Trilateral Seminar on R&D Policies Related to Emerging and Re-emerging Infectious Diseases

C – Plenary Session II: *Modeling and Simulation*

Invited Presentations

Panelist Presentations

Modeling SARS Transmission Dynamics and Control Efforts

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In this talk, previous modeling work and different approaches to analyzing SARS data will be briefly reviewed, then open problems highlighted, and the types of data as well as analytic methods discussed.

To understand the transmission dynamics, the following key parameters should be considered. The first is the effective or net reproduction number, R_t, which is defined as the mean number of secondary cases generated by an infectious case once the epidemic is underway. If $R_t > 1$ the incidence will tend to increase with time, and if $R_t < 1$ it will tend to decrease. The second parameter is the mean serial interval, S, defined as the time from the onset of symptoms in an index case to the onset of symptoms in a subsequent case infected by the index case. Together with R_t this determines the rate at which the epidemic spreads. The third parameter is the incubation period, the interval between infection and the onset of symptoms. The incubation period is important for determining the quarantine period. In general we need to estimate not only the means of these parameters, but also their distributions.

Data Used and Methods of Analysis from Previous Studies

Contact tracing data were usually used to estimate serial intervals and incubation periods (when cases are infected by known sources at known times, this is straightforward). Unlike R_t and S, the incubation period will not change during the course of the epidemic unless the characteristics of the infected population or virus itself change. Estimating R_t is a more difficult task, and the two first modeling papers (Lipsitch *et al.* 2003, Riley *et al.* 2003) using data from Singapore and Hong Kong adopted contrasting approaches, determined in large part by the data available. Riley *et al*. fitted a stochastic compartmental model to data on SARS hospital admissions using an approximate likelihood method. Their model included spatial effects but ignored super spreading events and heterogeneity in the number of secondary cases caused by each primary case. Lipsitch *et al*. used a similar compartmental model, but estimated R_t by fitting the predicted cumulative number of cases after various time points to observed data. This was done first deterministically, and then stochastically, using a Bayesian approach that accounted for variation in

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[1] In collaboration with Feng Dan, Han Xiaona and, Fang Liqun

serial intervals and heterogeneity in the number of secondary cases caused by each primary case. This approach therefore ignored spatial effects, but accounted for super spreading events and other important heterogeneities.

Subsequent to this work Wallinga & Teunis (2004) presented an entirely novel approach to estimating R_t, using only dates of symptom onset. The method, which represents a major methodological advance, uses a likelihood-based estimation procedure to infer who-infected-whom without requiring detailed contact tracing data or strong assumptions about the rate of growth of the epidemic. The approach was used to estimate the impact of control measures on reducing R_t, in Hong Kong, Vietnam, Singapore and Canada.

A number of other SARS modeling papers have been published. A model by Lloyd-Smith *et al.* (2003) emphasized the importance of hospital-transmission, but did not attempt to obtain estimates of relative transmission rates in the hospital and community. Chowell *et al.*(2003) used a similar deterministic approach to the first method used by Lipsitch *et al.* to estimate R_t, but did not attempt to quantify uncertainty in parameter estimates.

Other modeling work has addressed the international spread of SARS (Hufnagel et al., 2004), and demonstrated that air traffic volumes between countries are able to explain much of the international variation in numbers of SARS cases. Recently, more sophisticated statistical tools have been used to provide improved estimates of the distribution of incubation periods using full contact tracing and time of onset data (Kuk & Ma, 2005). Bayesian modeling methods have also been used to estimate incubation periods and relative transmission rates in hospitals and the community using Chinese data from Shanxi province giving times of onset, hospitalization and limited data on contacts with symptomatic SARS cases (McBryde *et al.*, 2005). Such an approach represents one of the most promising methods for providing a full analysis of SARS data where incomplete or ambiguous exposure data are available and times of onset and hospitalization are known.

Summary of Results

The distribution of serial interval, *S*, was described well by a Weibull distribution with a mean value of about eight days (Lipsitch). There was, however, wide variation (between one and 20 days). *S* tended to decrease as the epidemic came under control and time to effective isolation decreased.

Mean incubation periods were estimated to be about five or six days (Donnelly 2003, McBryde 2005), though there were non-negligible probabilities that for some people it exceeded 15 days in Hong Kong (Donnelly) and 20 days in Shanxi province (McBryde).

Remarkably similar estimates for R_t (initially about three, before the more effective control measures were in place) were obtained by the different methods and by the same methods in different locations. Control measures also appeared to be similarly effective at reducing R_t to below one in different countries (Wallinga).

Analysis of the Shanxi province data (McBryde) indicated that the rate SARS was initially transmitted in hospitals was three times higher than in the community, though once effective control measures were in place hospital transmissibility became almost negligible while community transmissibility fell by only about a half.

Conclusions

Mathematical models and new statistical techniques to fit these models to data have taught us a great deal about SARS transmission dynamics and control efforts, and provide valuable information to inform control policies. Nonetheless, there remain some important gaps in our knowledge. There is a need for a more detailed understanding of the relative roles of hospital and community transmission and the relative effectiveness of different control measures in each setting. It would be useful to assess the importance of household transmission in community spread. It would be useful to estimate how transmissibility varies during the course of infection, and to see how well this correlates with viral shedding data. To address these questions detailed data giving times of onset, hospitalization, isolation and quarantine, and type, timing, location and duration of exposures (ideally, even amongst those not acquiring SARS) would be of great value.

Epidemic Modeling and it's Applications in Emerging Infectious Diseases and Bioterrorism in Korea

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Introduction

Modeling of epidemics has a long history in the field of the epidemiology of infectious diseases. It has been developed since 19th century and has been used to make decisions to control many infectious diseases like malaria, AIDS, measles, SARS, and influenza; to estimate vaccine efficacy; and to develop prevention strategies to reduce the impact of bioterrorism. A deterministic model developed in 1928 by Reed and Frost in Johns-Hopkins University is a kind of classical epidemic modeling. The Reed-Frost model is a simple model having been based on the assumption that all susceptible persons would be infected by the same effective contacts.

Epidemics in a community depend on the natural history of the diseases, socio-cultural and population characteristics, health policy, climate, and other related factors such as nourishment. So, there are a lot of the variables which we must take into consideration in model development. Though simplification is an inevitable characteristic of any model, they have been very useful to develop policies and to make decisions for control of many infectious diseases. Modeling is practically essential to control of infectious disease. The examples can be easily found in measles, malaria, HIV/AIDS and other sexually transmitted infections, and the recent epidemic of SARS.

Infectious diseases are a great public health problem in Korea. Gastro-intestinal infectious diseases like bacillary dysentery or typhoid fever prevail every year by contaminated foods or drinking water. Annually thousands people suffer from vector-borne diseases like malaria and tsutugamushi disease. Also we have the same threat of many emerging infectious diseases and bioterrorism like other advanced countries.

In this presentation, I will introduce two examples of epidemic modeling and their use, one for pandemic influenza, and the other for small pox as a bioterrorist agent.

Pandemic Influenza Modeling and Table-top Exercise

Issues in pandemic influenza modeling. The impact of the next influenza pandemic is difficult to predict. It is dependent on how virulent the virus is, how rapidly it spreads from population to population, and the effectiveness of prevention and response efforts. Despite the uncertainty about the magnitude of the next pandemic, estimates of the health and economic impact remain important to aid public health policy decisions and guide pandemic planning for health and emergency sectors. Planning ahead in preparation for the influenza pandemic, with its potentially very high morbidity and mortality rates, is essential for hospital administrators and public health officials.

The World Health Organization (WHO) has presented guidelines for response plans at the international and national levels to pandemic influenza, and suggestions about priority order of pandemic influenza countermeasure due to concrete threats of current avian influenza in South-east Asia. Avian influenza A (H5N1) virus, first isolated from humans in 1997 in Hong Kong, is now one of the leading candidates to evoke a pandemic because it did not prevail among human population before, and is showing severe clinical symptoms with high mortality rate among affected patients. Fortunately, transmission between humans seemed to be rare until November 2005. So far, most cases were sporadic, among those who had intensive contact with ill or dead chickens. But the world should be prepared for an influenza pandemic because of the virus's unique characteristics of continuously changing and its adaptation ability.

The spread of pandemic influenza occupies most of the first chapter in terms of response plans of the 21 countries which presented them for posting on the WHO homepage by November 2005. This information should make it possible to determine better policies related to response to a potential pandemic than was possible previously by relying on the number of patients or the number of deaths that occurred. For example, by modeling the expected number of hospitalized patients/deaths and their space-time distributions, it is possible determine guidelines for antiviral use, vaccination strategies, clinical guidelines, and the needs for other health resources. Also, a numerical estimate of expected ill persons is necessary to develop an educational strategy of public communication, and other activities which take are meant to anticipate impending social and economic impacts and reduce social panic.

Pandemic impact estimation. The estimation of pandemic impact is based on previous pandemics; we had experienced at least 3 pandemics in 20th century. But the epidemiological characteristics, the impact of 1st wave, pathogenicity and virulence of the viruses and the primary victims of population were quite different from one another (Table1). It is impossible to calculate the exact number of victims, because we cannot know the infectivity, pathogenicity and virulence of the coming virus before a pandemic starts.

Table1. Previous Pandemics in the 20th century

	1918 Spanish flu	1957 Asian flu	1968 Hong Kong flu
Total waves (peak wave, season)	3 waves (2nd wave , September)	Double waves (1st wave, October)	4 yrs sequential waves
Attack Rate	30-40%	25%	25%
Mortality Rate	1-2%	0.37%	
Population affected	persons < 65 yrs (W shape)	infant, elderly (U shape)	infant, elderly (U shape)

Meltzer et al (1999) developed a pandemic impact model now accepted in many countries. The FluAid and FluSurge programs developed by Melter et al. also are widely used to predict impacts. The parameters of these models were calculated from the seasonal influenza epidemics and 1957 Asian flu in the United States. Using FluAid and FluSurge with Korean population parameters led to similar results to that of other countries (Table2).

Table2. Estimated impact of pandemic influenza in Korea (2003) by Flu Surge

Nation (Population)	Outcome	Attack rate 25% (range by scenario)	Attack rate 35% (range by scenario)
Korea (48 million)	Death	27,527(12,905-48,876)	38,538(18,067-68,426)
	Hospitalization	151,297(50,371-201,804)	211,816(70,519-282,525)
	Outpatients*	6,472,006 (4,983,131-9,206,971)	9,060,806 (6,976,385-12,889,758)

Modeling for interactive table-top exercise for emerging influenza. The Korea Centers for Disease Control (KCDC) developed a plan for a national table-top exercise for emerging infections in 2004. The task-force team included an epidemiologist, infectious diseases specialists, an interactive game expert, and officials of KCDC and some other part of government. After many discussions, we decided on using the "1918 Spanish flu" as a standard target model for the national table-top exercise. Why 1918 Spanish flu? Maybe the Spanish flu was a disaster that could be considered exceedingly rare. But we needed to have a model to determine the influence and spread of virulent emerging influenza in the Korean population and to grasp the characteristics of such infectious disease's spread and impact. Modeling provided a worst case scenario with the objective of actual training of the public health officials who needed to prepare for emerging infections and for the prevention and management of new epidemics.

Modeling and scenario development. The required parameters of the epidemic were set, considering the examples of pandemic that have actually occurred in history, especially the 1918 pandemic. An influenza pandemic was set as the epidemic model and the cases of SARS and avian influenza were also referred to. The SEIR model was used as a basic epidemic model. SEIR is composed of the following four stages. In determining the time difference that is used in an epidemic model, the stochastic model was used. The forecasted number of death, hospitalized patients, ICU patients and artificial respiratory apparatus needed by patients were calculated in advance on a weekly basis by regions.

The scenarios consisted of the forecast modeling of the pandemic and a specific on-the-spot exercise scenario. The forecast modeling of the pandemic was a model that forecasts the number of patients and the number of deaths in case of the pandemic, which included the forecast modeling method of necessary medical resources and method of considering the effect of medical treatment and isolation of patients, for example. For this exercise, the results of pandemic modeling which were used for on-the-spot exercises in 16 cities and provinces were dealt with. The on-the-spot exercise scenario was a specific scenario to be used for the exercise and was delivered to the response team during the exercise.

Organization and role of the table-top exercise team. Some 150 people from 14 government agencies and 16 cities and provinces participated in this exercise. Participants were divided into disease team, response team, control team and Central Countermeasures Committee. The disease team, consisted of staff from the Center for Disease Control, simulation experts played the role of imposing the situation where a pandemic has occurred and widely spread and evaluating the response plan prepared by the response team. The response team, drawn from 16 cities, provinces and quarantine stations, played the role of preparing and reporting countermeasures against the outbreak of a pandemic. In every city or province, health officers covering the relevant city or province, one epidemiology examiner, and one health officer belonging to participating city, county or district (a total of three people); and also in every quarantine station, a quarantine officer participated. For the smooth progress of the exercise, the 16 cities and provinces were regrouped into four regions to prevent the possible confusion that might occur from operating too many teams. The control team, consisted of the personnel from Center for Disease Control who were dispatched for the smooth progress of the exercise and simulation experts (senior researchers from the Korea Institute for Defense Analyses), played the role of building networks between teams, including the proceedings and management of the exercise.

The Central Countermeasures Committee consisted of the Central Support Group for Disaster Recovery, Central Working Group for Disease Control and Advisory Board. The Central Countermeasures Committee played the role of providing opinions on the questions and requests for medical resources from the response team, evaluating the response plan prepared by the response team, preparing countermeasures at the central government level, and relaying them to the response team.

The exercise includes disease team's provision of attack scenario, response team's preparation of response plan, and the disease team's evaluation of the response plan.

Phases in the pandemic and important examination points. In this exercise, we set up four phases: 1) the surveillance phase when a patient suspected to have been infected with the pandemic is known; 2) early response phase when the disease is spread in some regions; 3) full-scale response phase when the spread of the disease occurs in many occasions all over the nation; and 4) emergency phase when medical resources have dried up and a social crisis occurs. In this exercise, only the first three phases were dealt with.

The exercise included a disease team's provision of an attack scenario, response team's preparation of a response plan, and the disease team's evaluation of the response plan.

Evaluation of countermeasures. The evaluation of countermeasures prepared by the response team was conducted in two stages. The Central Countermeasures Committee made the evaluation after the first evaluation by the disease team was completed. The disease team evaluated the response plan in terms of rapidity, accuracy, rationality and organizing ability by checking whether the plan contains all the items suggested in the evaluation chart which had been drawn up beforehand. The evaluation of the response table using the emergency management exercise computer program was made by applying appropriateness of hospitalization, isolation, and medication using antiviral agents as evaluation standards. The disease team evaluated the countermeasures with two grades; good and poor, and sent the results to the Central Countermeasures Committee. The Central Countermeasures Committee, in turn, evaluated the appropriateness of the countermeasures and gave instructions for the next phase.

Result of the evaluation. Since the participants in each city and province had a very short time for the exercise, there was a suggestion that they should participate in future exercises while working at the same time. Also there was some opinion that cooperation was not satisfactory.

The recognition of current conditions and countermeasures against prevalence was satisfactory, but the countermeasures by each region and community were not sufficient, according to the analysis of the response plan. On the other hand, the evaluation concluded that the effects of the preliminary exercise were valid because the region that participated in the preliminary exercise got a high score.

The National Security Council (NSC) Secretariat announced that it will take account of the exercise in developing a national level crisis management model that will be conducted in the future. Also, it will construct the decision-making system and the cooperation system among related government agencies to define the role of each organization. At the same time, it suggested that the Ministry of Health and Welfare would have to lead other government agencies when the emerging infectious disease pandemic is prevalent. The Advisory Board said that the exercise was meaningful because national-level government agencies discussed countermeasures of an emerging infectious disease pandemic together, which happened for the first time in Korea. It also suggested that it's necessary to estimate the monitoring the emerging infectious disease pandemics, to assure cooperation among government medical agencies, to establish a priority system in giving antiviral agents, and to prepare for measures to involve the press.

The Central Working Group for Disease Control suggested the necessity of establishing a priority system in administering antiviral agents and the standards for patient diagnosis. As for patient diagnosis of an emerging infectious disease pandemic, it recommended considering various factors including the capability to diagnose the patient at the time of prevalence, the scope of diagnosis when the number of patients has increased, the report of case outbreaks according to the classification of patients (doubt, presumption, definite diagnosis), and Institute of Health & Environment's BL-3 utilization methods. Also, it said that the priority system for anti-viral administration is needed at each step. It said that the strength of this exercise were the prompt prevention measures and investigation of the cause of outbreak, prompt isolation and treatment, securing the protective tools and press-related activities, and organizing the disease control and epidemic investigation team. There are also several things to introduce. For example, it is necessary to request the related government agencies to prohibit public congregation, and there was no reference made to the symptoms of patients (the authorities have to prohibit the use of some terms such as "mysterious disease"). In addition, the collection of samples according to the symptoms of patients and disinfection according to the features of epidemic (for example: disinfection in toilets and kitchens in Cholla-nam-Do is for preventing waterborne disease) are needed. Also organizing the media team and a media strategy are needed. The site manager of the Central Support Group for Disaster Recovery said that establishing a priority system for antiviral agents and conversion of isolation rooms in university hospitals are needed. However, the control team concluded that the interaction among the teams were active in spite of the time limit.

Bioterrorism Modeling and Use

Why small pox? Smallpox is one of the agents of highest concern agents (Category A) for use as a biological weapon. Category A agents have characteristics of easy dissemination, high morbidity and mortality, and the ability to cause social disruption. Smallpox is of concern because of its high mortality (averages 30 percent, but is significantly higher in unimmunized older adults, infants, and persons with underlying immune system compromise), person-person transmission, lack of effective treatment, and lack of immunity among the general population. The primary mode of transmission of variola is through respiratory droplets. Aerosol transmission occurs but is uncommon. It maintains infectivity for prolonged periods out of its host, so contaminated clothing and bedding can be infectious. Secondary attack rates are estimated at 37-87 percent among unvaccinated contacts. The greatest infectivity from rash onset of the diseases occurs between seven and 10 days.

Modeling work was required to develop a smallpox response plan to determine effective control measure strategies.

Smallpox modeling. Modeling is the simplest explanation consistent with reality to abstract and simplify real situation and to be more amendable to experimentation or analysis. In epidemic modeling with a compartment model, the dynamics of infectiousness at the population level were divided into several compartments. For example in the SEIR compartment, the population was divided into susceptible, infected, infectious, and immune. In this model, the numbers can be calculated by means of differential equations.

Epidemic parameters and assumptions of the model. 1) R0 (Basic Reproductive Number) three to five; 2) average latent period - 11 days; 3) average duration of infectiousness - 14days ; 4) constant population size (total population=500,000); 5) life expectancy of population - 70 years, rectangular type population distribution; 6) homogeneous mixing - all populations are susceptible at first; 7) recovery rate is constant; 8) fatality rate - 30 percent; 8) initial infectious number - 50 persons 9) intervention - vaccination/isolation (quarantine); and 10) vaccine efficacy – 90 percent.

Results.

Figures 1 – a and b: results without intervention and ineffective intervention

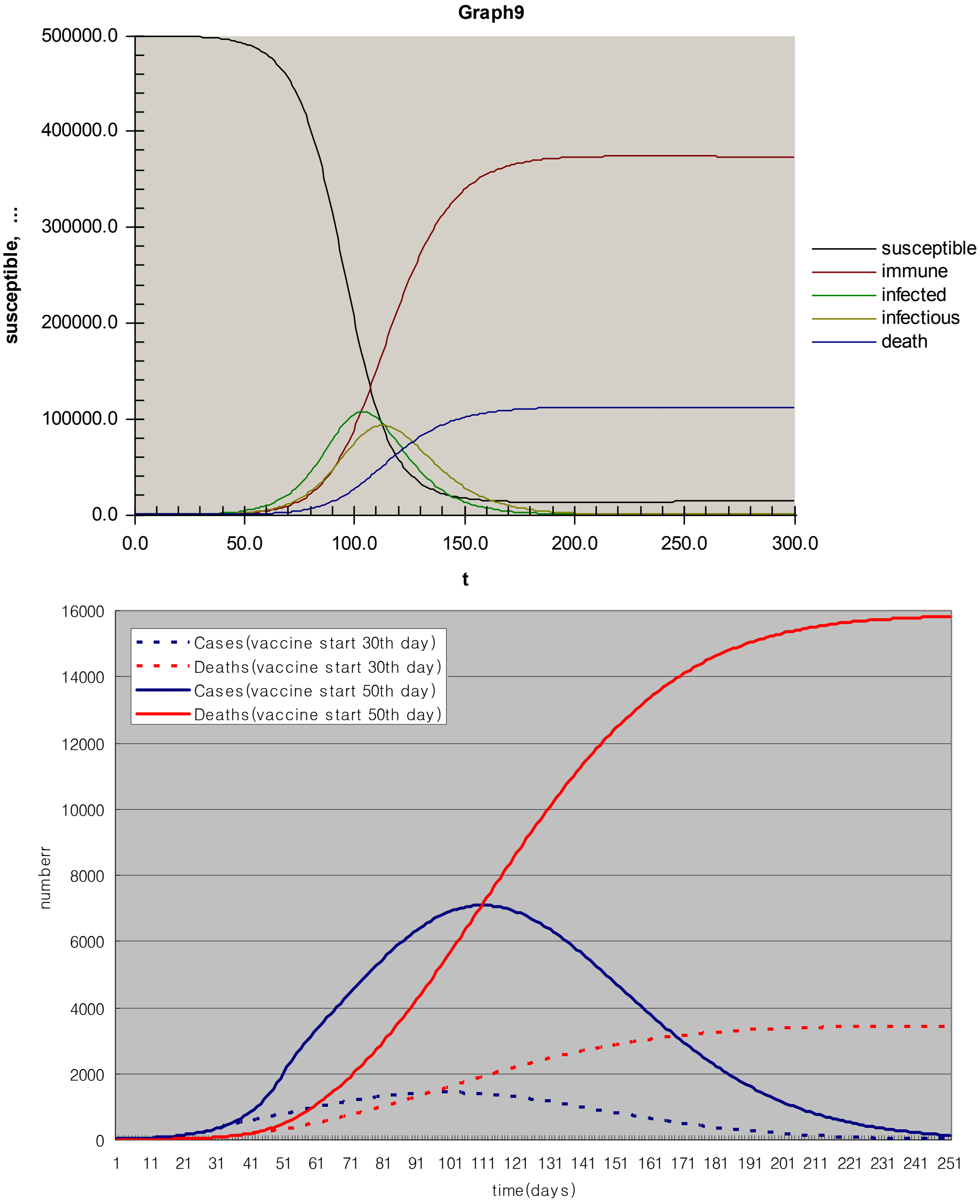


Fig 2. 50% vaccination within 50 days (left) and 25 days (right) in case of R0=5 (blue line: No of Cases, red line: No of Deaths; dotted line: vaccination started at 30th day of epidemic, line: vaccination started at 50th day of epidemic)

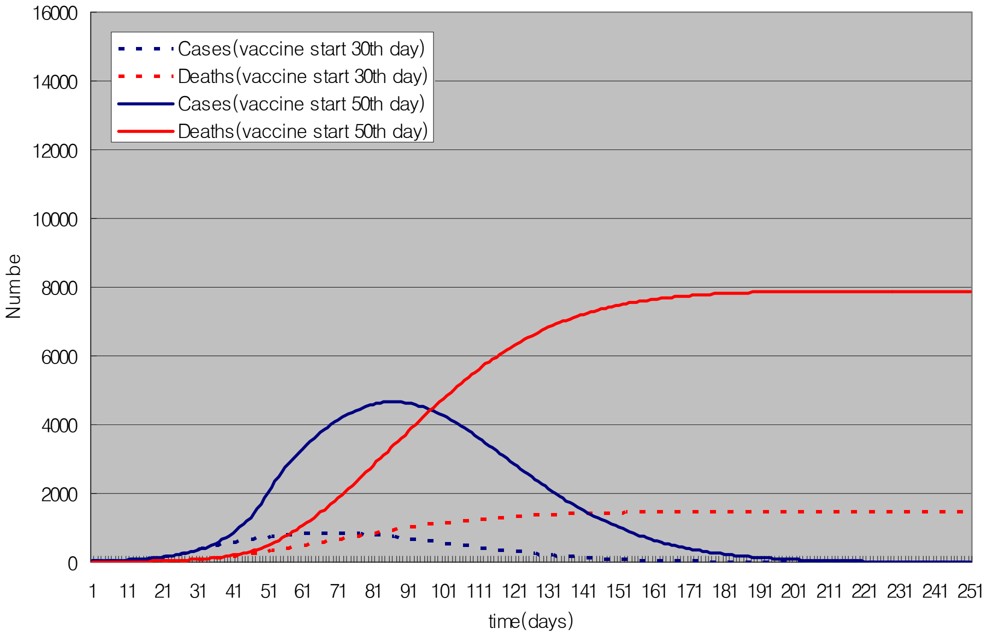
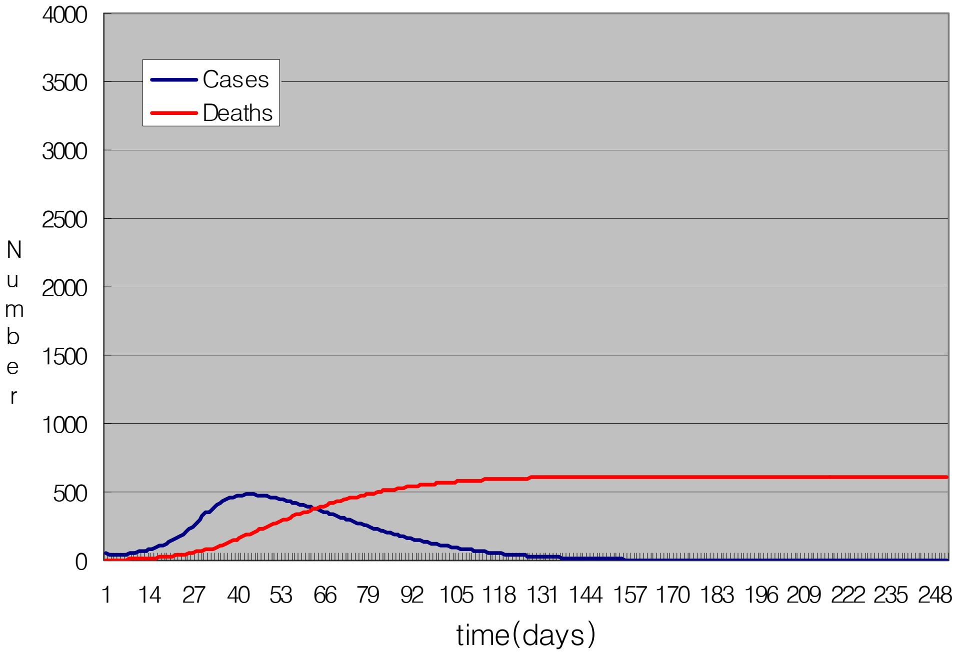


Fig3. Effective infected cases isolated to reduce R0=2.5 with 50% vaccination within 25 days (Vaccination started at 30th epidemic day)



Summary. To control a smallpox epidemic, early start of vaccination and fast coverage are more important than the vaccine coverage rate itself to reduce the number of cases and deaths. If the infected patients were isolated effectively to reduce 50 percent of transmission, and the vaccination started within 30 day of the epidemic, the smallpox epidemic size would be minimized. How to detect of an epidemic in the early phase and how fast vaccination of the population can be accomplished in a short period of time should be the keys for preparing for a small pox epidemic.

Modeling and simulation

- Panel discussion

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Modeling and simulation can provide a way of understanding dynamic complexity!

Introduction of an ongoing project:

A Novel Sero-epidemiology Approach to the Identification of Target Population for Chemotherapy in schistosomiasis japonica Control

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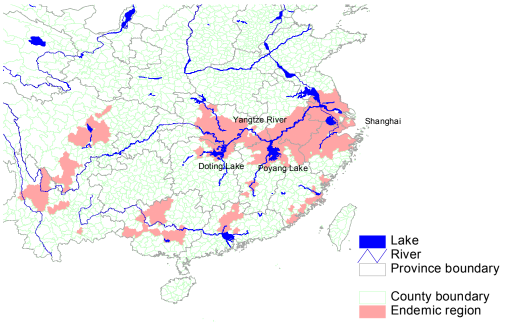
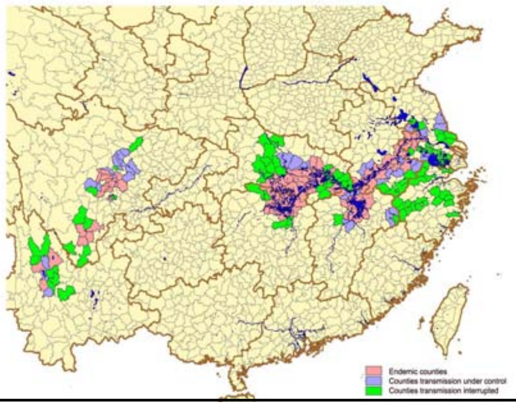
The distribution of schistosomiasis in China in the 1950's



Distribution of schistosomiasis in China in 2001



Distribution of schistosomiasis cases in 2003

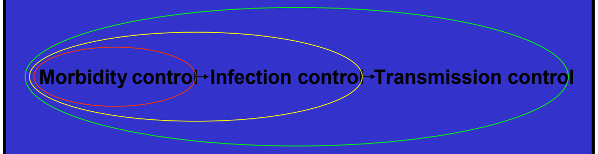
Zhou XN, et.al., manuscript

Province	Population in endemic county (x10000)	Population in endemic township (x10000)	Population in endemic village (x10000)	No. current cases	No. cases		
					Acute cases	Chronic cases	Advanced cases
Shanghai	639.14	405.57	305.61	0	2*	0	0
Jiangsu	3897.71	2386.90	1242.16	25438	116	22541	2781
Zhejiang	2975.39	1716.77	957.00	1187	2*	0	1187
Anhui	2103.64	1177.51	601.56	60647	256	54751	5640
Fujiang	1077.43	319.31	83.28	0	0	0	0
Jiangxi	1706.49	830.41	442.67	131253	126	127468	3659
Hubei	3652.52	2144.67	952.75	295383	247	290879	4257
Hunan	1741.51	902.48	612.59	205461	234	199819	5408
Guangdong	773.55	184.70	73.29	0	0	0	0
Guangxi	1215.52	278.14	80.46	0	0	0	0
Sichuan	3132.95	1655.41	1023.29	76888	58	75321	1509
Yunan	491.14	239.61	162.86	46750	73	46677	0
Total	**23406.99**	**12241.48**	**6537.52**	**843007**	**1114**	**817456**	**24441**

Need for a robust surveillance system

- The strength of the available data will depend on the surveillance system.
  - Is data being collected in the same way in all areas?
  - Are the diagnostic tests being used the same way?
  - Given high transmission in some areas of the lake regions, what is the relevance of antibody testing?
  - Given that chemotherapy has been used intensively over the past 15 years, what is the diagnostic efficiency of stool examination?

Basic strategies for schistosomiasis control



Intervention

Mass chemotherapy → Selective chemotherapy → Chemotherapy + transmission control

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- Direct parasitological techniques have become relatively insensitive following widespread chemotherapy which resulted in generally lower worm burdens
- Immunodiagnostic technology, owing to its rapid, affordable and easily acceptable (high compliance) advantages, has been widely adapted in the control activities of the infection

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Immunodiagnostic techniques in China

— Antibody-based serological assays

- **Test profile**

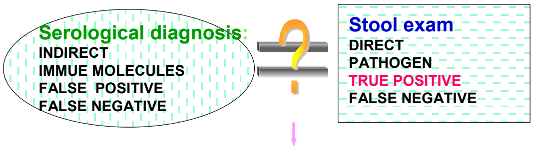
Test	The year for the test available
Intradermal test (ID)	1950
Cercaria huellen reaction (CHR)	1951
Circumoval precipitin test (COPT)	1958
Indirect haemagglutination (IHA)	1958
Indirect immunofluorescence assay (IFA)	1975
Counter immunoelectrophoresis (CIE)	1973
Enzyme linked immunosorbent assay (ELISA)	1978
Assay with reagent strips	2000

- **Antigen profile: crude, purified, recombinant…**

— Antigen-based assays

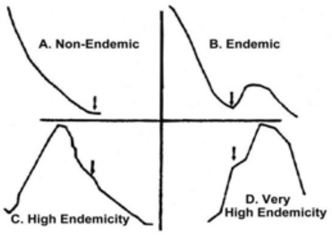
McAb probes	Ig isotype	target antigen
3D8A	IgM	CCA
IIID10	IgM	CCA
NP28-58	IgG1	140 kDa(SEA)
H4	IgG1	70 kDa(SEA/HSP)
8SE4	IgG1	MAA
JG3	?	CAA
31/32	?	31/32 kDa
AT 1 (anti-rSjCTPI)	IgG1	TPI

- Almost all assays of both antibody and antigen detections were performed poorer in the field in terms of sensitivity and specificity than in the laboratories where they were developed
- None of the available immuno-diagnostic assays has been improved sufficiently enough to offer an alternative to stool exams
  - antibody-based serological assays can not distinguish active infections from previous infection or re-infection
  - antigen-based assays are also not valuable as expected



Is it appropriate to use only one cut-off value for serum positive validation in endemic area to define treatment target?

Is the current standard appropriate?



Antibody frequency distribution curves for amebiasis in populations with various levels of endemicity.
The *x* axis represents the titer; the *y* axis is the frequency

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Project Aim

What do we need for target identification in an endemic area?

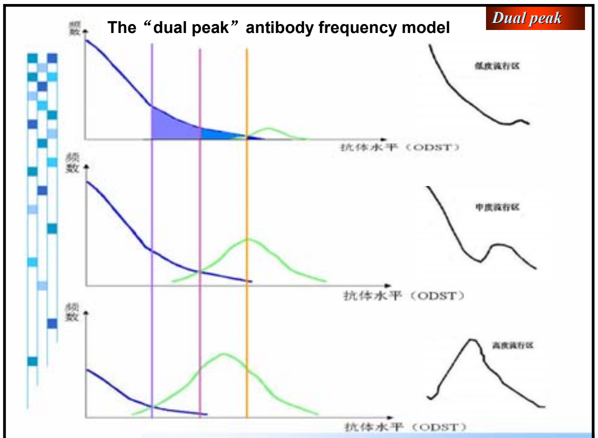
	CLINIC USE	PUBLIC HEALTH USE
TARGET	individuals	Population in the community
PURPOSE	Cure individual patients	Lower the prevalence and intensity of the area
DIAGNOSTIC ASSAY REQUIREMENTS	Technologies detecting single sample to identify definitive positive case	Technologies detecting samples in batches to identify target population for treatment -- cost -effective

➢ Research is needed to correlate the quantitative sero-reactivity of a given community rather than an individual to transmission parameters, which would lead to the possibility of estimating the prevalence, monitoring transmission change and identifying the target individuals for treatment by use of epidemiologic interpretation of serological data

Could quantitative full frequency distribution of testing results(titers) do this?

Dual peak

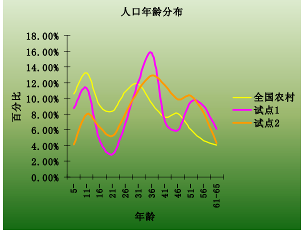
The "dual peak" antibody frequency model



SAMPLING

- Study Area

  Anhui(A)、Hubei(H)、Jiangxi(J) and Zhejiang(Z)



	# of Subjects	Portion of Stool Pos.
Z	3386	0
A	784	6.3%
H	~2500	~10%
J	~1000	~20%

Project Aim

A novel diagnostic system

- **Application software for modeling and target identification**
  - **Sampling**
  - **Data input and antibody distribution analysis**
  - **"dual peak" model construction**
- **The most appropriate antibody detection assay**

Issues for research for schistosomiasis control

- The rapidly developing economy will result in changes for schistosomiasis transmission
  - Population migration
  - Mechanization of agriculture reducing bovine contamination
  - … …
- Anti-flood policy means snail infested areas may persist, What will be the long term effects of Three Gorges Dam?
- Need to examine cost-effectiveness of these transmission control strategies

modeling and simulation

•sound public health infrastructure
•control programme successful in meeting targets
•political will and long term commitment of resources

- Simulation provides a method for checking your understanding of the world around you and helps you produce better results faster:
  - Predict the course and results of certain actions.
  - Understand why observed events occur.
  - Identify problem areas before implementation.
  - Explore the effects of modifications.
  - Confirm that all variables are known.
  - Evaluate ideas and identify inefficiencies.
  - Gain insight and stimulate creative thinking.
  - Communicate the integrity and feasibility of your plans.

Status quo for Modeling and Simulation in China from Literature Search – need more study

- Chinese CNKI
  - **中国50岁以上人口死亡率的数值仿真 (modeling and simulation of the death rate for over 50-year-old Chinese population)**
  - **应用系统动力学模型对SARS疫情传播及主要防控措施效果的计算机模拟仿真研究 (simulation of SARS transmission and the effects of control measurements using a systemic dynamic model)**
- PubMed
  - **Yu IT, Li Y, Wong TW, Tam W, Chan AT, Lee JH, Leung DY, Ho T.Evidence of airborne transmission of the severe acute respiratory syndrome virus. N Engl J Med. 2004 Apr 22;350(17):1731-9.**
  - **Spear RC, Hubbard A, Liang S, Seto E. Disease transmission models for public health decision making: toward an approach for designing intervention strategies for Schistosomiasis japonica. Environ Health Perspect. 2002 Sep;110(9):907-15.**
  - **Guo HC, Liu L, Huang GH, Fuller GA, Zou R, Yin YY. A system dynamics approach for regional environmental planning and management: a study for the Lake Erhai Basin. J Environ Manage. 2001 Jan;61(1):93-111.**

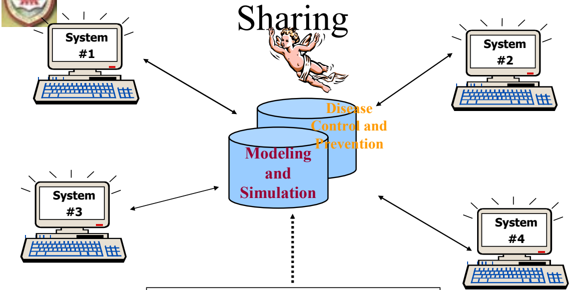
Things should consider and reinforce

- Big population call for extensive data "translation"
  - Samples that are too large may waste time, resources and money, while samples that are too small may lead to inaccurate results.
  - Simulation is to enhance knowledge
- Proper trainings are requisite especially in areas like, Healthcare implementation, Medical and Design of Experiments: one should not blindly use a simulation software without understanding its underlying assumptions.
  - Most experts in simulation modeling would agree that "programming" of the model represents only 25 to 50 percent of a sound simulation study.
  - The so-called "easy-to-use" simulation packages require a significant amount of technical competence and experience. The simulation analyst must also be knowledgeable in simulation methodology.

Things should consider and reinforce

- Interdisciplinary collaboration is needed
  - Commercial software can only reduce the time to "program" a model for problems of modest complexity. However, for most real-world problems, programming in some form is required
  - Computer scientists, Statisticians, Epidemiologist and even field staffs need to communicate frequently
- International collaboration should be emphasized
  - Data collection(in the same way in all area) and exchange
  - Intellectual communication and technique support

"Perfect World" Behavior Sharing



In a perfect world, we'd all speak the same language

Modeling and Simulations

Moran Ki, MD, PhD
Eulji University,
Daejeon, Korea.

Modeling and simulations of infectious diseases are useful tools to estimate epidemic size and determine effective intervention methods. Models are idealized, simplified representations of reality. Simple but unrealistic models can be illuminating, while realistic but complex models are often necessary though they demand much more work. Unrealistic and complex models are a worst case scenario and simple and realistic models are ideal but rare. Therefore, a simple model should be the first designed, and complex models can always be added to represent reality.

In this discussion, I would like to point out two presenters that we were not able to talk about but that we should keep in mind when applying modeling and simulations.

There are several different types of modeling. In analytical modeling, real-time estimation of generation time and reproduction numbers helps track changes in epidemic spread and the effectiveness of control measures. Historical modeling is needed to gain knowledge about our enemy. We can examine the potential impact of targeted control measures, e.g. movement restrictions, "ring" vaccinations, contact tracing, and workplace closure with predictive modeling. A combined approach to modeling can inform us of implementation measures for control policies.[1]

Incubation period (IP) is the time between infection and showing symptoms. Often, infections are only treated when a person becomes aware of their infection when they become symptomatic. For some diseases, symptoms occur before the person is infectious like with small pox and SARS. In these cases, early isolation can be effective intervention. For other diseases, symptoms begin after the person is infectious (e.g. influenza, HIV), and contact tracing and prophylactic immunizations are needed for intervention. With some diseases, symptoms and infectiousness occur together (e.g. tuberculosis), and in this situation early isolation, contact tracing and immunization are necessary.[2]

Therapy can also be an effective control if it reduces infectiousness. However, even when therapy reduces infectiousness, if it can not cure the disease (eradicate the virus), epidemic size will increase even with therapy. For example, ART therapy can decrease AIDS mortality rates (Figure 1). However, anti-retroviral therapy (ART) also increases the incidence and prevalence of AIDS. In this example, I assumed a relative infectiousness of treated people to be 0.7. I did batch runs by proportion and treated p from 0 ~ 100% (Figure 2).

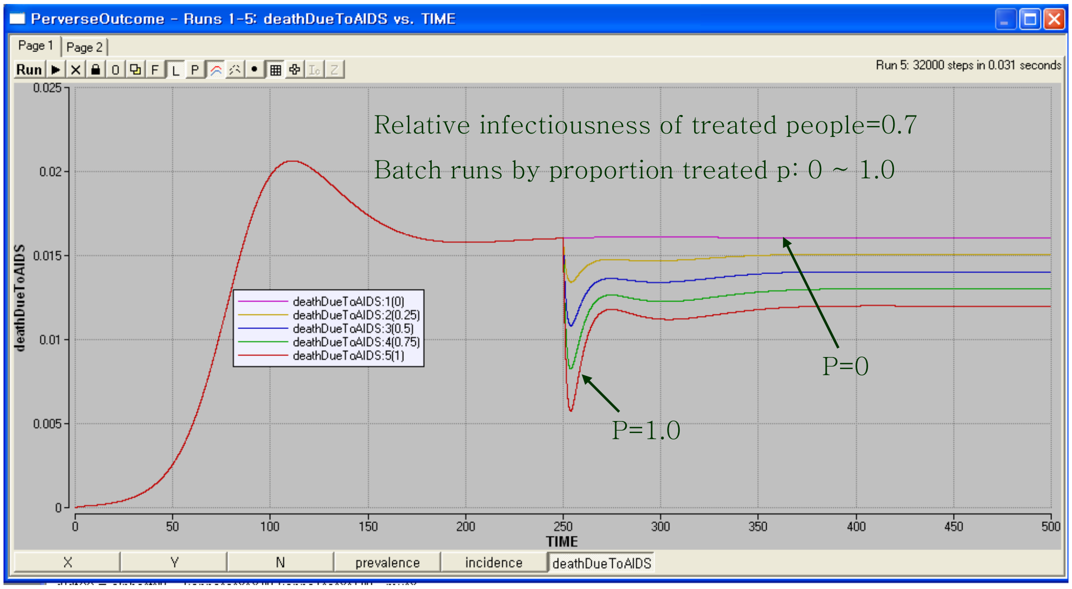
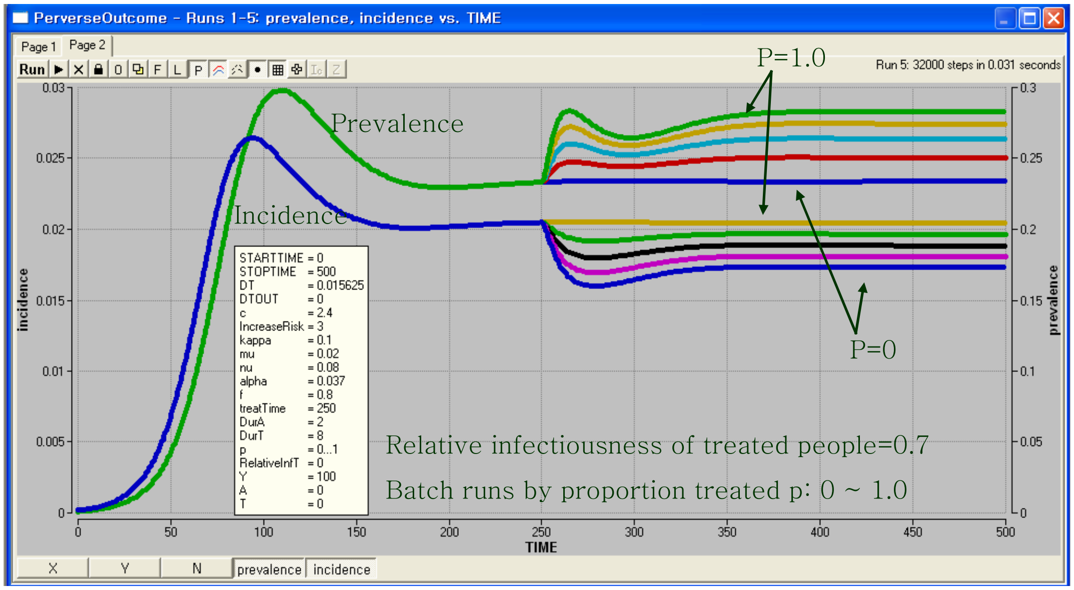


Figure 1. Changing pattern of mortality rate of AIDS by proportion of treatment with ART.



```
STARTTIME    = 0
STOPTIME     = 500
DT           = 0.015625
DTOUT        = 0
c            = 2.4
IncreaseRisk = 3
kappa        = 0.1
mu           = 0.02
nu           = 0.08
alpha        = 0.037
f            = 0.8
treatTime    = 250
DurA         = 2
DurT         = 8
p            = 0...1
RelativeInfT = 0
Y            = 100
A            = 0
T            = 0
```

Figure 2. Changing pattern of incidence and prevalence of AIDS by proportion of treatment with ART.

Why does ART increase the incidence of AIDS? ART can reduce the infectivity of AIDS by reducing the viral load. This means that the progression from HIV to AIDS and death can be delayed. Therefore, life expectancy is increased. However, it also increases sexual risk behaviour because of a return to good health. As a result, the incidence and prevalence of AIDS increases. So should we stop ART treatment? I think we need to consider many different aspects of this result. First, we don't know the effect of combination intervention, such as ART plus other interventions (e.g. behavioral change, and combination therapy) for this model. Second, AIDS patients who are being treated with ART can work, and can therefore contribute to the economic growth of their country, teach their children, and maintain their families. The effects on the economy of the country and cost-effectiveness of ART vs. other interventions are also very important. There are many indirect effects that this model does not account for.

Let's talk about 'R_0' more. R_0 is the average number of secondary cases generated by an index case in a naïve population. In heterogeneous populations (high risk +low risk), R_0 is the largest eigenvalue of the next generation operator. It determines: 1) whether, on average, an epidemic will grow or fade; 2) how much work needs to be done to control the epidemic; and (3) the probability of the pathogen evolving into a more transmissible form.

I'd like to discuss an important concept in modeling called the network approach.
In Figure 3, the sick individual (dark red color) has four close contacts, and three of those contacts are sick; so, the R_0 is 3 for the first generation.

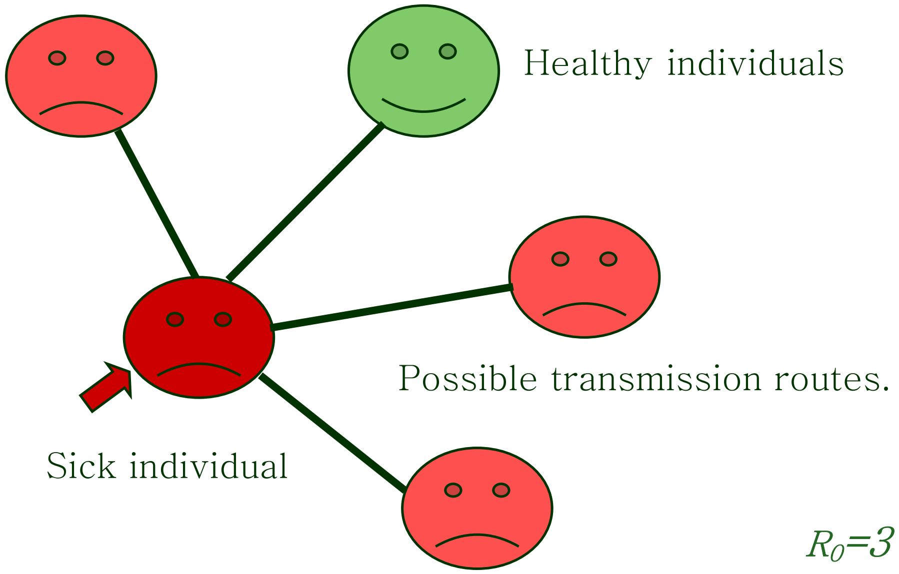
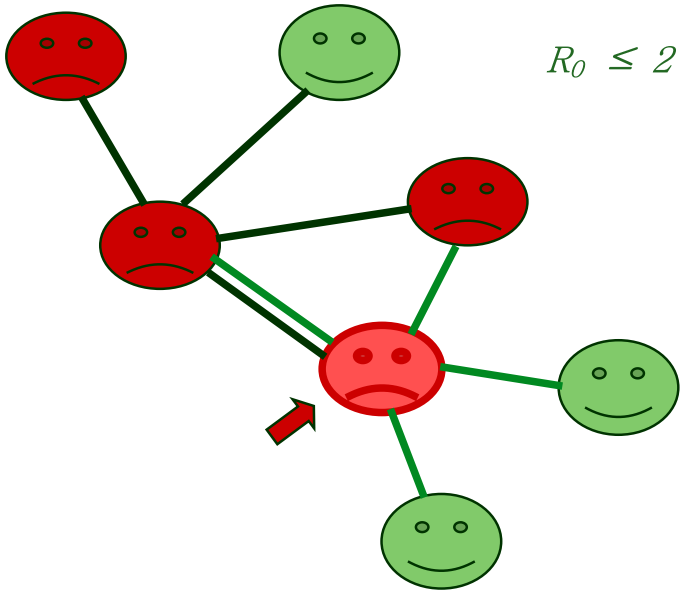


Figure 3. The first generation in network approach.



In figure 4, although the secondary individual also has four close contacts, because of the local nature of the connections they will only cause a maximum of 2 cases. For the second generation, the R_0 is less than 2. Therefore, if we consider a local network which is densely connected or overlapped, R_0 decreases very quickly.

The network approach shows that targeted control is very effective. However, untargeted mass-vaccination is the most commonly modeled intervention. Therapy can also be a control (if it reduces infectiousness), but effects have only been analyzed for blanket use. Targeting intervention in populations at the greatest risk is often more efficient and feasible, particularly if time or resources are limited.[3]

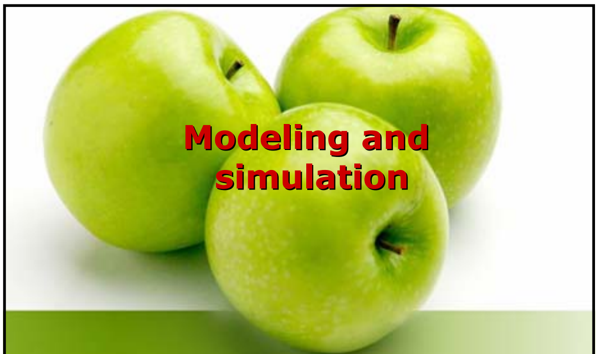
However, the theories to analyze such interventions are not very well developed. A key form of targeting for outbreaks of a novel disease is with spatial locality or network location with respect to cases (e.g. ‘ring vaccination/isolation/culling’, contact tracing & isolation). The aim is to reduce the density of susceptibles ‘close’ to the infective.

In conclusion, our “good” simulations are as follows: (1) minimal feasible complexity; 2) mathematically well-defined, models should be constructed with well characterized stochastic processes not ‘ad-hoc’ behavioral models; 3) if predictions are being made, unknown parameters need to be robustly estimated using the model from epidemiological data; 4) where data is unavailable, a detailed sensitivity analysis needs to be undertaken; and 5) even if models are only being used to explore dynamics, sensitivity analysis is important to understand mechanisms.[4]

For the effective control of infectious disease with models and simulations, we need effective information systems (laboratory and clinical data) for communicable disease control as a permanent infrastructure, and closer collaboration between academic and service providers on new developments in communicable disease control. We also need enhanced monitoring of veterinary infections and 'minor' zoonoses, particularly in resources poor settings.

References

1 Anderson RM & May RM. Infectious diseases of humans: dynamics and control. Oxford: Oxford University Press (1991).
2 Fraser, C., Riley, S., Anderson, R.M. & Ferguson, N.M. (2004) PNAS 101, 6146-6151.Factors that make an infectious disease outbreak controllable.
3 Ferguson, N. M., Donnelly, C. A. & Anderson, R. M. The foot-and-mouth epidemic in Great Britain: pattern of spread and impact of interventions. Science 292, 1155-60 (2001).
4 White PJ et al. Vicious and Virtuous Circles in the Dynamics of Infectious Disease and the Provision of Health Care: Gonorrhea in Britain as an Example. J Infect Dis 2005;192:824–836.



Modeling and simulation

Moran Ki, MD, MPH, PhD
Thursday, December 15, 2005
Eulji University School of Medicine

Contents

- Comments on modeling and simulation
- Questions on the presented topics
- Suggestions

Models are idealized, simplified representations of reality.

Type of modeling

- Analytical modeling:
  - Real-time estimation of generation time and reproduction number helps track changes in epidemic spread and effect of control measures.
- Historical modeling
- Predictive modeling:
  - Examines the potential impact of targeted control measures.
- Combined approach modeling:
  - Can inform control policy implementation.

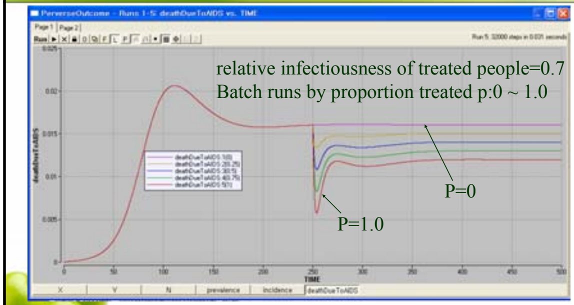
Incubation Period and Intervention

- IP is the time between becoming infected and becoming symptomatic.
- Symptoms occur before the person is infectious (e.g. Smallpox, SARS)
  - → Early Isolation is effective.
- Symptoms begin after the person is infectious (e.g. Influenza, HIV)
  - → Contact tracing, prophylactic immunizations are needed.
- Symptoms and infectiousness occur together (e.g. Tuberculosis)
  - → Early isolation, Contact tracing and Immunization.

Therapy and Incidence

- Therapy can also be a control, if it reduces infectiouseness.
- Even if therapy reduces infectiouseness, if it can not cure (eradicate the viruses), epidemic size increase by therapy.
  - e.g. HIV and ART (Anti retroviral therapy)

ART decrease AIDS mortality

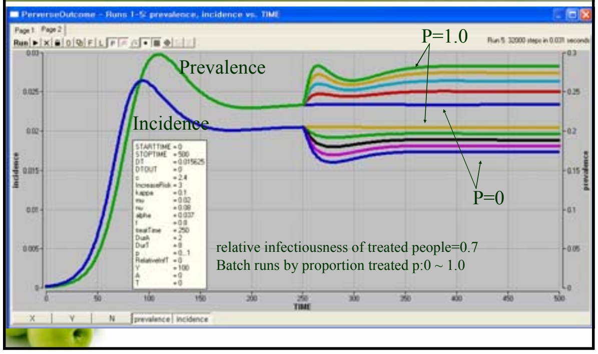


relative infectiousness of treated people=0.7
Batch runs by proportion treated p:0 ~ 1.0

P=0

P=1.0

ART increase incidence and prevalence of AIDS



P=1.0

Prevalence

Incidence

STARTTIME = 0
STOPTIME = 500
DT = 0.015625
DTOUT = 0
c = 2.4
IncreaseRisk = 3
kappa = 0.1
mu = 0.02
nu = 0.08
alpha = 0.037
f = 0.8
treatTime = 250
DurA = 2
DurT = 8
p = 0..1
RelativeInfT = 0
Y = 100
A = 0
T = 0

P=0

relative infectiousness of treated people=0.7
Batch runs by proportion treated p:0 ~ 1.0

Why ART increase incidence?

- ART
- → Infectivity ↓ (viral load↓)
- → Life expectancy ↑
- → Sexual risk behaviour ↑
- → Incidence ↑
- → Prevalence ↑

Should we stop ART?

- We need to consider…
- ART + other interventions (e.g. behavioral change, combination therapy)
- Cost-effectiveness
  - Treatment vs. other interventions
  - Pts can contribute to economical growth because they can work by treatment.

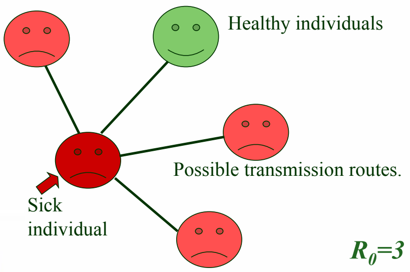
R_0

- R_0:
  - the average number of secondary cases generated by an index case in a naïve population.
  - In heterogeneous population (high risk +low risk), the largest eigenvalue of the next generation operator.

- It determines whether an epidemic will grow or fade out on average.
- It determines how much work needs to be done to control the epidemic.
- It determine the probability of the pathogen evolving into more transmissible form.

Network approach

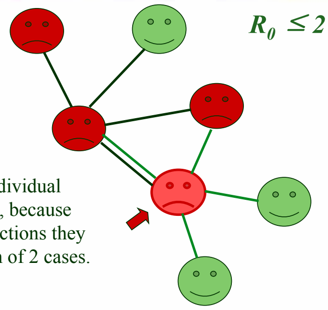
Why do we need a network approach?



$R_0=3$

Why do we need a network approach?

$R_0 \leq 2$



Although this secondary individual also has four close contacts, because of the local nature of connections they can only cause a maximum of 2 cases.

Targeted control policies

- Mass-vaccination is the most commonly modeled intervention, but is untargeted.
- Therapy can also be a control (if it reduces infectiouseness), but effects have again only been analyzed for blanket use.
- Targeting intervention at populations at greatest risk is often more efficient and feasible, particularly if time or resources are limited.
- However, the theory to analyze such interventions is much less developed.

- A key form of targeting for outbreaks of novel disease is by spatial locality or network location with respect to cases.
  - ..e.g. ‘ring vaccination/isolation/culling’, contact tracing & isolation.
- Aim is to reduce density of susceptibles ‘close’ to be that of the infectives.

“Good” simulations

- Minimal feasible complexity
- Mathematically well-defined.
  - Models should be constructed with well characterized stochastic processes, not ‘ad-hoc’ behavioral models.
- If predictions are being made, unknown parameters need to be robustly estimated using the model from epidemiological data.
- Where data in unavailable, detailed sensitivity analysis need to be undertaken.
- Even if models are only being used to explore dynamics, sensitivity analysis is important to understand mechanisms.

Questions on the Presented Topics

SARS again?

- SARS epidemic can be returned?
- If they return,
  - Would it be similar?
  - Are there any modeling and simulations on new epidemic of SARS in China?
- What are the most important lessons from SARS in China?

Pandemic modeling questions

- Eradication of any outbreak requires early detection and a well-planned, rapidly executed response.
- For flu, outbreak probably needs to be “small” and geographically contained.
- More feasible if evolution of transmissibility is incremental.
- Options:
  - Prophylactic vaccination (if H5 trial vaccine available)
  - Antiviral (NAI) prophylaxis
  - ‘Increasing social distance’ (school /workplace closure, movement restriction, isolation)

- Key modeling questions:
- Is any combination of the above capable of controlling a pandemic?
- What resources are required?
- Can we be sure?

Small pox

- Table top exercise- Even if the estimation is not correct, it would be necessary.
- What is the most important response for the first line?
- Do we have enough vaccines?
- Is the vaccine safe?
- How about the vaccinee?

Suggestions

- Many needs:
- Effective information systems (laboratory and clinical data) for communicable disease control- as a permanent infrastructure;
- Closer collaboration between academic and service provider on new developments in communicable disease control;
- Enhanced monitoring of veterinary infections and ‘minor’ zoonoses, particularly in resources poor settings.

Thank you!
Happy Christmas!

CONTAINMENT OF AN EMERGING INFLUENZA PANDEMIC:

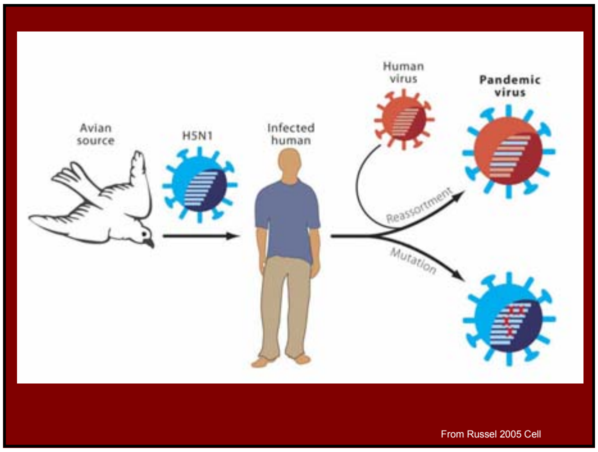
How much time can we buy?

Marc Lipsitch, Christina Mills, James Robins
Harvard School of Public Health

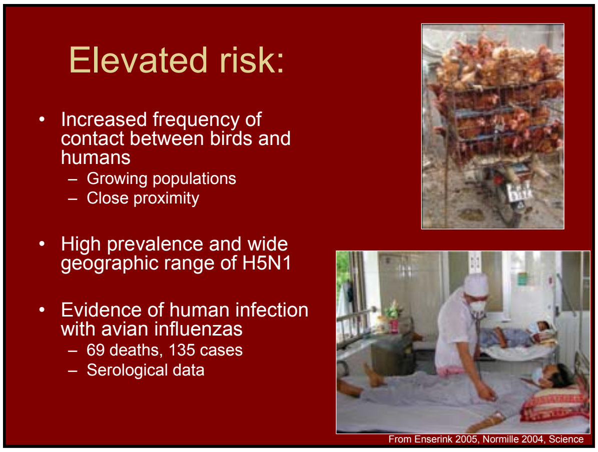
Carl Bergstrom
Univ. of Washington

From Normile 2005 Science

“The world has moved closer to a[n influenza] pandemic than at any time since 1968”
– WHO, Geneva (2005)



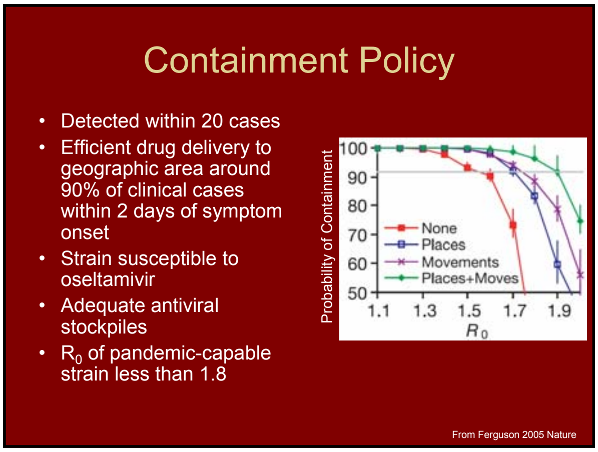
From Russel 2005 Cell



Elevated risk:

- Increased frequency of contact between birds and humans
  - Growing populations
  - Close proximity
- High prevalence and wide geographic range of H5N1
- Evidence of human infection with avian influenzas
  - 69 deaths, 135 cases
  - Serological data

From Enserink 2005, Normille 2004, Science



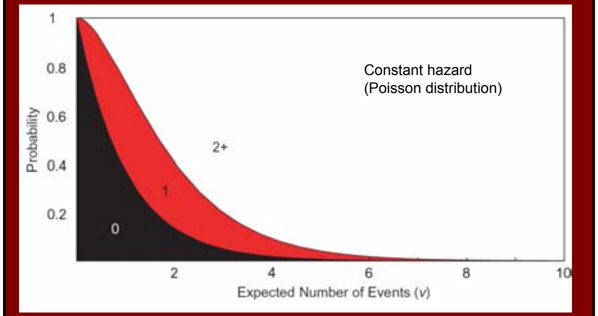
Containment Policy

- Detected within 20 cases
- Efficient drug delivery to geographic area around 90% of clinical cases within 2 days of symptom onset
- Strain susceptible to oseltamivir
- Adequate antiviral stockpiles
- R_0 of pandemic-capable strain less than 1.8

From Ferguson 2005 Nature

How likely are multiple introductions?

- Historical data
  - No pandemic-capable strain contained
  - Genetic heterogeneity might suggest multiple
  - No inference in the absence of heterogeneity
- Single emergence does not affect process
  - Constant hazard
  - Escalating hazard



From Mills 2005

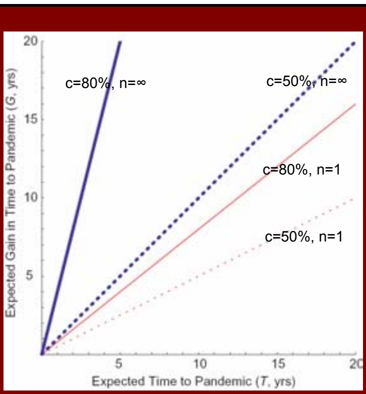
Benefit of Containment

- Expect containment to fail eventually
  - – Success probability not 100%
  - – Limited ability to undertake repeated attempts
- Containment may “buy time”

Gain =

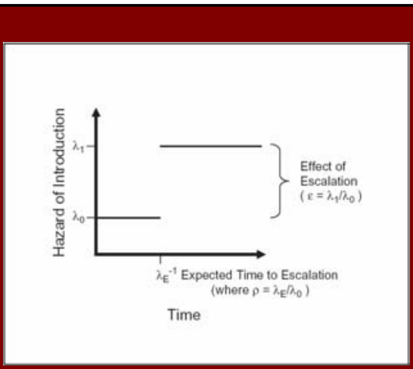
E[Time to pandemic | containment –

Time to pandemic | status quo]



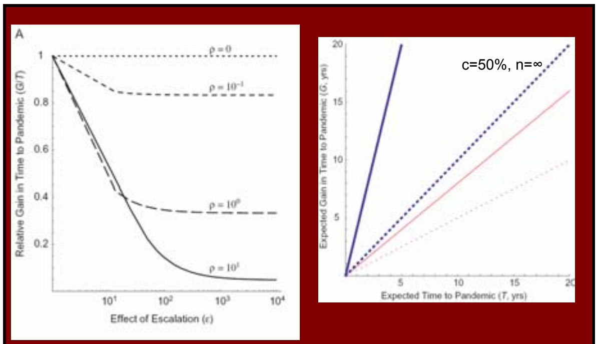
c: success probability of a given containment attempt
n: number of containment attempts

From Mills 2005



Escalating hazard of introduction model

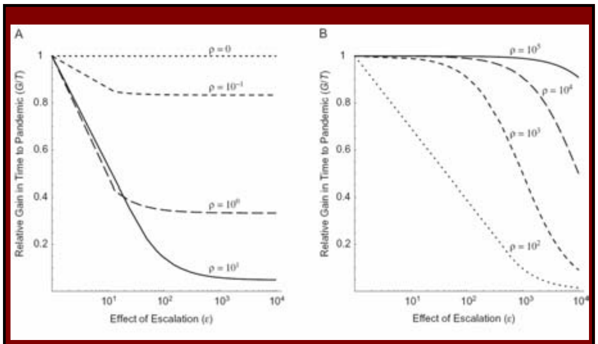
From Mills 2005



c=50%
n=∞

ε: effect of escalation (λ_1/λ_0)
ρ: relative hazard of escalation (λ_E/λ_0)

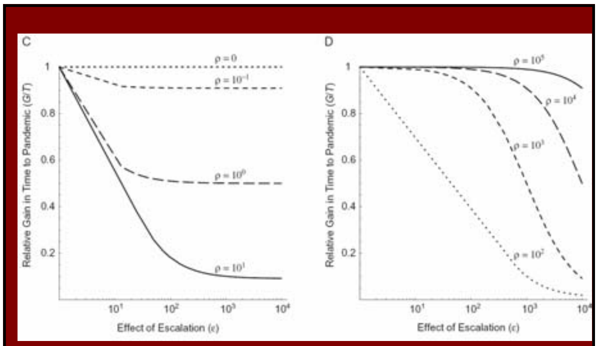
From Mills 2005



c=50%
n=∞

ε: effect of escalation (λ_1/λ_0)
ρ: relative hazard of escalation (λ_E/λ_0)

From Mills 2005



c=100%
n=1

ε: effect of escalation (λ_1/λ_0)
ρ: relative mag. of esc. (λ_E/λ_0)

From Mills 2005

Conclusions

- For most realistic scenarios, expected gain is small
  - Less than double time to a pandemic
- If hazard is high, important to "buy time"
  - Action plan for first event
  - Lead time
- Containment alone is unlikely to prevent a pandemic

Multi-pronged strategy

- Risk reduction
  - Animal practices, bird-human contact
- Local containment
  - Antiviral stockpile in Asia, surveillance
- Global transmission prevention
  - Social distance measures, vaccines,
- Harm reduction
  - Surge capacity, antivirals, vaccines