Strategies for containing an emerging influenza pandemic in South East Asia[1]

Modeling pandemic spread and possible control plans of avian flu H5N1

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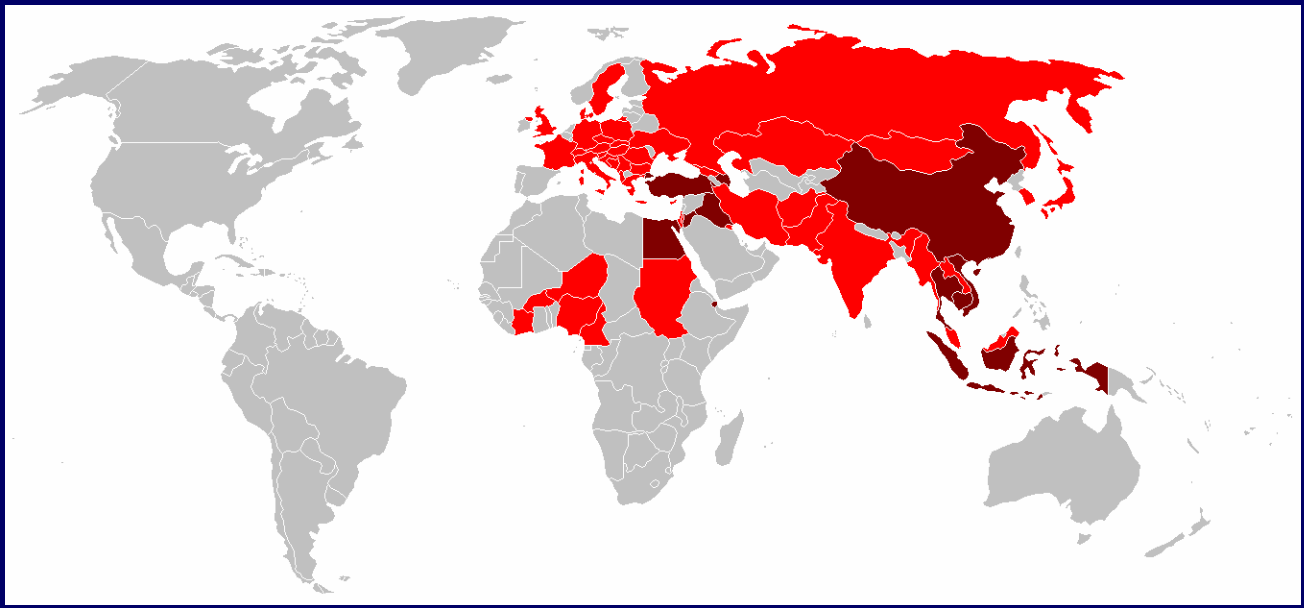
[1] Nature. 2005 Sep 8;437(7056):209-14.

Why care about about H5N1?

- Highly pathogenic influenza A virus
- Endemic in avian populations in East Asia
- Can infect several species, including humans (217 cases, 123 deaths)
- No current human-to-human transmission capability
- Mutation or reassortment may result in a virus with sustainable human-to-human transmission



Some bird flu biology

- Eight single RNA strands
- Hemagglutinin (H5N1)
  - antigenic glycoprotein
  - responsible for binding the virus to the cell that is being infected
- Neuraminidase (H5N1)
  - aids in the efficiency of virus release from cells
  - inhibiting neuraminidase limits the severity and spread of viral infections

Why make mathematical models?

- Powerful tools
  - Ability to alter parameters to reflect several factors
    - place of outbreak (population density)
    - reproduction number (R_o)
    - time until containment measures taken
    - generation time (T_g)
    - sizes of average household, workplace, and schools (primary sites of transmission)
    - and more
  - Ability to model numerous complex aspects of interest
      - spread of flu
      - success of intervention strategies
      - evaluation of benefit/cost for realistic containment plans

Main goal

i.e., What is the purpose of modeling the spread of bird flu?

- To identify public health interventions that may be able to stop a pandemic in its earliest stages
  - To determine what <u>containment strategies</u> best contain what outbreak situations
    - Prophylaxis treatment (ostelmivir)
      - Anti-viral that inhibits neuraminidase
    - Social distance measures
      - Closing schools, work places, etc.
      - Quarantine of infected regions

S → I → R Model

Susceptible → **I**nfected → **R**ecovered

Single site

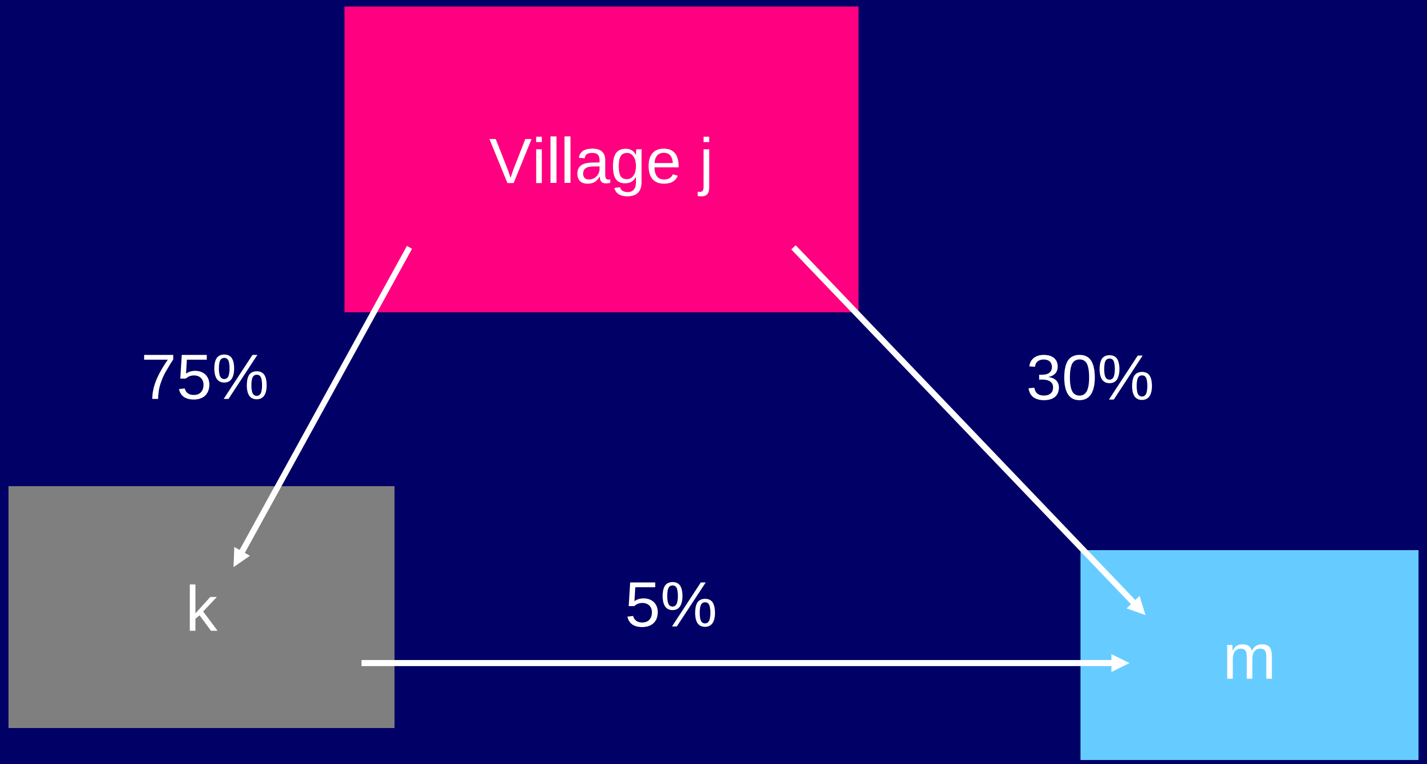
$$S + I \xrightarrow{r} I + I \qquad I \xrightarrow{a} R$$

Multi site The above two equations, plus

$$S_j \xrightarrow{\alpha_{jk}} S_k \qquad I_j \xrightarrow{\beta_{jk}} I_k \qquad R_j \xrightarrow{\gamma_{jk}} R_k$$

Movement between communities

- Inter village movement
- Multi site modeling
- Probability-based



ODEs in the model

From the multi site equations and by the law of mass action

$$\frac{dS}{dt} = -rSI \quad - \sum \alpha_{jk} S_j + - \sum \alpha_{kj} S_k$$

$$\frac{dI}{dt} = rSI - aI \quad - \sum \beta_{jk} I_j + - \sum B_{jk} I_k$$

$$\frac{dR}{dt} = aI$$

ODEs work best when the size of the infected population is huge.

Stochastic differential equations

$$\frac{dS}{dt} = -rSI \quad - \sum \alpha_{jk} S_j + - \sum \alpha_{kj} S_k$$

$$\frac{dI}{dt} = rSI - aI \quad - \sum \beta_{jk} I_j + - \sum B_{jk} I_k$$

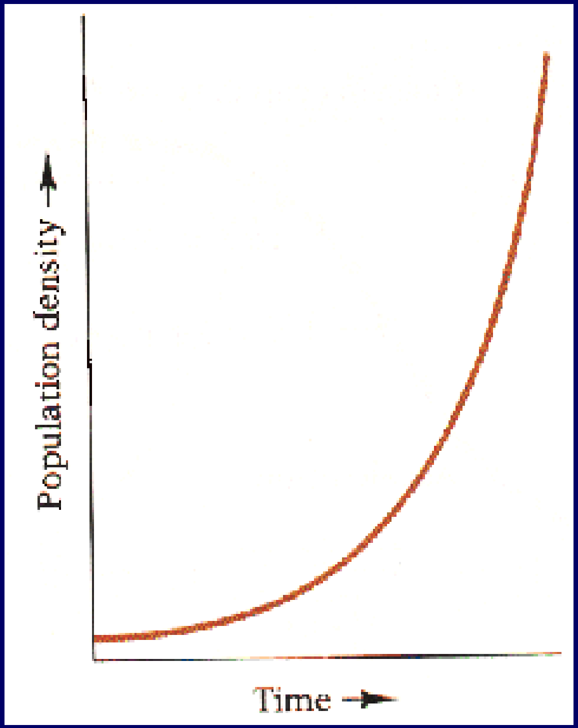
$$\frac{dR}{dt} = aI$$

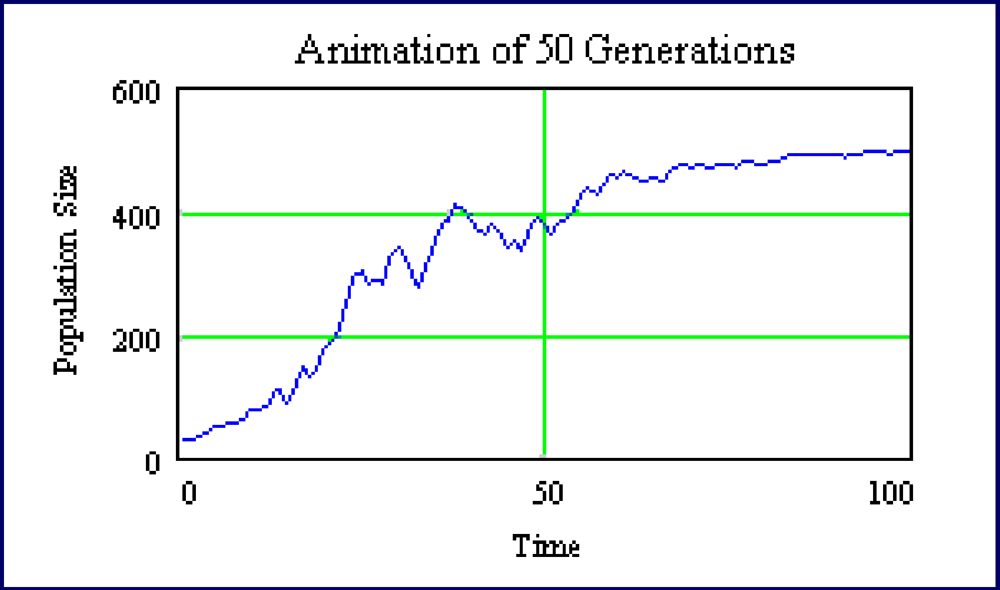
Plus noise

(+ ΔN) for all three equations

SDEs work best when the infected population size is moderate.

Comparison of model types





- Non-stochastic exponential growth curve

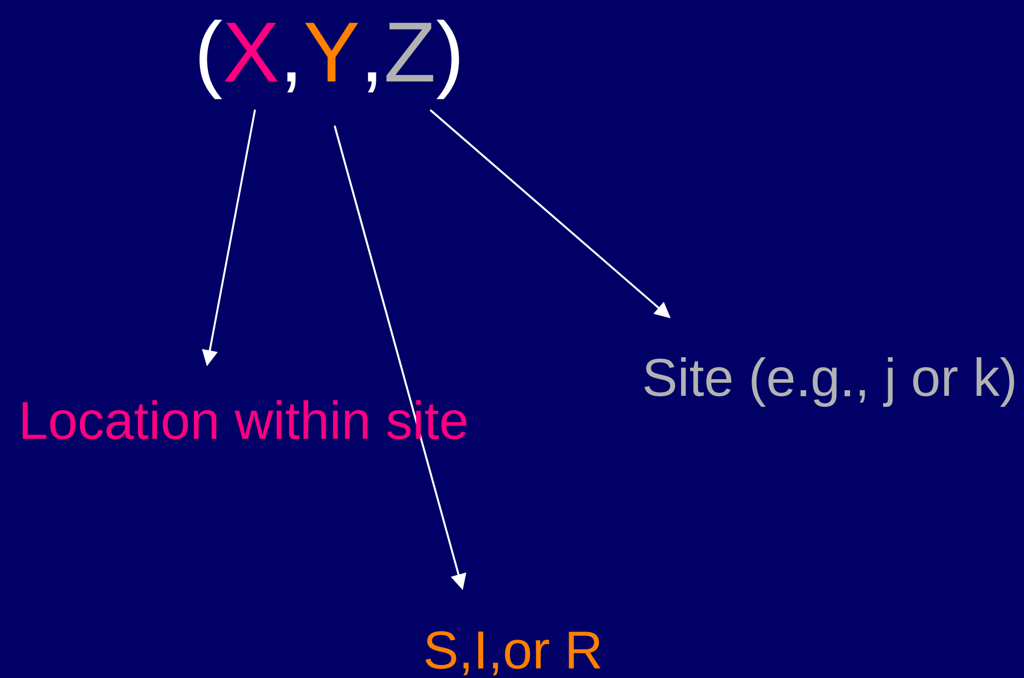
- Stochastic curves
  - More realistic
  - Noise

Agent-based modeling

- So called because follows the movements (and interactions) of individuals
- Also accounts for two types of individual movement (intra village and inter village) as well as the spread of infection
- Works best when the infected population is small

Agent based modeling, cont.

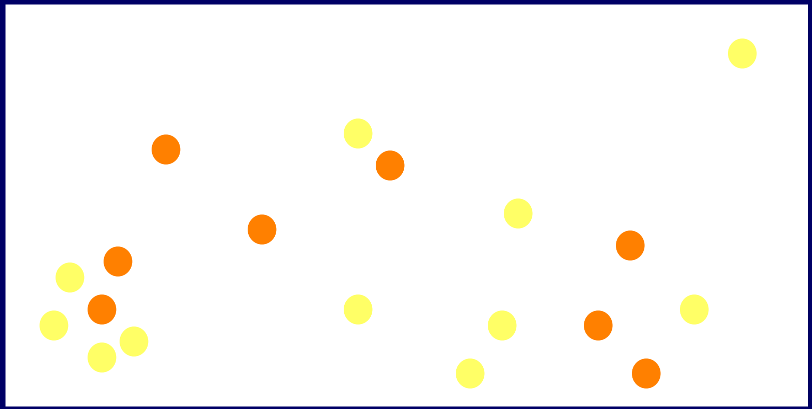
- Every individual can be represented with three (or more, depending on the complexity of the model) values



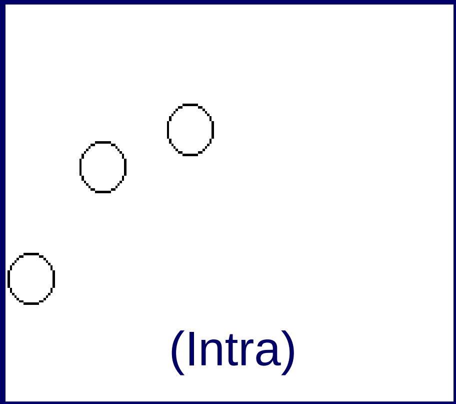
More agent based modeling

- Initially, assign status to each individual (x_1, x_2,…x_{n-1}, x_n)
  - 0 = susceptible
  - 1 = infected
  - 2 = recovered
  - (3 = vaccinated), etc.

All individuals move around according to parameters we set (often random movement determined by random number generator or clumps of interactions at households, schools, and workplaces), to most accurately represent human interactions



0 and **1** at same (x,y) coordinates yields **1** and **1**



Terminology of SIR model

- Most important term for understanding this paper, Ro, the reproduction rate of the infection

$$R_0 = \frac{rS_0}{a}$$

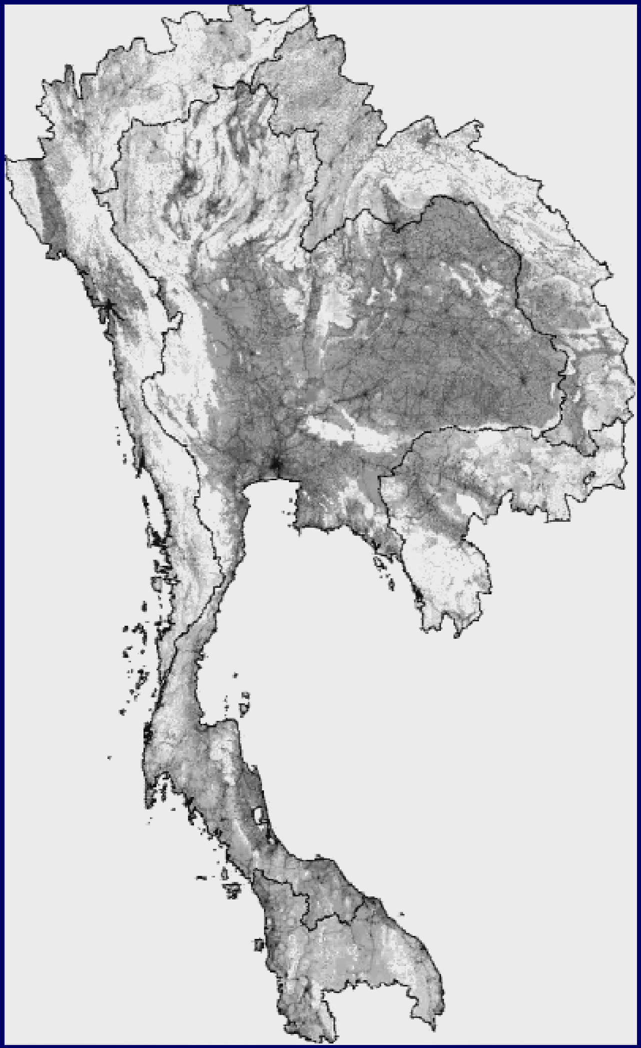
  - Ro = 1 means every infected person infects one susceptible
  - Ro = 2 means every infected person infects two susceptibles
  - Ro < 1 indicates no ensuing epidemic
  - Ro > 1 indicates an epidemic

- Generation time, T_g
  - Average time elapsed from the infection of individuals to when their contacts are infected

Model assumptions

- R_o similar to that of past pandemics (1.1-2.0; $\overline{1.8}$)
- T_g of 2.6 days
- Only 50% of infections are clinically recognizable
- Reassorted virus infects primarily one individual
- Outbreak will start in the most rural third of the population
- Closing schools and workplaces increases contact rates in the house and randomly by 100% and 50%, respectively
- The ratio of within-place to community transmission?
- The antiviral efficacy/take-up
- The heterogeneity in infectiousness (e.g. superspreaders)

Example of simulated pandemic emergence in Thailand

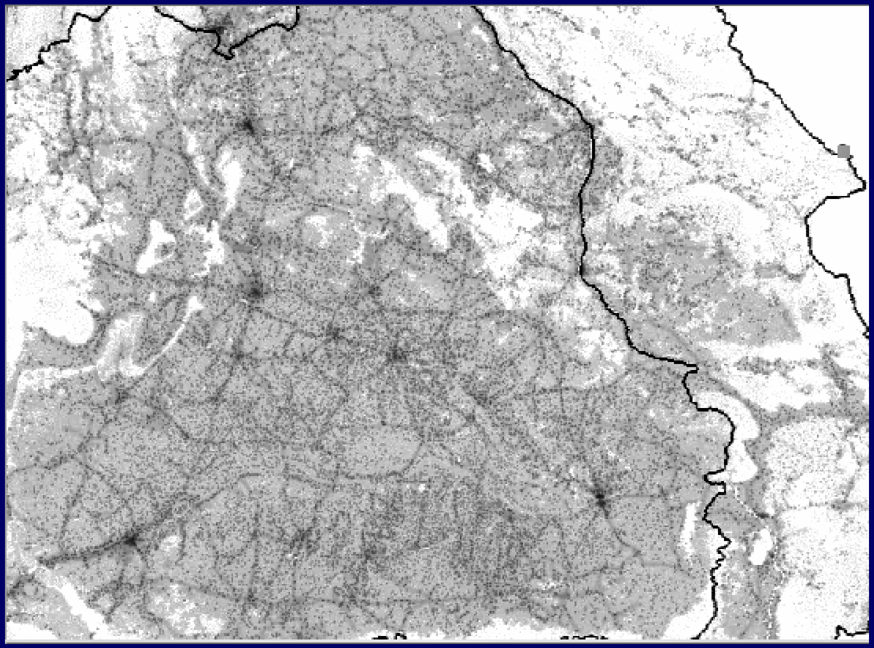


- Population density of susceptibles
- Areas with infected individuals
- Areas which have recovered

R_0=1.5, 300 days of spread

Simulation of successful containment

Implementation of a social+5km radial prophylaxis policy combined with 5km area quarantine



Blue = areas in which treatment is occurring

R_0=1.8, 100 days of spread

Fig. 1 - Properties of Thai population

- Data we are given (not generated by our model)
- Model takes into account
  - (a) population density
  - (b) age distribution
  - (c) household sizes
  - (d) distribution of school sizes
  - (e) probability of traveling over a certain distance to work
  - (f) weekly influenza-related death in 1918 Britain pandemic
  - (g) viral shedding data (measures level of infectiousness)

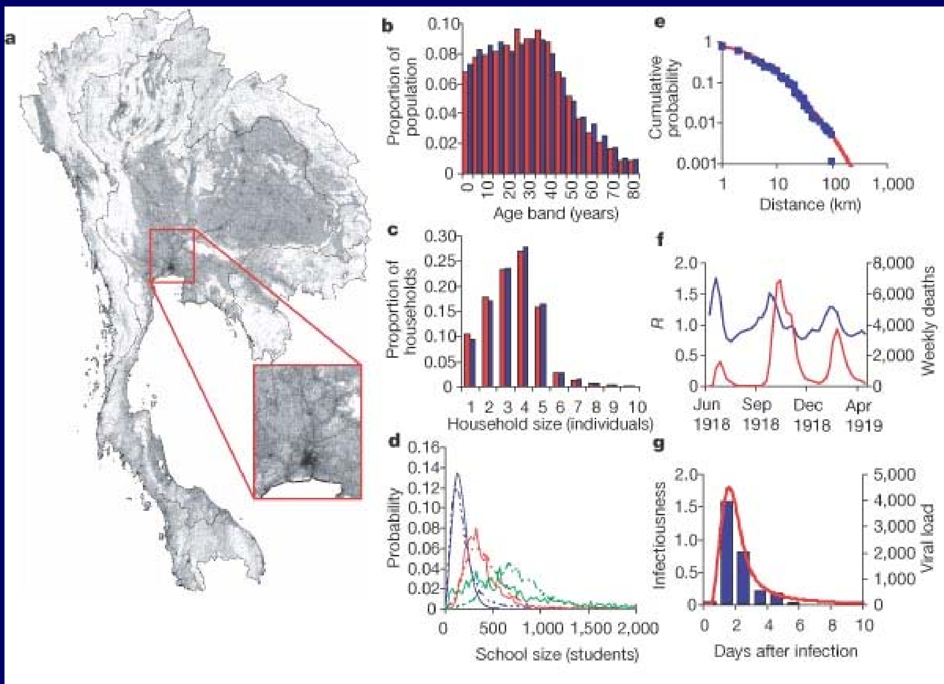
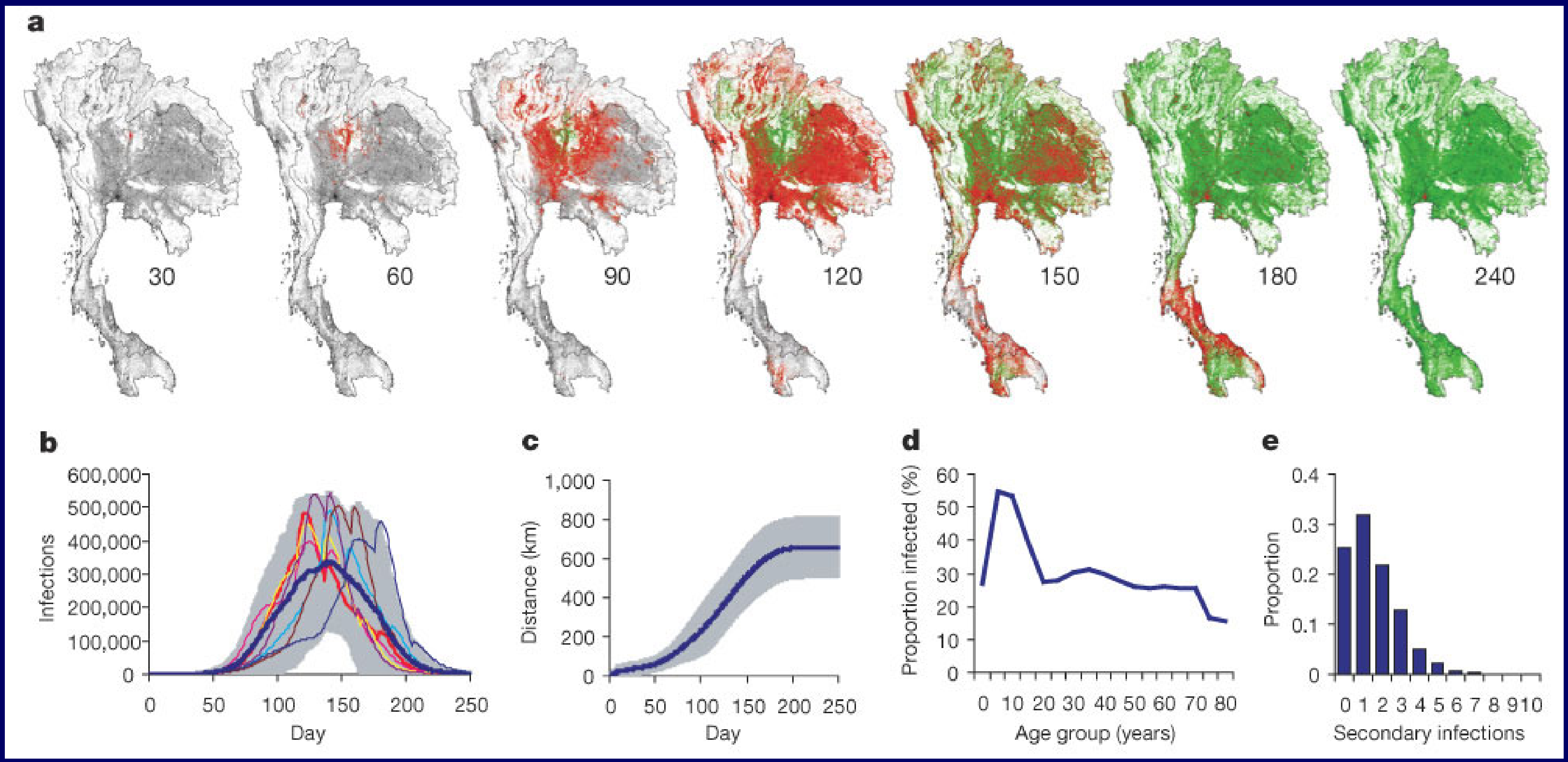


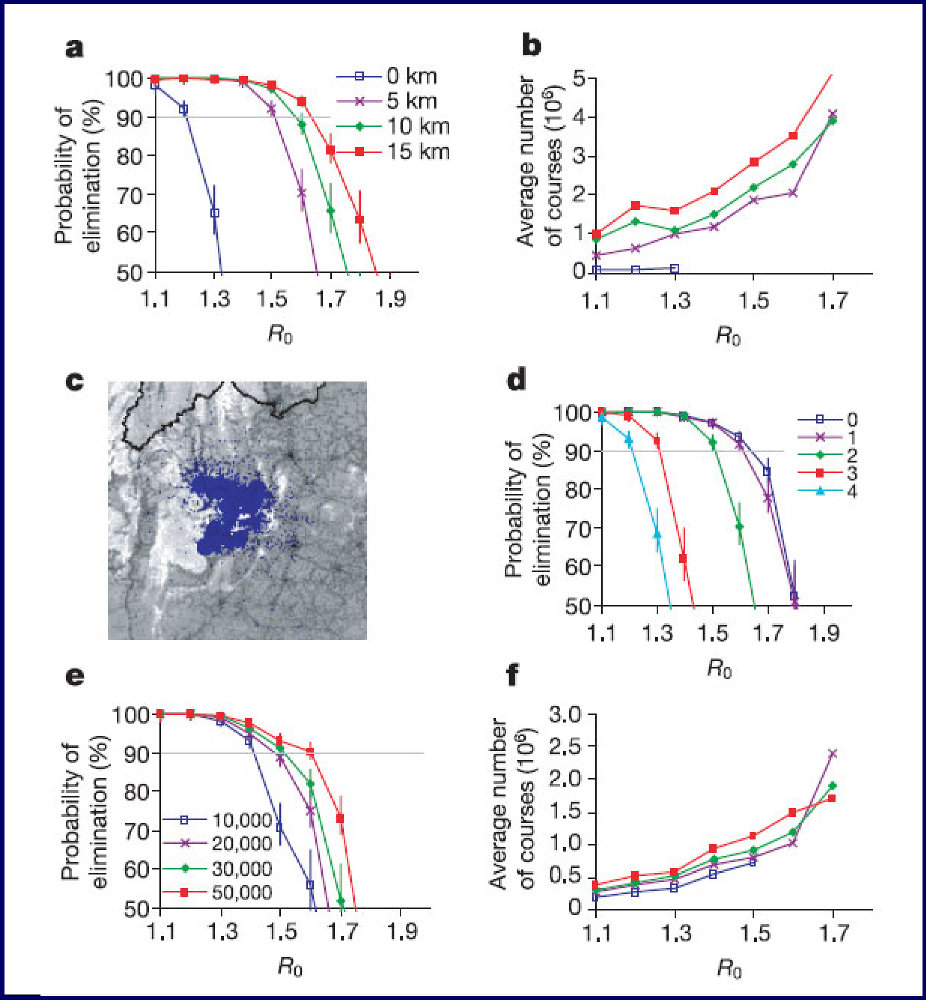
Fig. 2 - Expected spread pattern of an uncontrolled epidemic



- Generated by the model

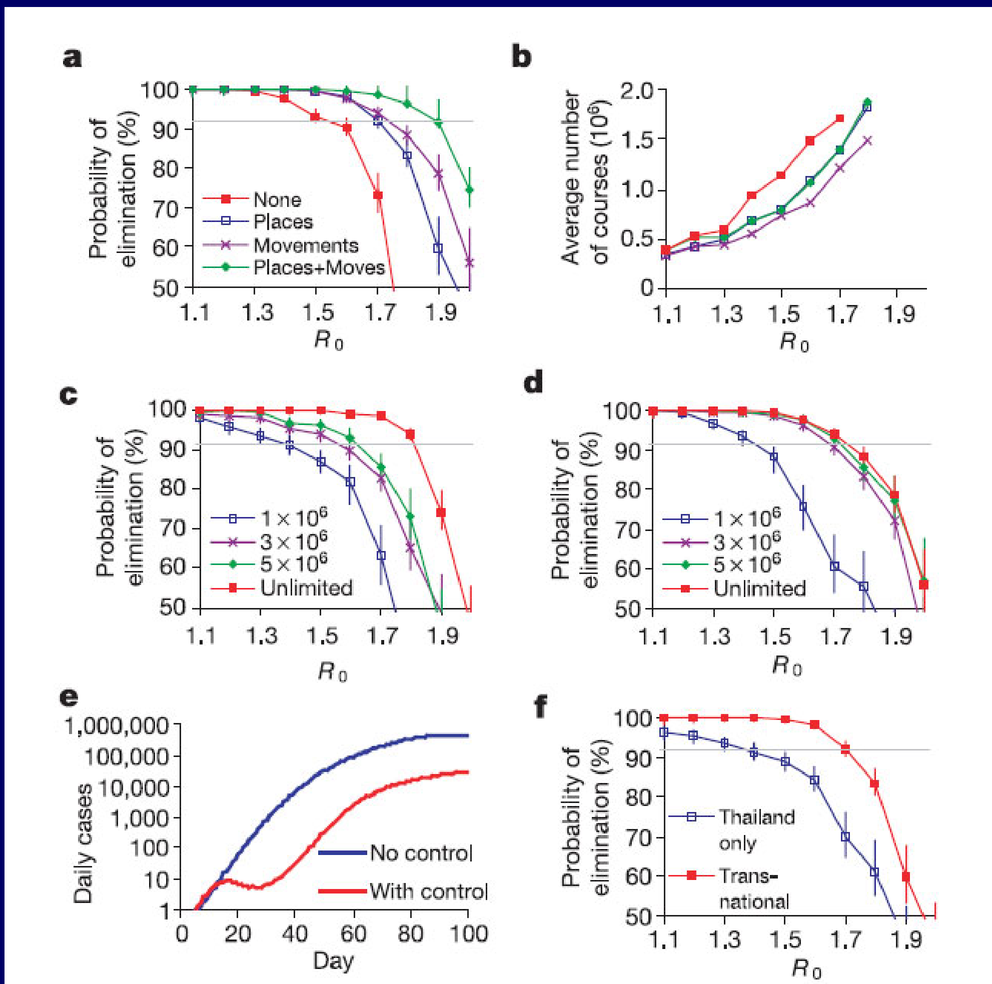
$R_0 = 1.5$

Fig. 3 - Prophylaxis strategies



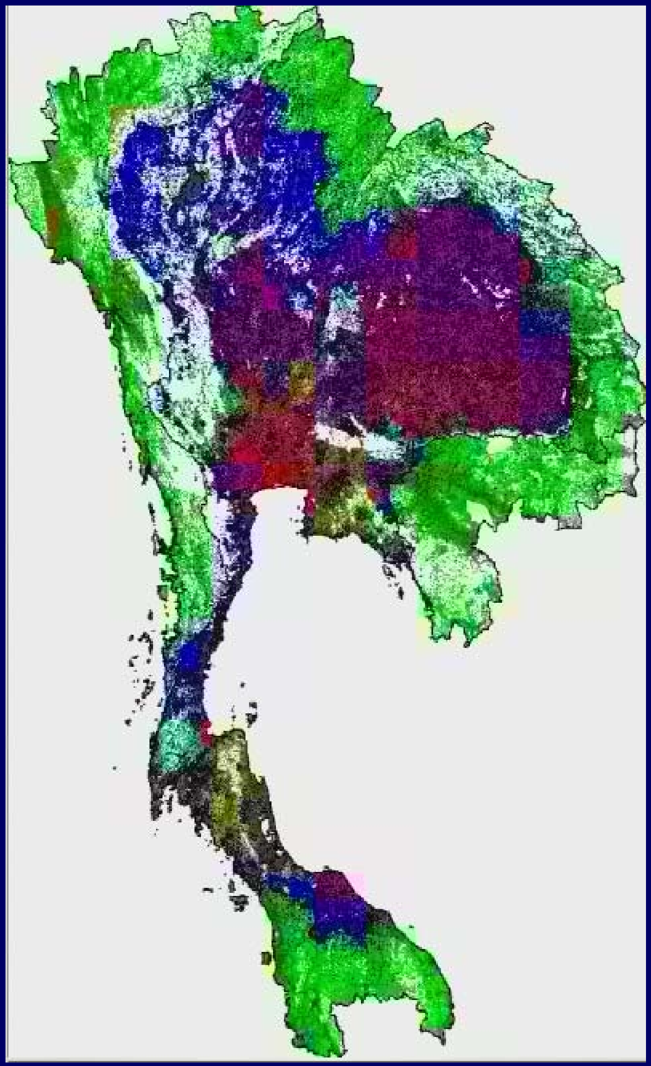
- Demonstrates that different values of R_0 requires different containment strategies for optimal disease control
- The problem? In early outbreak stages, not enough time will have elapsed to calculate R_0
- Take home message: be prepared

Fig. 4 - Social distance measures



- Similar to Fig. 3 but accounts also for the implementation of social distance measures

Simulation of containment failure



- Failure due to single-country policy implementation
- Assumes social+5km radial prophylaxis policy combined with 5km closure of 90% of schools and 50% of workplaces

R_0 = 1.7; 300 days spread

Conclusions

- Must have at least 3 million antivirals in stockpile
- Geographically targeted distribution of antivirals strategies is more feasible and effective than blanket prophylaxis
- Viruses with $R_o < 1.8$ can be contained
- Several countries must be prepared to take public health measures if the outbreak should occur in a border region
- Early detection and distribution of antivirals are essential

Questions? Concerns?