional stable manifold:

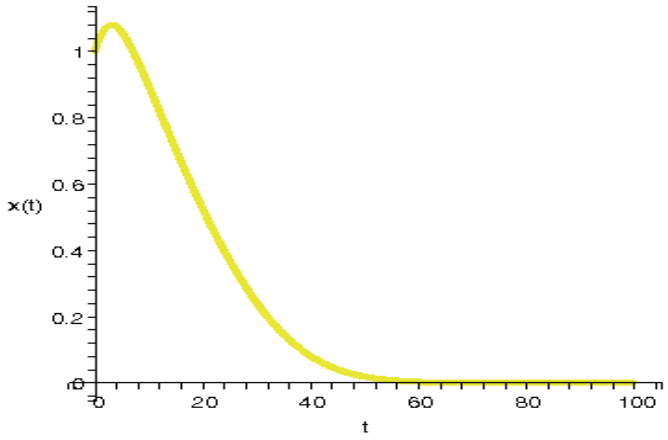

FIG. 0.5. *Numerical example with* $\alpha_A = 0.1, \widetilde{\beta} = 0.5, \widetilde{q} = 0.3, \gamma_1 = 0.4, q_1 = 0.2, \mu = 0.2$, *and initial population* $S(0) = 1, E(0) = 0, Q_A(0) = 0, I(0) = 1$, *where system approaches endemic equilibrium.* $X(t)$ *is* $W_1(t) = S(t)/I(t)$ *which goes to zero.*

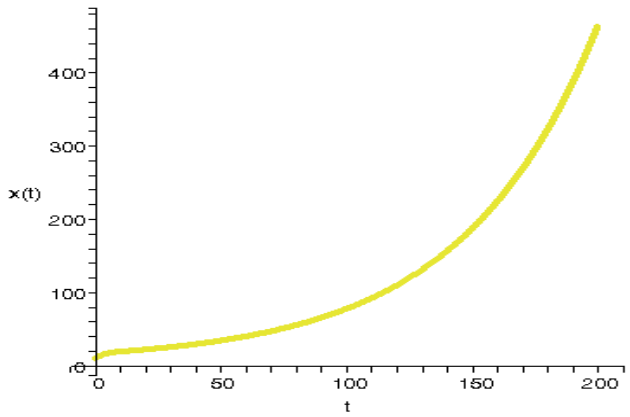

FIG. 0.6. *Numerical example with* $\alpha_A = 0.1, \widetilde{\beta} = 0.5, \widetilde{q} = 0.3, \gamma_1 = 0.4, q_1 = 0.2, \mu = 0.2$*, and the initial population be* $S(0) = 10, E(0) = 0, Q_A(0) = 0, I(0) = 1$*, where the system approaches DFE.* $X(t)$ *is* $W_1(t) = S(t)/I(t)$ *which goes to a nonzero equilibrium and* $S(t) \to 14.58322$.

3. (i) If adherence to quarantine results in decreased contact rate c and transmission probability β so that the effective infection rate $\tilde{\beta} = \dfrac{\beta c}{1 + aN}$ is sufficiently lowered. The epidemic can be successfully contained, regardless of the initial population sizes at the onset of outbreak.

(ii)If $\tilde{\beta}$ is not sufficiently lowered, the epidemic will persist and the susceptible population $S(t)$ will be depleted eventually.

(iii)If $\tilde{\beta}$ is decreased but not sufficiently so, to less than A_2 but greater than $\tilde{q}$. Then the system could approach either the DFE or the endemic steady state, depending on the initial values of the system.

That is, if the quarantine were not adhered faithfully and the false sense of security that all infective persons are in quarantine lead to increased $\tilde{\beta}$, the quarantine might in fact have an adverse on contributing to the persistence of the epidemic.

For illustration, we consider the hypothetical case where $\beta < \tilde{q} = \sigma_1 + \rho_1 + \gamma_3$. Since $\beta > \tilde{\beta}$ when $c = 1$, the system goes to DFE with no quarantine implemented. However, when $\mu + q_1 < \beta < \tilde{q}$ the system will converge to the endemic equilibrium. This demonstrates the possibility that, under appropriate parameter values, a quarantine program which is not sufficiently comprehensive ($q_1 < \beta - \mu$) could have the adverse effect of changing a system which would have approached DFE without quarantine to converging to the endemic equilibrium instead. When $\alpha_A = 0$, the stability condition for E_∞ becomes $\beta < \tilde{q}\mu/(\mu + q_1)$. Hence an effective Level A quarantine is always helpful in containing the epidemic.

4. If, for some disease unlike SARS in its ability to infect during asymptomatic stage, some fraction of the quarantined population is not fully isolated and can still infect others (i.e. $\alpha_A > 0$), then quarantine might also effect the outbreak adversely. A numerical example is as follows: Let $\alpha_A = 0.1, \beta = 0.5, \mu = 0.5, \tilde{q} = 0.7, q_1 = 0.1, \gamma_1 = 0.01, A_2 = 0.35$. Here $\widetilde{E}_{12} = (0.08, 0.4, +\infty)$ is a global attractor. On the other hand, if there is no quarantine (i.e. $q_1 = 0$ and hence $\alpha_A = 0$), DFE is the global attractor.

Note that a condition for these cases to emerge is $\tilde{q} > A_2$, or equivalently $\gamma_1/\tilde{q} < \alpha_A$. Hence if the there is a nonzero reduction in the infection rate of the quarantined class α_A which is larger than the ratio of the progression rate of the quarantined persons γ_1 to the removal rate of the unquarantined infectives $\tilde{q}$, adverse effect could take place with implementation of quarantine.

To keep this adverse scenario from occurring, one would need either (i) significant reduction of infection by the quarantined individuals (small α_A), or (ii) quick isolation of quarantined persons at onset (large γ_1) compared to the removal of infective class (small $\tilde{q}$). Similar possible adverse effect of intervention measures has also been observed in models of infectious diseases (e.g. Andesrson et al 1991, Hsieh and Velasco-Hernandez 1995).

TABLE 0.1

Affected area	Basic reproduction number [Literature cited]	Effective quarantine rate q_1^* needed to contain outbreak
Hong Kong	2.7 [Donnelly et al.]	0.267
	3 [Lipsich et al.]	0.314
Toronto	3.3 [Wallinga]	0.361
Taiwan	3.77 [Hsieh et al.]	0.435

5. Quarantine for SARS with the assumption that $\alpha_P = \alpha_A = 0$: If all other pertinent parameters remain the same, we have $R_Q = R_0\mu/(\mu + q_1)$. Hence, the implementation of quarantine alone would reduce the mean reproduction number of an infective individual by a factor of $1 - \mu/(\mu + q_1)$.

Using the pertinent parameters estimated from the Taiwan SARS data by Hsieh et al. (2004), the effective quarantine rate q_1 was estimated to be 0.0375. Donnelly et al. (2003) gave the maximum likelihood estimate for the mean time from exposure to onset of symptoms at 6.37 days, consequently the mean progression rate from exposure to onset is approximately $\mu = 1/6.37 = 0.157$. We then conclude that, *if all other parameters remain unchanged*, the quarantine in Taiwan would result in a reduction of 19.3% ($\mu/(\mu + q_1) = 0.807$) for the mean reproduction number by an infective individual. One can conclude that quarantine alone would be difficult to contain the epidemic (i.e. reduce R_0 down to below one) in Taiwan. For a given affected areas with a basic reproduction number R_0, we need to have an effective quarantine rate of $q_1 > q_1^* = (0.157 - 1/R_0)/0.157$ for R_Q to be less than 1.

6. The effectiveness of quarantine for infectious diseases like SARS, for which no infection is being prevented during the quarantine period, can only be indirect and therefore must be combined with other intervention measures in order to fully contain the outbreaks.

An SEIR/QH Model Structured by Disease Age

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Ying-Hen Hsieh (National Chung Hsing University, Taichung, Taiwan)

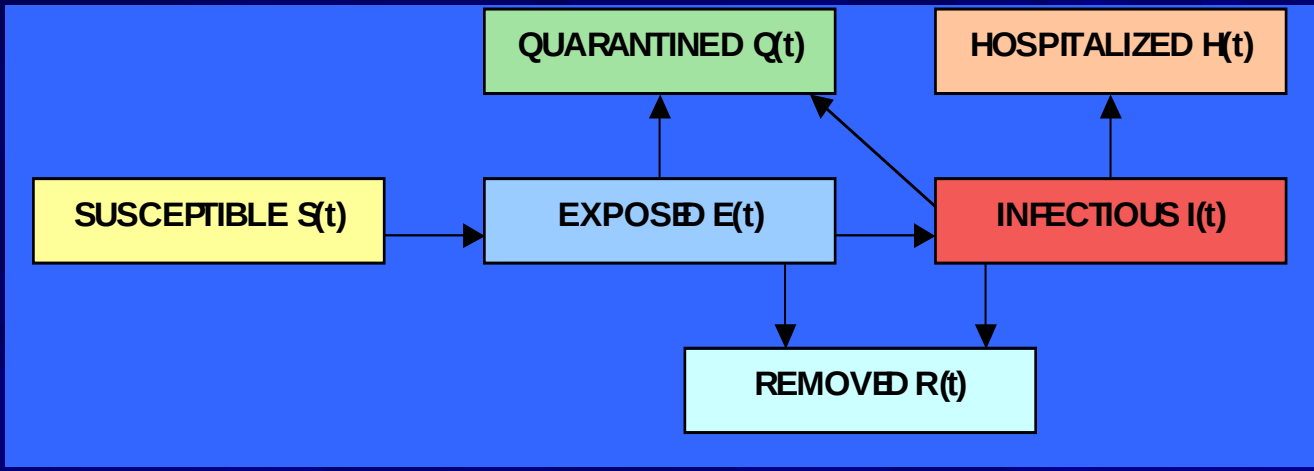
Jianhong Wu (York University, Toronto, Canada)

Chwan-Chuan King (National Taiwan University, Taipei, Taiwan)

Jiunn-Shyan Julian Wu (Center for Disease Control, Taipei, Taiwan)

Chuan Jen Chyan (Tamkang University, Tamsui, Taiwan)

Model Compartments



S(t) = the number of susceptibles at time t

E(t) = the number of exposed (infected but not yet infectious) at time t

I(t) = the number of infectious at time t

Q(t) = the number of quarantined at time t

H(t) = the number of hospitalized at time t

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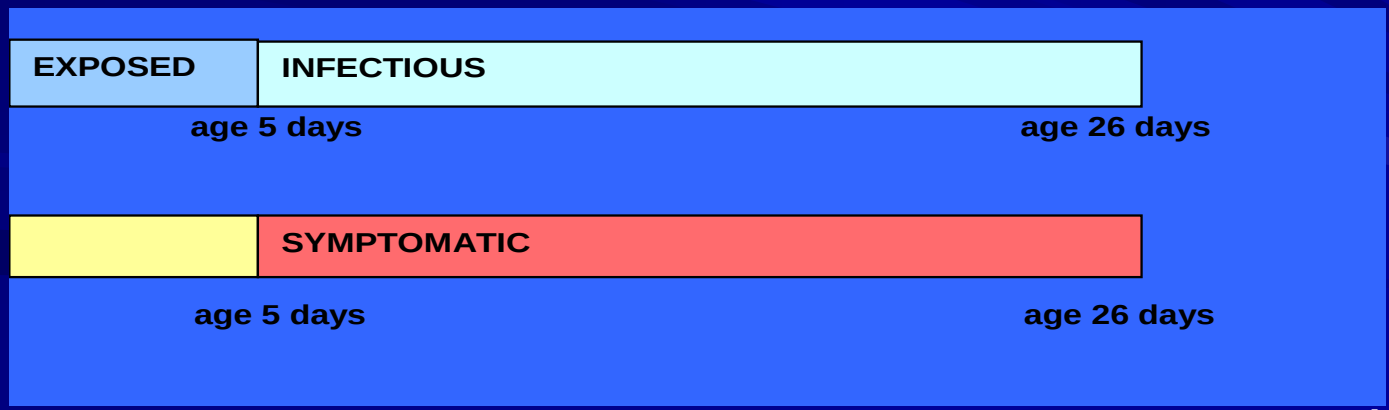
Disease Age

Let i(a,t) denote the density of infectives of disease age a at time t.

The infection is acquired at age 0. An infective is non-infectious from age 0 to age r = 5 days, and infectious for s = 21 days, from age r = 5 days to age r + s = 26 days. The number of exposed and infectious at time t are

$$\int_0^r i(a,t)\,da \quad \text{and} \quad \int_r^{r+s} i(a,t)\,da$$

The symptomatic period begins at 5 days.



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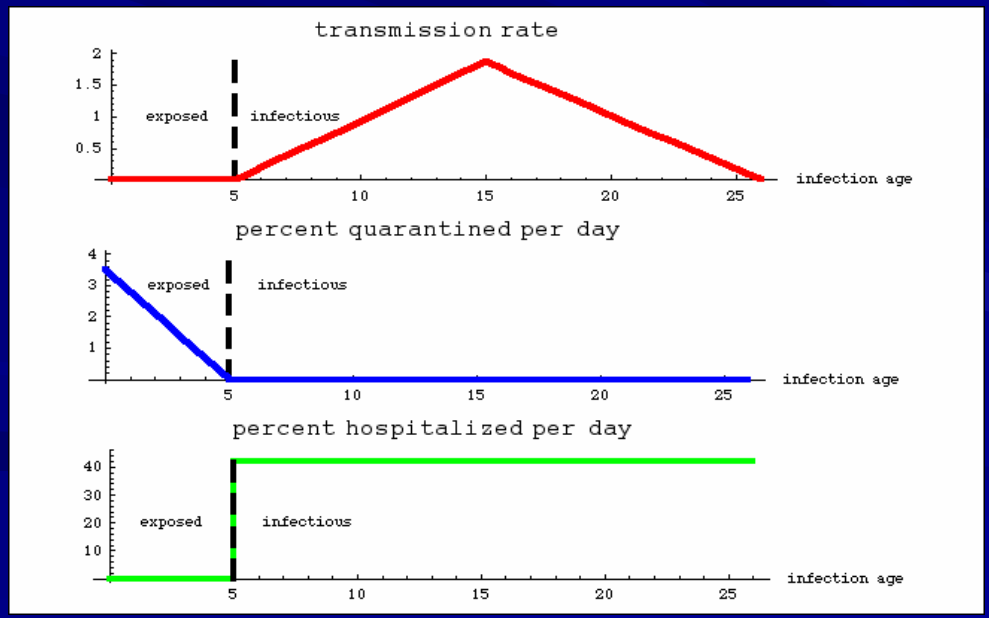
Equations and Parameters for SARS in Taipei area

$$S'(t) = -\left(\int_{\tau}^{\tau+s} \alpha(a)\, i(a, t)\, da\right) S(t)$$

$$\frac{\partial}{\partial t} i(a, t) + \frac{\partial}{\partial a} i(a, t) = -(\beta_H(a) + \beta_Q(a) + \beta_R(a))\, i(a, t)$$

$$i(0, t) = \left(\int_{\tau}^{\tau+s} \alpha(a)\, i(a, t)\, da\right) S(t)$$



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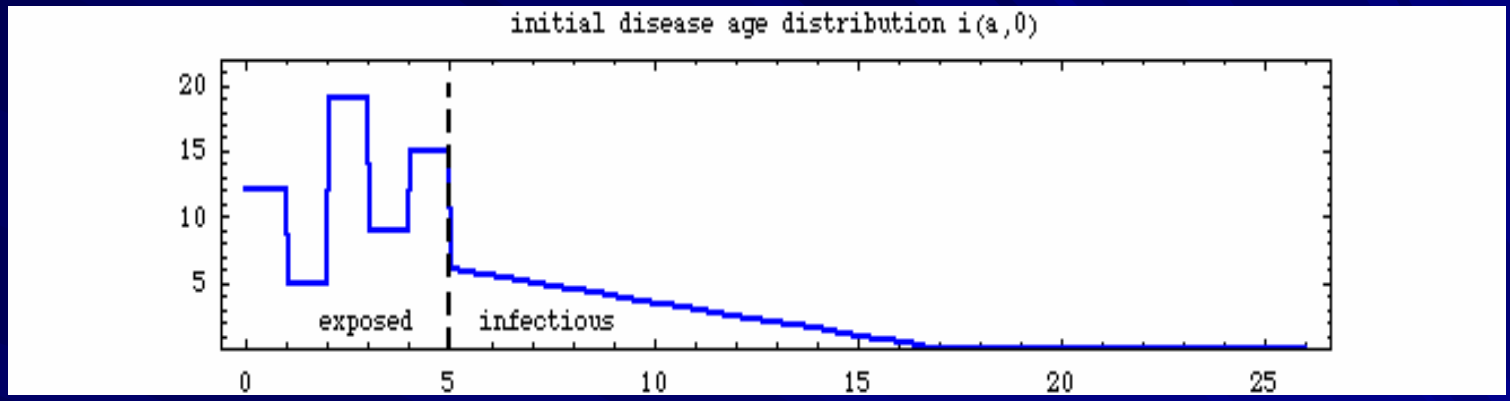

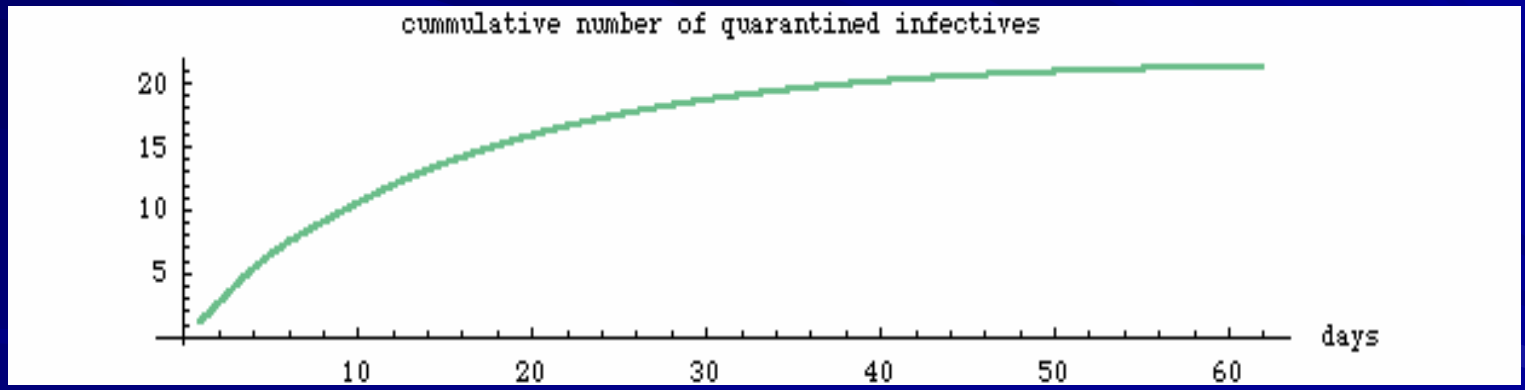

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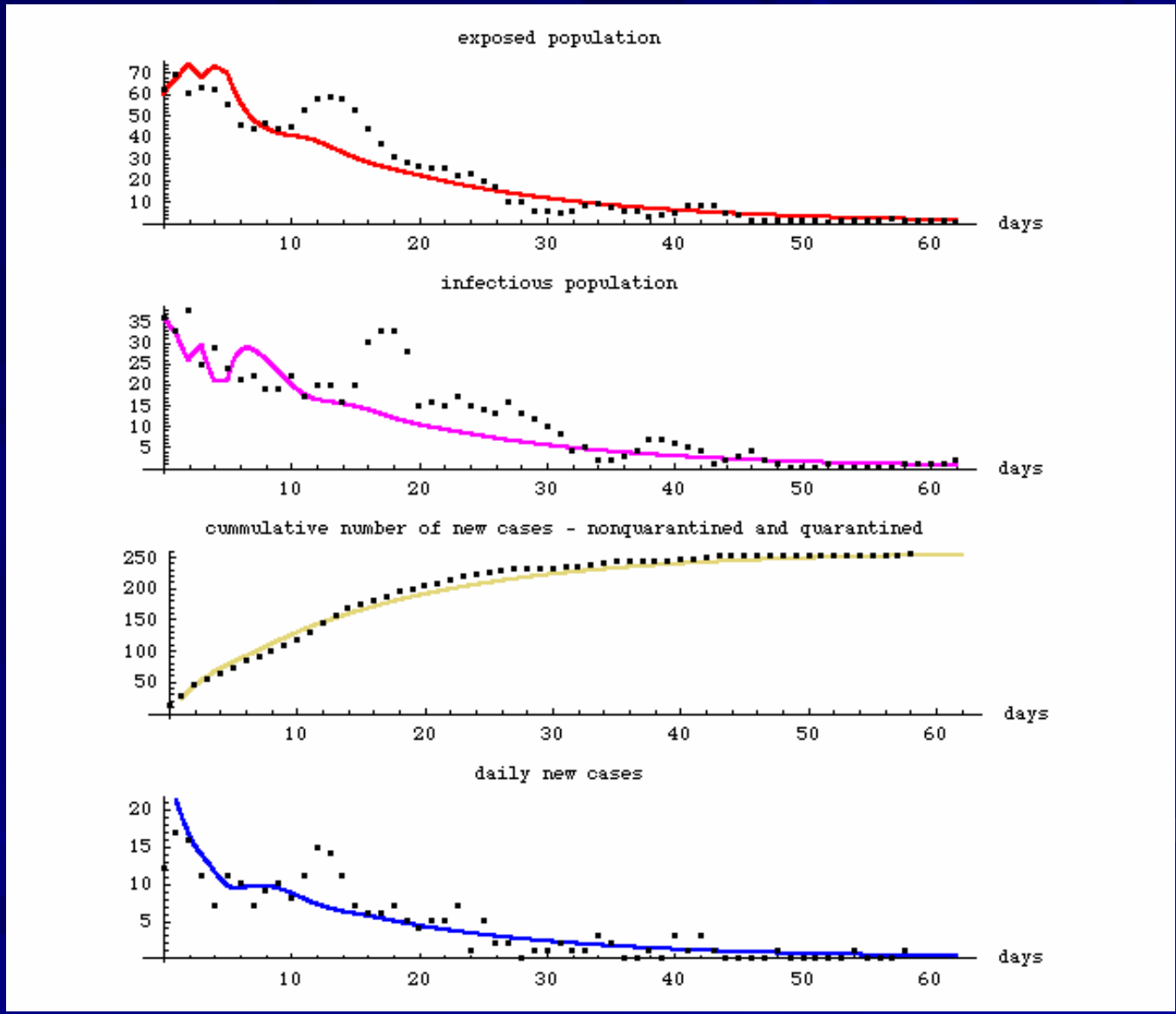

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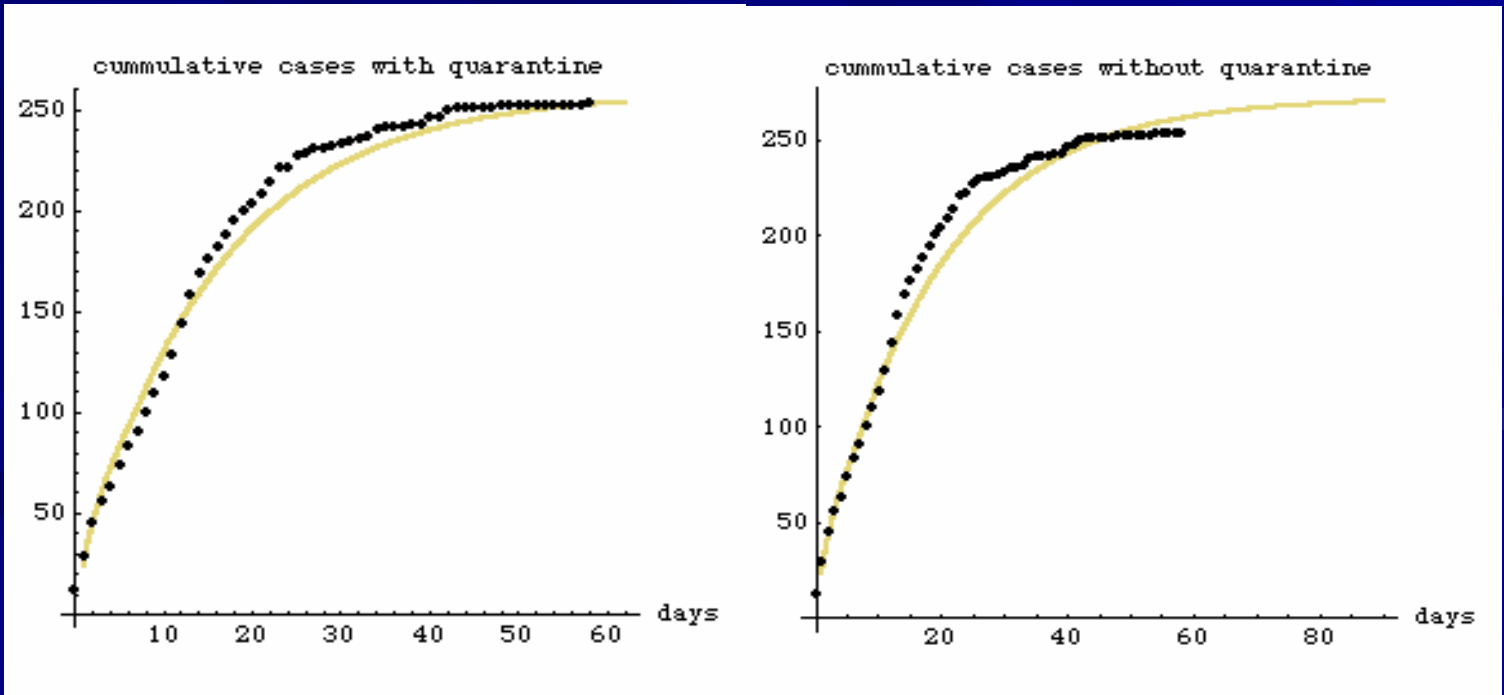
The Role of Quarantine in Taiwan SARS

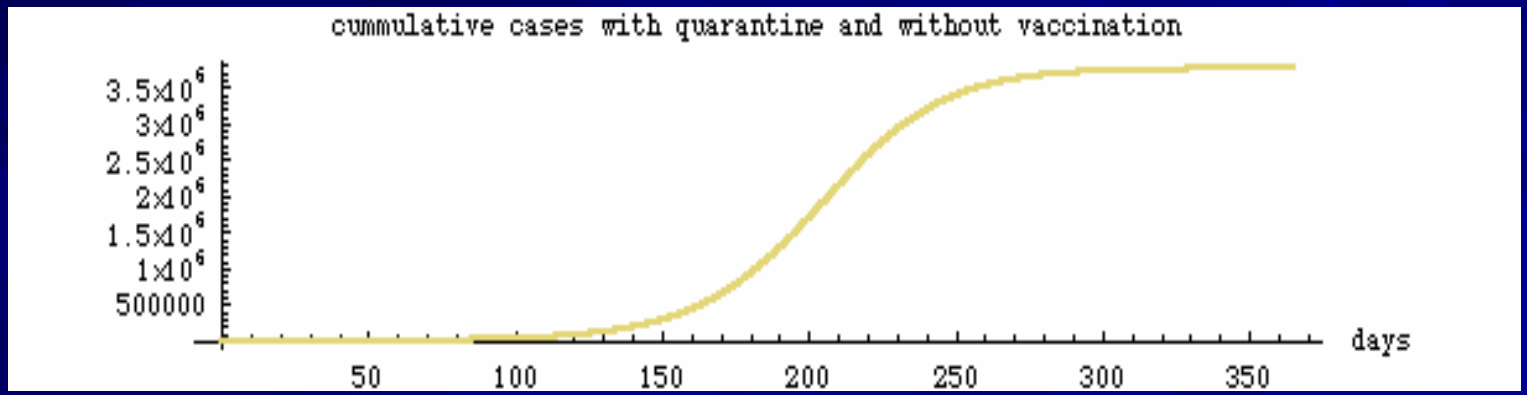
With quarantine measures as simulated by the previous model there were 253 new cases (real data: 254) in Taipei area after April 24, with 22 having been quarantined. With the quarantine coefficient $b_Q(a) = 0$ in the model the total number of new cases is 270. Hence quarantine after April 24 prevented 17 cases or 6.3%.

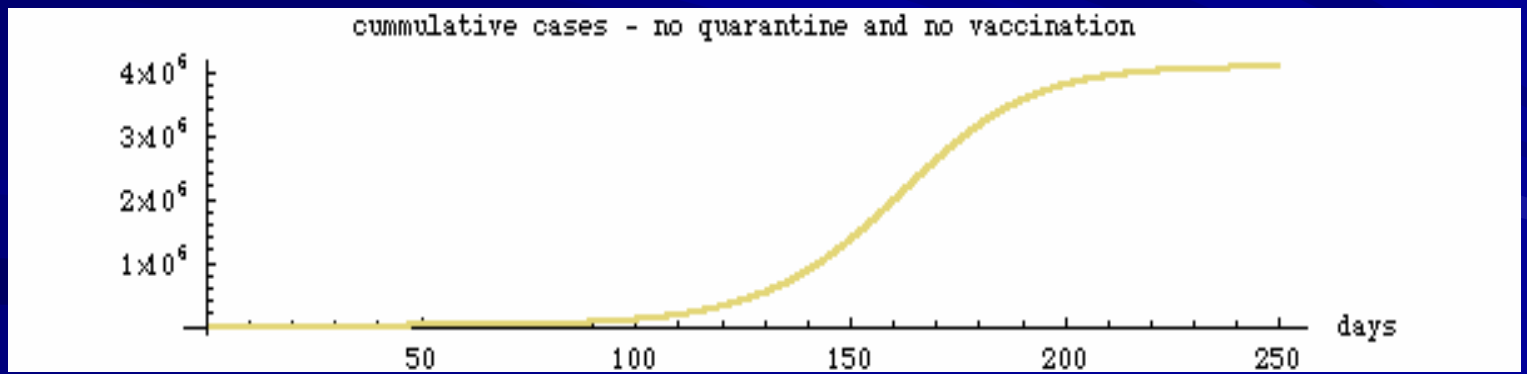


Question:

What if SARS had been like Influenza (or avian flu) in its asymptomatic infections?

Simulation of the model with the infectives infectious 2 days before on-set of symptoms (p=2)





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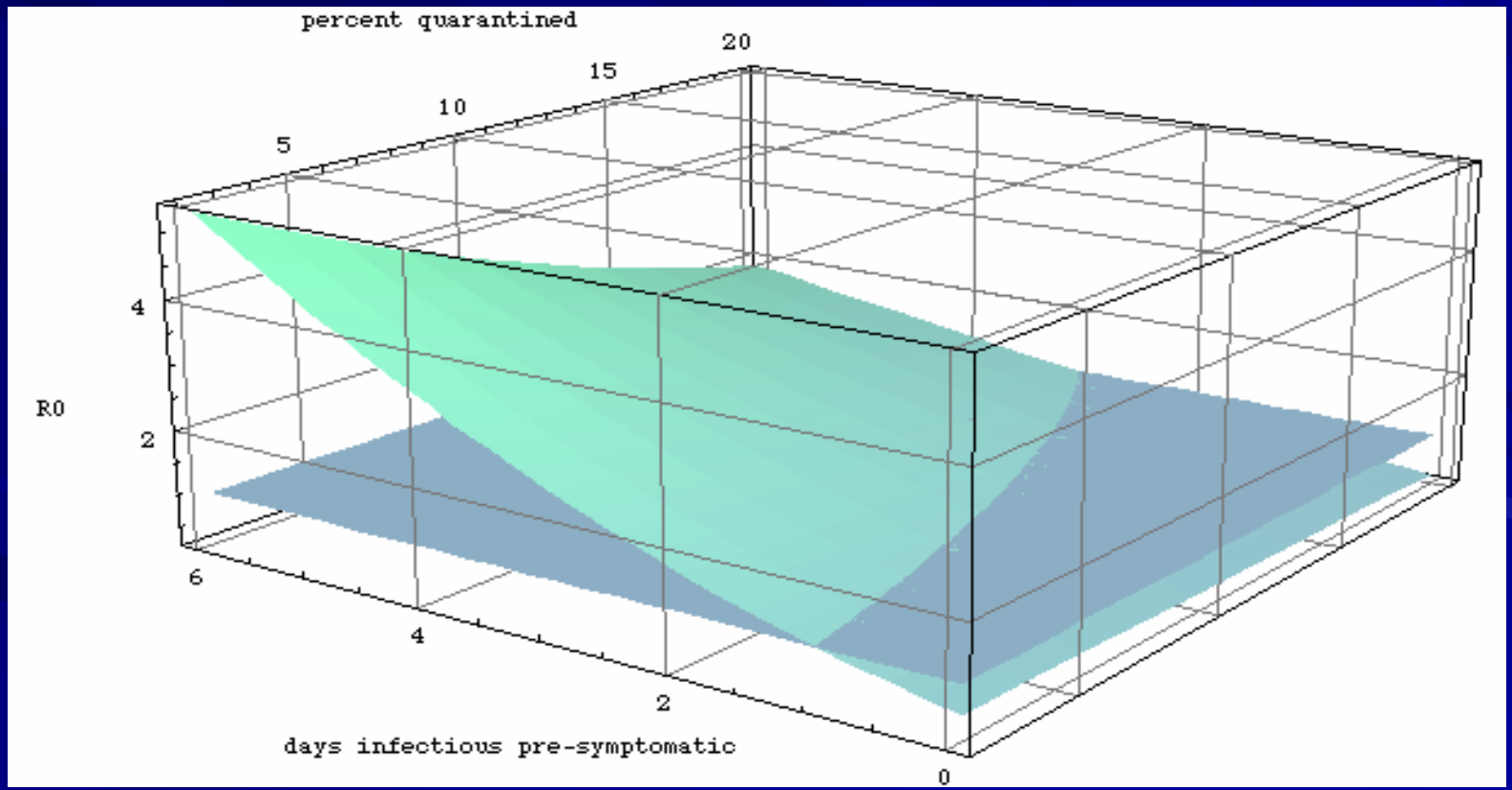
Calculation of R0

$$R0 = \int_{r}^{r+s} \alpha[a]\ Exp\left[-\int_{0}^{a} (\beta_Q[b] + \beta_H[b])\ db\right] da$$

Let the transmission rate a(a) be the same as before. The graph of R0 as a function of the number of days of infectiousness pre-symptomatic and the maximum quarantine rate is



Genes Associated with Susceptibility to SARS-CoV (Ho *et al*., unpublished work)

- 108 unrelated laboratory-confirmed SARS patients and 242 age-comparable healthy Taiwanese controls were enrolled to be genotyped by Mass Array for 282 loci of single nucleotide polymorphism (SNPs) located on 65 candidate genes.
- Severity of SARS infection was significantly associated with differences in genotype distribution of three genes:

1. fibrinogen-like protein (Fgl2) at amino acid #53 with 53E being a dominant risk variant,
2. CXCL10/IP-10 at G-938A upstream to the start codon with –938A being a risk and –938G being a protective variant,
3. heme oxygenase 1 (HO-1) at T-497A with -497A being a dominant risk variant.

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Questions:

- Is clinical severity associated with infectiousness?
- Is risk genotype for clinical severity associated with infectiousness?
- Is risk genotype associated with susceptibility to SARS?
- Joint effect?

Statistical Analysis

- Only HO-1(-497A/*) is weakly protective for susceptibility to SARS (K.F. Cheng et al., unpublished work)
- Sample size too small, especially for study of joint effect.

Table. 100 SARS cases by clinical severity and risk genotype frequency of Fgl2(+158T/*), CXCCL10/IP-10(-938AA), and HO-1(-497A/*). ("+ + +" denotes occurrence of all three risk genotypes, "+ - -" denotes occurrence of first genotype only. No one has genotype combination of "- + -".)

Clinical severity	Genotype							Total (%)
	---	+--	++-	--+	-++	+-+	+++	
Unknown (%)	1 (0.083)	0 (0.000)	0 (0.000)	0 (0.000)	0 (0.000)	0 (0.000)	0 (0.000)	1 (0.010)
Mild (%)	6 (0.500)	1 (0.100)	0 (0.000)	9 (0.231)	0 (0.000)	2 (0.077)	0 (0.000)	18 (0.180)
Intermediate (%)	4 (0.333)	7 (0.700)	1 (1.000)	23 (0.590)	5 (0.714)	16 (0.615)	1 (0.200)	57 (0.570)
Severe (%)	1 (0.083)	2 (0.200)	0 (0.000)	7 (0.180)	2 (0.286)	8 (0.308)	4 (0.800)	24 (0.240)
Total (%)	12 (0.120)	10 (0.100)	1 (0.010)	39 (0.390)	7 (0.070)	26 (0.260)	5 (0.050)	100 (1.000)

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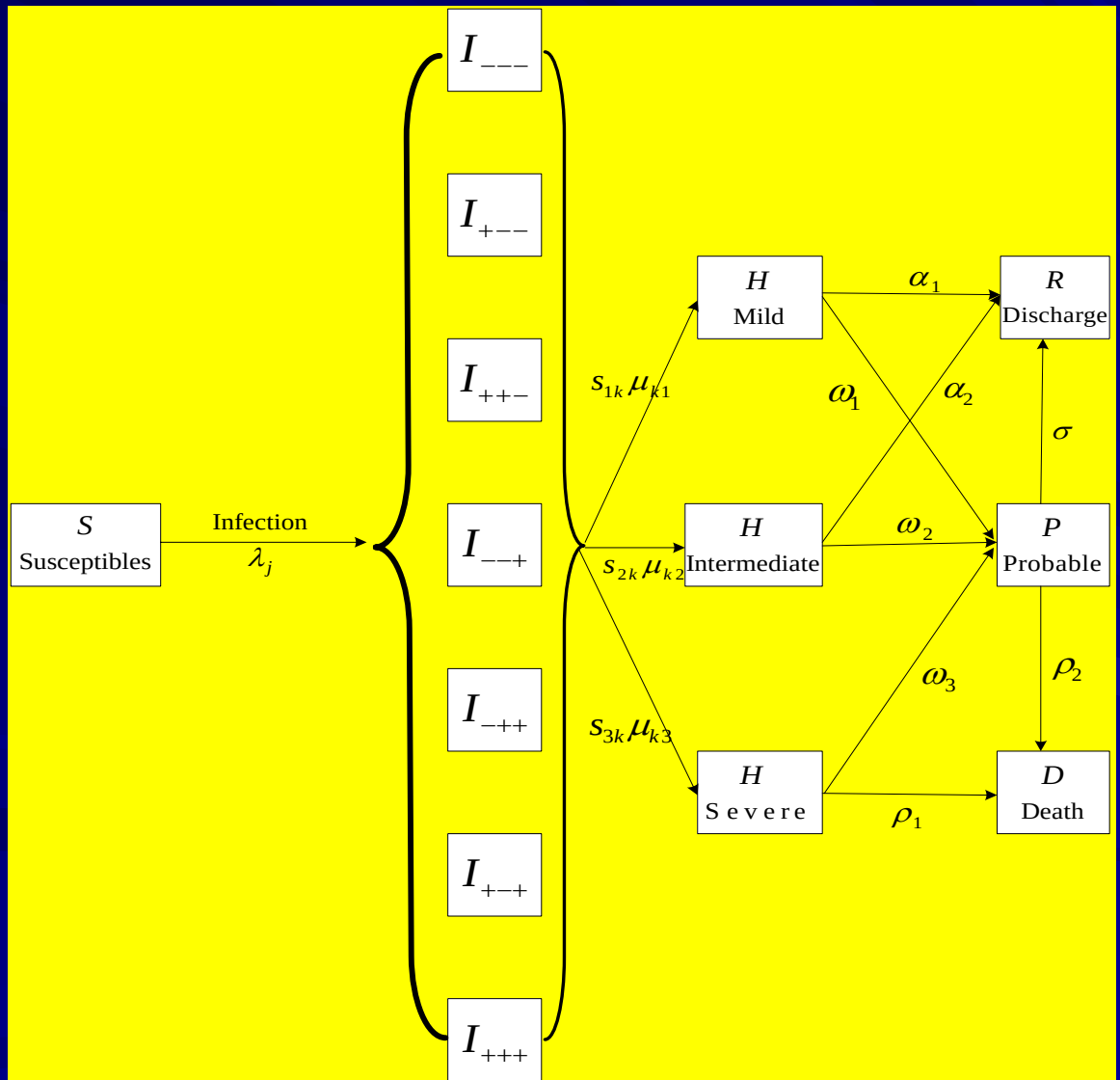
Model with Infective (I) cases divided by risk genotypes, and Hospitalized (H) cases divided by clinical severity (Reference for model: Hsieh et al. 2004, *EID*)



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Model 1 Equations

$$\lambda_{j,n} = \left[\frac{1}{1 + a(P_n + R_n + D_n)}\right]\left[\sum_{k=1}^{m} \beta_{jk} I_{k,n} + \sum_{l=1}^{3} \gamma_{jl} H_{l,n}\right]$$

$$I_{j,n+1} = I_{j,n} + \lambda_{j,n} - \left(\sum_{k=1}^{3} s_{kj}\mu_{jk}\right) I_{j,n}; \text{ where } j = 1, 2, \ldots m,$$

$$H_{1,n+1} = H_{1,n} + \sum_{k=1}^{m} s_{1k}\mu_{k1} I_{k,n} - (\omega_1 + \alpha_1) H_{1,n}$$

$$H_{2,n+1} = H_{2,n} + \sum_{k=1}^{m} s_{2k}\mu_{k2} I_{k,n} - (\omega_2 + \alpha_2) H_{2,n}$$

$$H_{3,n+1} = H_{3,n} + \sum_{k=1}^{m} s_{3k}\mu_{k3} I_{k,n} - (\omega_3 + \rho_1) H_{3,n}$$

$$P_{n+1} = P_n + \sum_{k=1}^{3} \omega_k H_{k,n} - (\sigma + \rho_2) P_n$$

$$R_{n+1} = R_n + \sigma P_n + \alpha_1 H_{1,n} + \alpha_2 H_{2,n}$$

$$D_{n+1} = \rho_2 P_n + \rho_1 H_{3,n}$$

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Some Preliminary Results

1. Infectiousness of hospitalized group γ_{jl} is not significantly different for patients with different clinical severity

2. Infectiousness of the infective groups with β_{jk} different genotypes (k) are not significantly different

Questions:

- Is severity associated with infectiousness?

NO

- Is risk genotype associated with infectiousness?

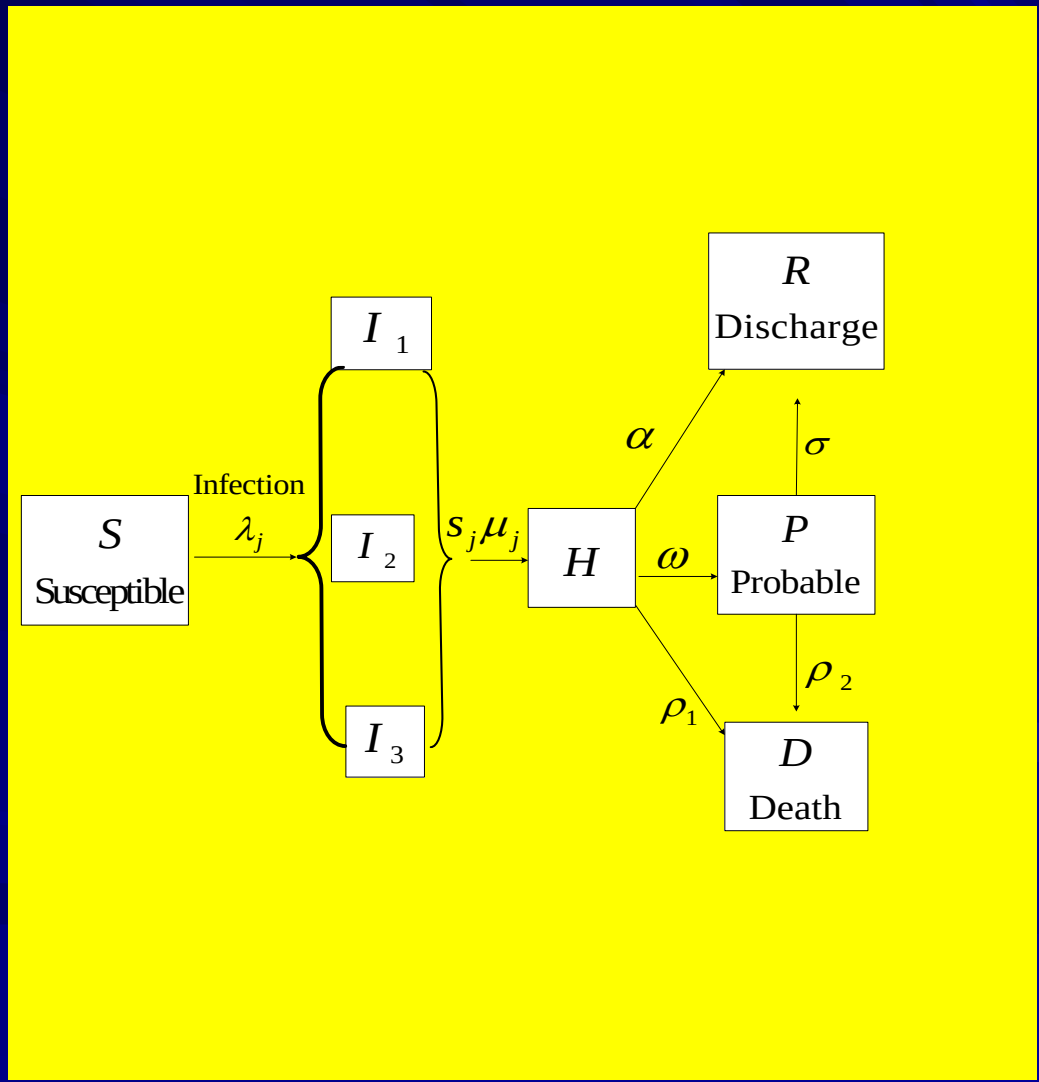
NO

- Is risk genotype associated with susceptibility to SARS?

Albert Einstein:

- Models should be as simple as possible, but not more so.

Simplified Model with Infective (I) cases divided by risk genotypes



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Model 2 Equations

$$\lambda_{j,n} = \alpha_j \lambda_n = [\frac{1}{1 + a(P_n + R_n + D_n)}][\beta_j I_n + \gamma_j H_n]$$

where $I_n = \sum_{j=1}^{m} I_{j,n}$ and $m = 2$ or 3,

$$I_{j,n+1} = I_{j,n} + \lambda_{j,n} - s_j \mu_j I_{j,n}$$

where $j = 1, 2, ...m,$

$$H_{n+1} = H_n + \sum_{j=1}^{m} s_j \mu_j I_{j,n} - (\omega + \alpha + \rho_1) H_n$$

$$P_{n+1} = P_n + \omega H_n - (\sigma + \rho_2) P_n$$

$$R_{n+1} = R_n + \sigma P_n + \alpha H_n$$

$$D_{n+1} = \rho_2 P_n + \rho_1 H_n$$

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Table. Parameter estimates for genotype combinations of three genotypes grouped by Fgl2(+158T/*). (+ - -) denotes this risk genotype only, (- * *) denotes no, and (+ * *) are all others.

Parameter	Estimated value	95%CI	p value
Genotype (+ - -) N=10			
Intrinsic infection rate by I-class	β =0.4441	(0.4434-0.4448)	<0.0001[1]
Severity-dependent constant	a=0.0016	(0.0007-0.0024)	0.0002[2]
Infection rate by H-class	γ_3=0.0459	(0.0456-0.0461)	0.0018[3]
Genotype (+ * *) N=32			
Intrinsic infection rate	β =0.4048	(0.3921-0.4176)	<0.0001[4]
Severity-dependent constant	a=0.0019	(0.0009-0.0028)	0.0002[5]
Infection rate by H-class	γ_3=0.0460	(0.0408-0.0512)	0.0017[6]
Genotype (- * *) N=58			
Intrinsic infection rate	β =0.3215	(0.2980-0.3450)	<0.0001[7]
Severity-dependent constant	a=0.0024	(0.0013-0.0035)	0.0002[8]
Infection rate by H-class	γ_3=0.0467	(0.0371-0.0563)	0.0017[9]

[1]p value of $\alpha_1\beta$
[2]p value of $\alpha_1 a\beta$
[3]p value of $\alpha_1\gamma$
[4]p value of $\alpha_2\beta$
[5]p value of $\alpha_2 a\beta$
[6]p value of $\alpha_2\gamma$
[7]p value of $\alpha_3\beta$
[8]p value of $\alpha_3 a\beta$
[9]p value of $\alpha_3\gamma$

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Table. Parameter estimates for three genotypes grouped by CXCCL10/IP-10(-938AA). (* + *) denotes having this gene and (* - *) are all others.

Parameter	Estimated value	95%CI	p value
Genotype (* + *) N=13			
Intrinsic infection rate	β =0.2572	(0.2561-0.2584)	<0.0001[1]
Severity-dependent constant	a=0.0030	(0.0013-0.0047)	0.0002[2]
Infection rate by H-class	γ_3=0.0461	(0. 0456-0.0466)	0.0016[3]
Genotype (* - *) N=87			
Intrinsic infection rate	β =0.3759	(0.3233-0.4285)	<0.0001[4]
Severity-dependent constant	a=0.0020	(0.0010-0.0030)	0.0002[5]
Infection rate by H-class	γ_3=0.0466	(0.0252-0.0680)	0.0017[6]

[1]p value of $\alpha_1\beta$
[2]p value of $\alpha_1 a\beta$
[3]p value of $\alpha_1\gamma$
[4]p value of $\alpha_2\beta$
[5]p value of $\alpha_2 a\beta$
[6]p value of $\alpha_2\gamma$

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Table. Parameter estimates for the three genotypes grouped by HO-1(-497A/*). (- - +) denotes this gene only, (* * +) denotes no, and (* * -) are all others.

Parameter	Estimated value	95%CI	p value
Genotype (- - +) N=39			
Intrinsic infection rate	β =0.3294	(0.3188-0.3399)	<0.0001[1]
Severity-dependent constant	a=0.0023	(0.0010-0.0035)	0.0002[2]
Infection rate by H-class	γ_3=0.0464	(0.0422-0.0507)	0.0016[3]
Genotype (* * +) N=38			
Intrinsic infection rate	β =0.3827	(0.3727-0.3927)	<0.0001[4]
Severity-dependent constant	a=0.0020	(0.0014-0.0026)	0.0002[5]
Infection rate by H-class	γ_3=0.0466	(0.0425-0.0507)	0.0016[6]
Genotype (* * -) N=23			
Intrinsic infection rate	β =0.3693	(0.3632-0.3754)	<0.0001[7]
Severity-dependent constant	a=0.0020	(0.0009-0.0031)	0.0002[8]
Infection rate by H-class	γ_3=0.0466	(0.0441-0.0491)	0.0016[9]

[1]p value of $\alpha_1\beta$
[2]p value of $\alpha_1 a\beta$
[3]p value of $\alpha_1\gamma$
[4]p value of $\alpha_2\beta$
[5]p value of $\alpha_2 a\beta$
[6]p value of $\alpha_2\gamma$
[7]p value of $\alpha_3\beta$
[8]p value of $\alpha_3 a\beta$
[9]p value of $\alpha_3\gamma$

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Conclusions (Part I)

- Fgl2(+158T/*) is associated with higher susceptibility of SARS-CoV virus, and hence is a risk variant for SARS infection.

- CXCCL10/IP-10(-938AA) and HO-1(-497A/*) are associated with lower susceptibility of SARS-CoV, thus offer protection for SARS.

- CXCCL10/IP-10(-938AA) is rare, and occurs in our case data only in combination with other two genes.

Table. Parameter estimates for genotypes grouped by occurrence of Fgl2(+158T/*) and CXCCL10/IP-10(-938AA). (+ + *) denotes presence of both, (* * *) denotes all others.

Parameter	Estimated value	95%CI	p value
Genotype (+ + *) N=6			
Intrinsic infection rate	β =0.2858	(0.2855-0.2860)	<0.0001[1]
Severity-dependent constant	a=0.0023	(0.0009-0.0038)	0.0002[2]
Infection rate by H-class	γ_3=0.0459	(0. 0458-0.0460)	0.0017[3]
Genotype (* * *) N=94			
Intrinsic infection rate	β =0.3634	(0.3020-0.4247)	<0.0001[4]
Severity-dependent constant	a=0.0021	(0.0010-0.0031)	0.0002[5]
Infection rate by H-class	γ_3=0.0466	(0.0217-0.0715)	0.0016[6]

[1]p value of $\alpha_1\beta$
[2]p value of $\alpha_1 a\beta$
[3]p value of $\alpha_1\gamma$
[4]p value of $\alpha_2\beta$
[5]p value of $\alpha_2 a\beta$
[6]p value of $\alpha_2\gamma$

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Table. Parameter estimates for genotypes grouped by occurrence of Fgl2(+158T/*) and HO-1(-497A/*). (+ * +) denotes both, (* * *) denotes all others.

Parameter	Estimated value	95%CI	p value
Genotype (+ * +) N=31			
Intrinsic infection rate	β =0.4322	(0.4256-0.4388)	<0.0001[1]
Severity-dependent constant	a=0.0017	(0.0008-0.0026)	0.0002[2]
Infection rate by H-class	γ_3=0.0460	(0. 0433-0.0487)	0.0017[3]
Genotype (* * *) N=69			
Intrinsic infection rate	β =0.3277	(0.2950-0.3614)	<0.0001[4]
Severity-dependent constant	a=0.0023	(0.0012-0.0034)	0.0002[5]
Infection rate by H-class	γ_3=0.0465	(0.0332-0.0602)	0.0017[6]

[1]p value of $\alpha_1\beta$
[2]p value of $\alpha_1 a\beta$
[3]p value of $\alpha_1\gamma$
[4]p value of $\alpha_2\beta$
[5]p value of $\alpha_2 a\beta$
[6]p value of $\alpha_2\gamma$

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Table. Parameter estimates for genotypes grouped by occurrence of CXCCL10/IP-10(-938AA) and HO-1(-497A/*) . (* + +) denotes presence of both (* * *) denotes all others.

Parameter	Estimated value	95%CI	p value
Genotype (* + +) N=12			
Intrinsic infection rate	β =0.2780	(0.2770-0.2790)	<0.0001[1]
Severity-dependent constant	a=0.0027	(0.0012-0.0042)	0.0002[2]
Infection rate by H-class	γ_3=0.0460	(0. 0456-0.0464)	0.0016[3]
Genotype (* * *) N=89			
Intrinsic infection rate	β =0.3706	(0.3168-0.4244)	<0.0001[4]
Severity-dependent constant	a=0.0021	(0.0010-0.0031)	0.0002[5]
Infection rate by H-class	γ_3=0.0466	(0.0248-0.0685)	0.0016[6]

[1]p value of $\alpha_1\beta$
[2]p value of $\alpha_1 a\beta$
[3]p value of $\alpha_1\gamma$
[4]p value of $\alpha_2\beta$
[5]p value of $\alpha_2 a\beta$
[6]p value of $\alpha_2\gamma$

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Conclusions (Part II)

- CXCCL10/IP-10(-938AA) is rare, and occurs in our case data only in combination with the other two genes. However, it always offer protection for SARS, most noticeably when combined with Fgl2(+158T/*), which by itself is a risk variant.
- HO-1(-497A/*) is weakly protective by itself, but is associated with higher susceptibility when combined with Fgl2(+158T/*).
- CXCCL10/IP-10(-938AA) is most important as a protective gene against SARS infection, however it is only present in combination with other two genes.

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In Plain English:

- Genotype 1 is bad, unless combined with genotype 2
- Genotype 2 is always good whenever it appears. But it appears rarely and only jointly with genotype 1 or 3.
- Genotype 3 is slightly good, but good when combined with a good genotype (2) and bad when combined with a bad genotype (1)

"Mathematics is a way of thinking clearly, no more, but no less."

"數學僅是一種思考的方式"

– Robert M. May, President of Royal Society, United Kingdom, in *Virus Dynamics* (2000 Nowak and May).

"I have deeply regretted that I did not proceed far enough at least to understand something of the great leading principles of mathematics; for men thus endowed seem to have an extra sense."

"我深悔沒有深入了解數學的原理，以建立了解事物的特殊官感"

-Charles Darwin (達爾文)

Other related papers on SARS

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5. Hsieh, Y.-H., C.W-S. Chen, and S.-B. Hsu. (2004) SARS outbreak, Taiwan, 2003. *Emerging Infectious Diseases*, February 2004, 10(2):201-206.
6. Hsieh, Y.-H., Chen, CWS. (2004) Mathematical modeling of SARS: Errata and updates. *J Epidem Com Health*, published online May 11, 2004. Available at: http://jech.bmjjournals.com/cgi/eletters/57/6/DC1.
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8. Hsieh Y,-H., Chen CWS, Hsu SB. SARS outbreak in Taiwan (reply to Hsueh and Yang). *Emerging Infectious diseases*, 10(8):1515-6, August 2004.
9. Hsieh YH, King CC, Ho MS, Chen CWS, Lee JY, Liu FC, et al. (2005) Quarantine for SARS: an old medicine for new diseases of 21st century? *Emerging Infectio Diseases*; **11**(2):278-82.

List of Collaborators

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- National Tsing Hua University: Sze-Bi Hsu (Department of Mathematics)
- Feng Chia University: Cathy W.S. Chen (Department of Statistics)
- Academia Sinica: Mei-Shang Ho (Institute of Biomedical Sciences)
- Center for Disease Control-Taiwan: Yi-Chun Wu, Hsiao-Ling Chang, Jiunn-Shyan Julian Wu
- US CDC: John Glasser
- Vanderbilt University: Glenn Webb
- York University: Jianhong Wu
- University of Bern: Shu-Fang Hsu Schmitz