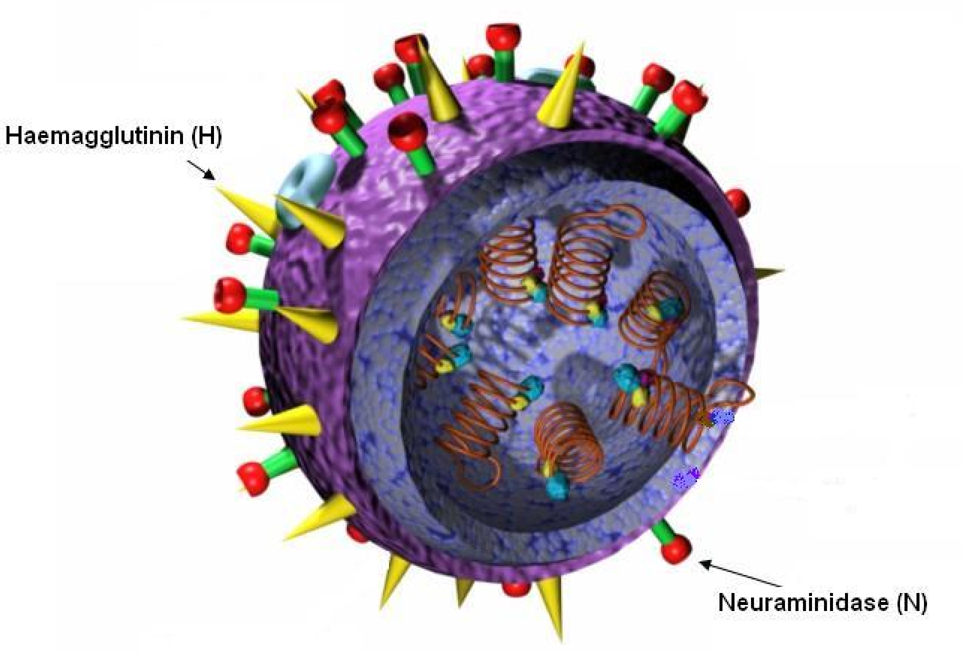
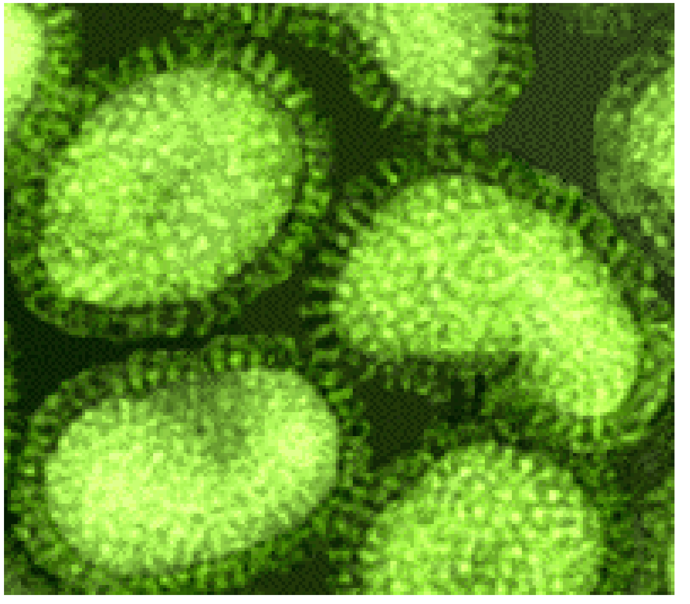
BIOST/STAT 578 A
Statistical Methods in Infectious Diseases
Lecture 8
January 29, 2009

Stochastic epidemic models: Pandemic influenza I

THE INFLUENZA VIRUS





Influenza Transmission

- Droplet

  - Droplet nuclei (air borne)

- Fomites (things)

20th Century Flu Strains & Pandemics

1918: "Spanish Flu" — 40-50 million deaths, ~ 2.0%

1957: "Asian Flu" — 1 million deaths, ~ 0.02%

1968: "Hong Kong Flu" — 1 million deaths

H1N1

H2N2

H3N2

H1N1

1920 1940 1960 1980 2000

Source: Royal Society for the Promotion of Health with modifications

Playing Roulette

Yearly chance of pandemic is about 1/33.3 or about 3%

On Influenza Epidemics

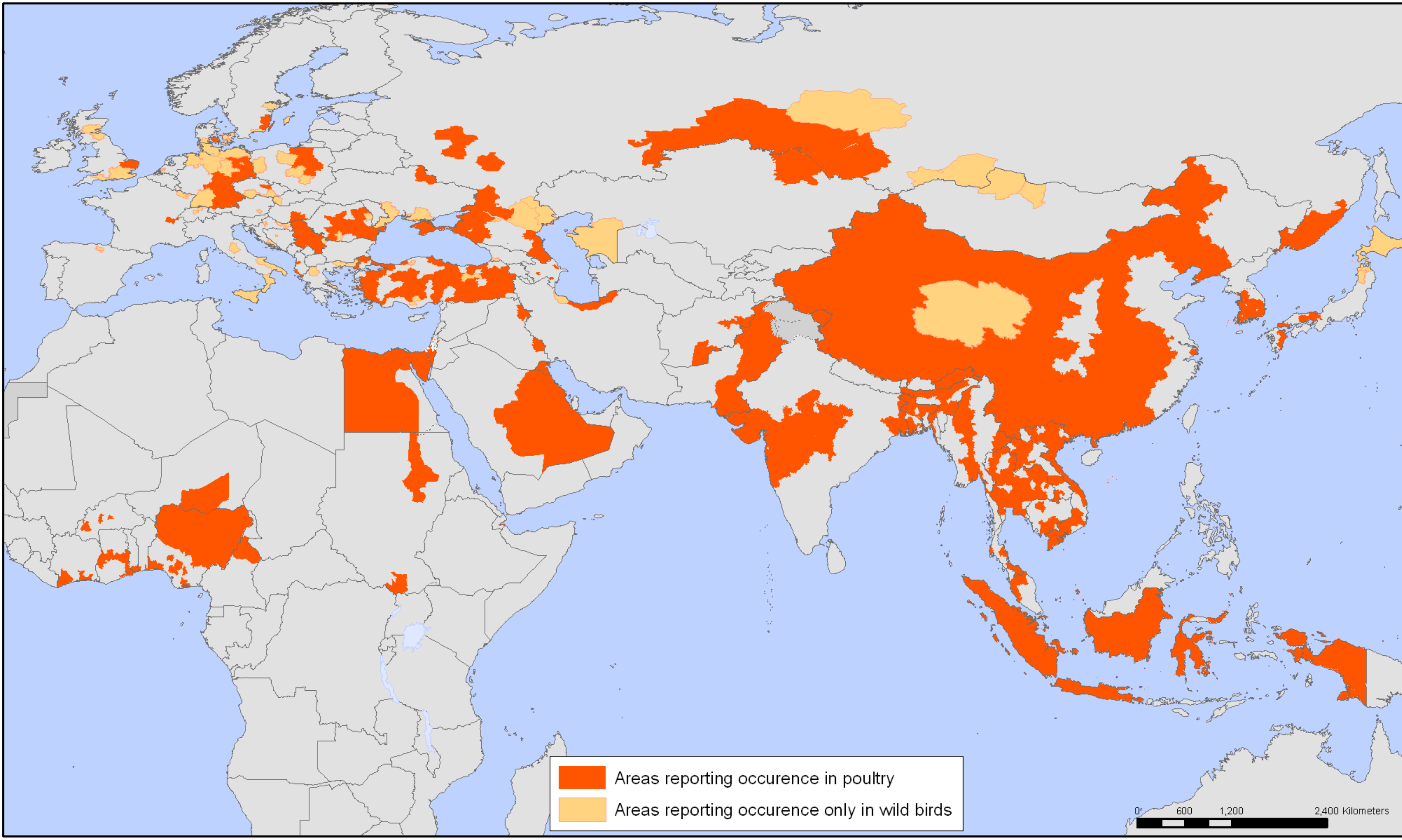
"God does not play dice with the universe" Albert Einstein

“**Except in the case of influenza**…” Me

“**If you’ve seen one influenza epidemic, you’ve seen one influenza epidemic!”**

Areas reporting confirmed occurrence of H5N1 avian influenza in poultry and wild birds since 2003

Status as of 12 December 2008
Latest available update



World Health Organization

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

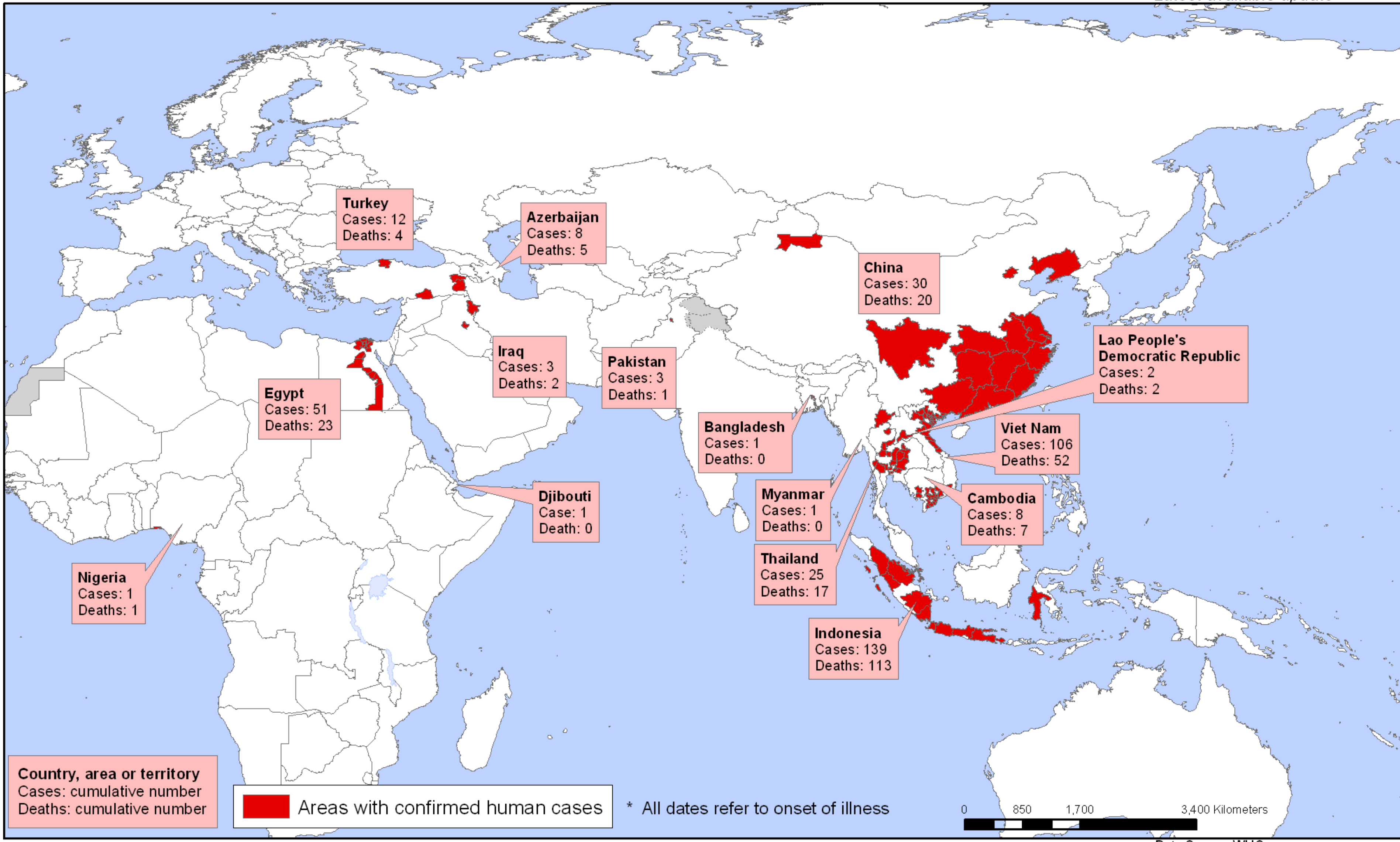
Data Source: World Organisation for Animal Health (OIE) and national governments

Map Production: Public Health Information and Geographic Information Systems (GIS), World Health Organization

Cumulative 397 reported cases, 249 deaths, 63% case fatality ratio in 15 countries
31 documented family clusters, human-to-human transmission has occurred.

Areas with confirmed human cases of H5N1 avian influenza since 2003 *

Status as of 16 December 2008
Latest available update



World Health Organization

Data Source: WHO
Map Production: Public Health Information and Geographic Information System (GIS)
World Health Organization


CHICKEN RUN
IV
Bird Flu!

Current WHO phase of pandemic alert

- WHO global influenza preparedness plan

Inter-pandemic phase	Low risk of human cases	1
New virus in animals, no human cases	Higher risk of human cases	2
Pandemic alert	No or very limited human-to-human transmission	3
New virus causes human cases	Evidence of increased human-to-human transmission	4
	Evidence of significant human-to-human transmission	5
Pandemic	Efficient and sustained human-to-human transmission	6

How Bad Could it Get Today?

- Global pandemic, first wave about 6 - 9 months, 2 billion cases
  - 1918 scenario: 10 - 62 million deaths
  - Contrast
    - 20 million AIDS deaths over 25 years
    - 811 SARS deaths over 8 months, $30 billion world economy

Containment of pandemic influenza at the source

- It is optimal to stop a potential pandemic influenza strain at the source
  - An effective method would be with pre-pandemic vaccination or rapid vaccination, even with a poorly matched vaccine (WHO) ~ 50 million doses (GSK)
  - Targeted antiviral prophylaxis with mobile stockpile (WHO) ~ 5 million courses oseltamivir (Roche)
  - Quarantine, social distancing, school closing, travel restrictions

  - Longini, et al. *Science* 309 (2005).
  - Longini and Halloran. *Science* 310 (2005).
  - Ferguson, *et al. Nature* 437 (2005*)*

Draft

WHO pandemic influenza draft protocol for rapid response and containment

Updated draft 30 May 2006

World Health Organization

Pandemic Influenza in the US or Other Countries Once the Pandemic Spread is Global

- Firstly, since early vaccination is key in slowing the spread, countries should be prepared with vaccine stockpiles
- Hard to contain as it comes in
- Once widespread, slow transmission until well-matched/pandemic vaccine is available
  - Rapid vaccination with a possibly poorly match vaccine/pre-pandemic vaccine
  - Targeted antiviral prophylaxis
  - Quarantine, social distancing, school closing, travel restrictions

- Germann, T.C., Kadau, K., Longini I.M. and Macken C.A.: *PNAS* 103 (2006)
- Ferguson, N.M., *et al*.: *Nature* 442 (2006)
- Halloran, M.E. and Longini, I.M.: *Science* 311 (2006)
- Halloran, M.E., Ferguson, N.M., Eubank, S., Longini, I.M., *et al.* : *PNAS* 105 (2008)

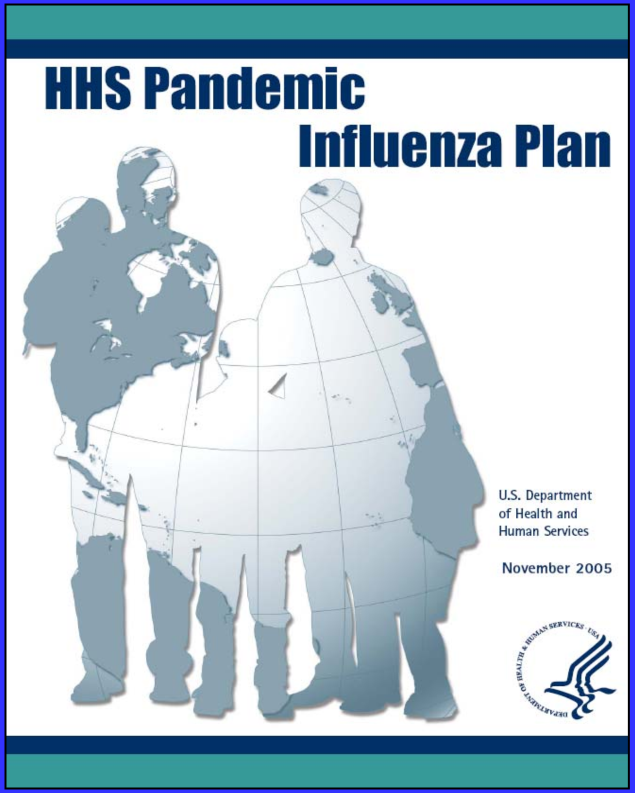
US Plan


I'M SURE THE FEDERAL GOVERNMENT HAS A PLAN FOR SUCH DISASTERS.
BIRD FLU
BIRD FLU
DUCT TAPE

HHS Pandemic Influenza Plan

Strategic Plan (Part 1)

- Outlines planning assumptions and doctrine for the HHS pandemic influenza response



Public Health Guidance for State and Local Partners (Part 2)

- 11 Supplements provide detailed guidance

www.pandemicflu.gov

Measures of Vaccine Efficacy*

- $\{VE(t)_S , VE(t)_P , VE(t)_I\}$
- VE_S Vaccine Effect on Susceptibility
  - Classical III vaccine trials
    - Many times observe

    $VE_{SP} = 1 - (1 - VE_S)(1 - VE_P)$
  - Phase I and II vaccine trials
    - Correlates of immunity
  - Virus challenge studies in humans or animals

*Halloran, Longini, Struchiner: Design and interpretation of vaccine field studies. *Epidemiol Rev* **21**, 73- 88 (1999).

Measures of Vaccine Efficacy

- VE_P Vaccine Effect on Clinical Disease
  - Possible phase III vaccine trials if infection in both symptomatic and symptomatics is included
  - Usually only VE_{SP} is available
  - Virus challenge studies in humans or animals

Measures of Vaccine Efficacy

- VE_I Vaccine Effect on Infectiousness
  - Vaccine trials in households or other small transmission groups
  - Teased out of indirect effects (community randomized vaccine trials, modeling)
  - Virus challenge studies in humans or animals

Measures of Vaccine Efficacy

- VE_C Combined Efficacy
  - Combination of VE_S , VE_P , VE_I, relative infectiousness of asymptomatics (*m*) and pathogenicity (*k*).

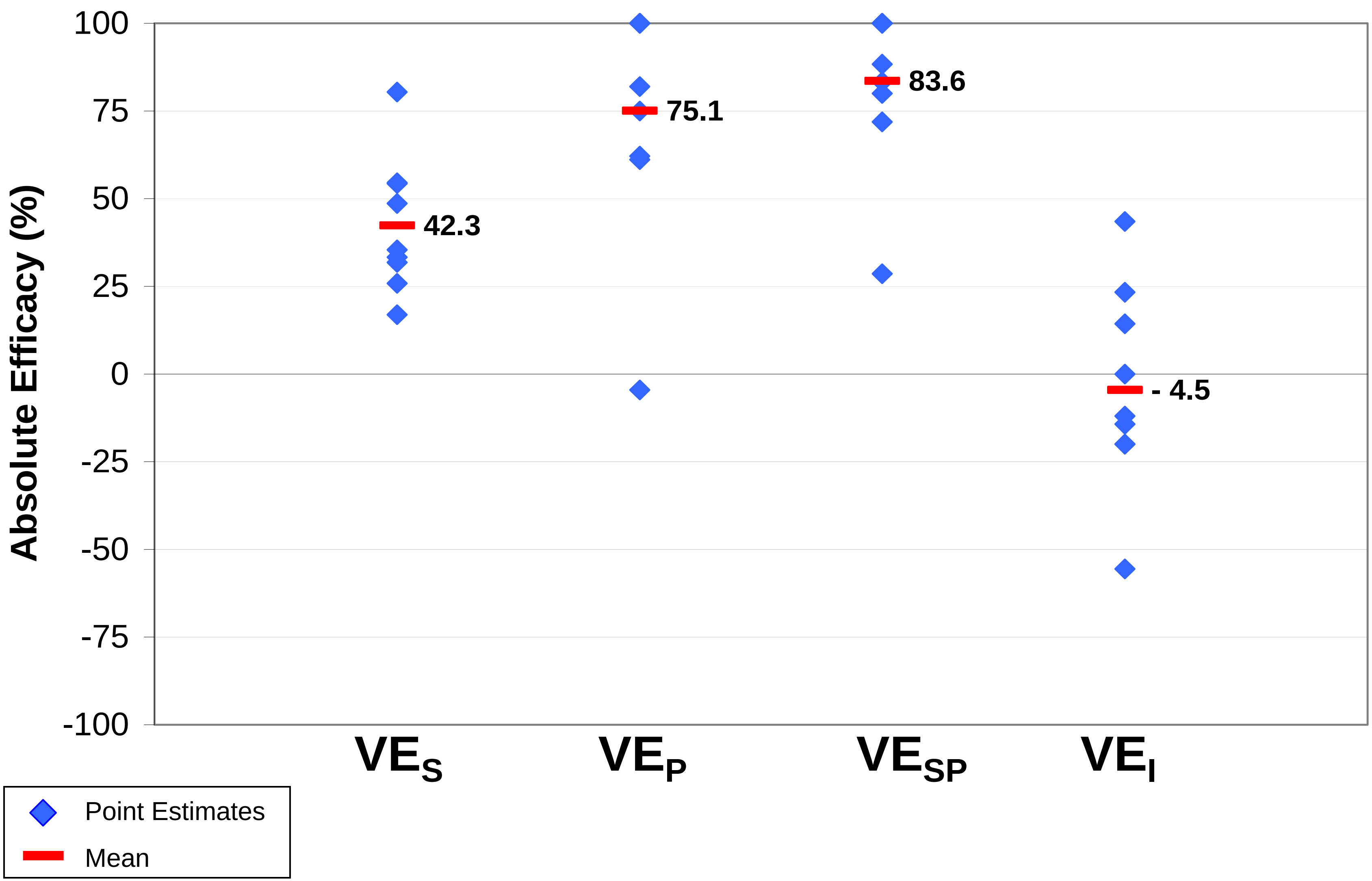
$$VE_C = 1 - \frac{R_1}{R_0} = 1 - \frac{\theta\phi((1-\psi k)m + \psi k)}{(1-k)m + k},$$

where, $\theta = 1 - VE_S$, $\phi = 1 - VE_I$, and $\psi = 1 - VE_P$

Old Challenge Studies in Humans

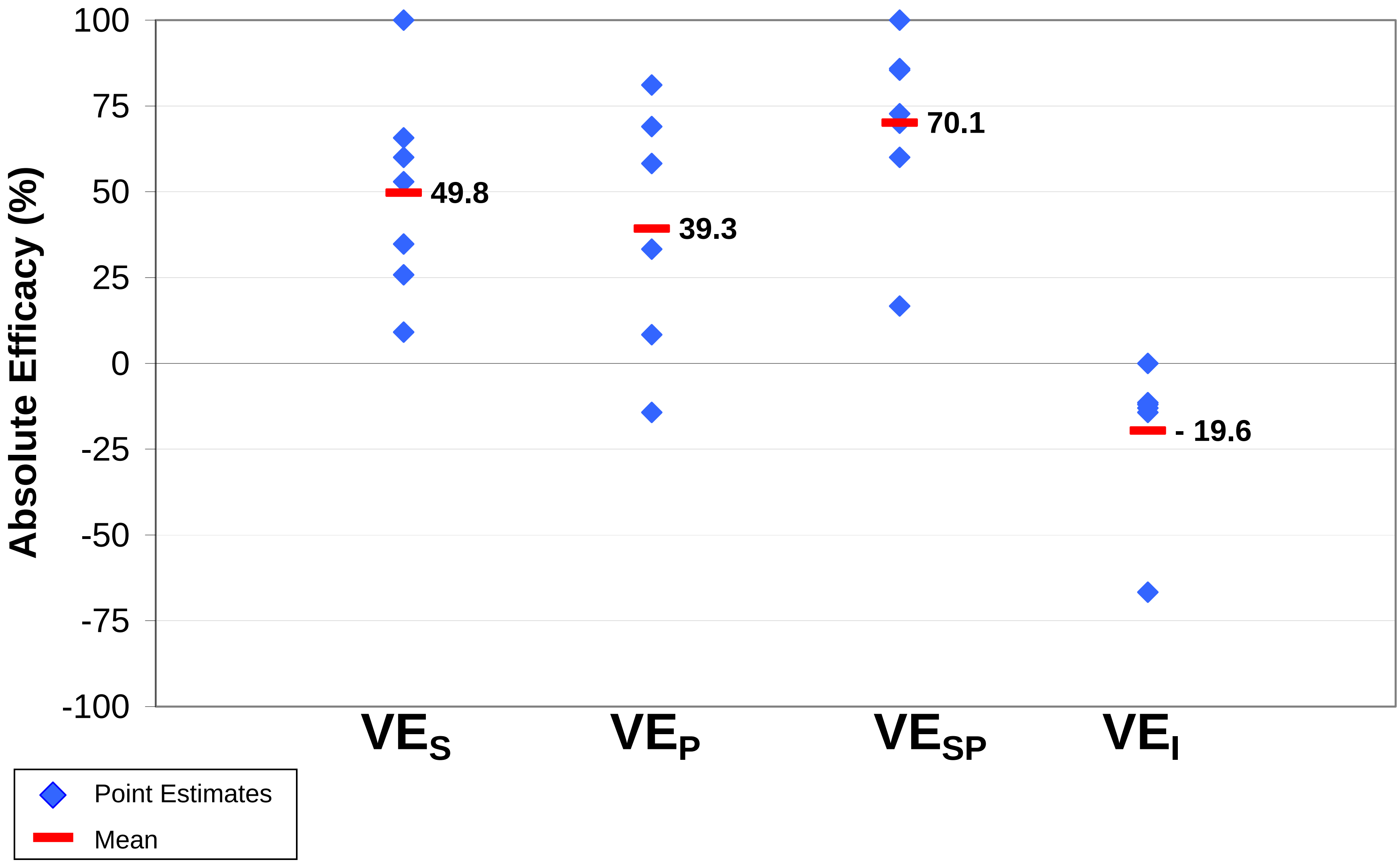
- Vaccine Efficacy Estimates Based on Challenge Studies in Seronegative Adults
- Homologous and Heterologous Challenge
- We can estimate VE parameters without phase III trial, but how applicable?

Absolute Efficacy of Live Influenza Vaccine



Source: Basta, Halloran, Longini: *Amer J Epidemiol* (2008)

Absolute Efficacy of Inactivated Influenza Vaccine



Source: Basta, Halloran, Longini: *Amer J Epidemiol* (2008)

A Note On Seroprotection

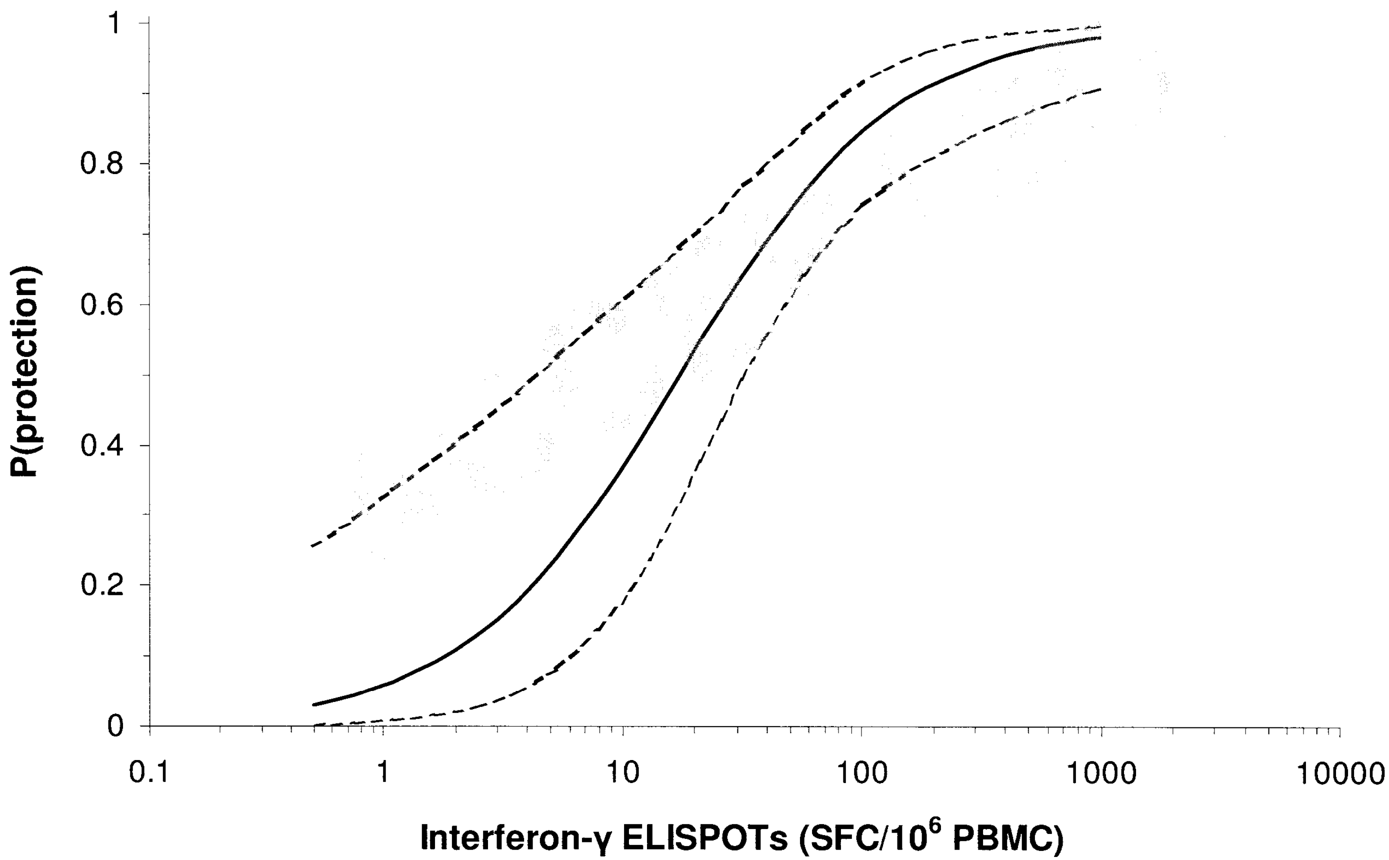
- An HI titer of at least 1:32 to 1:40 is considered to result in protection for 50% of the population (Plotkin, et al. *Vaccines*, 2008)
- A CHMP requirement for immunogenicity is seroprotection > 70%

Infection rates by pre-season antibody titer: influenza A(H3N2) epidemic season 1977-1978 and 1980-1981 combined, Tecumseh, Michigan *

Pre-season antibody titer (1:X)	No. observed	Fraction Infected	Antibody Efficacy
< 8	836	0.23	-
8	267	0.14	0.39
16	153	0.06	0.74
32	137	0.09	0.61
64	87	0.05	0.78
≥ 128	26	0.00	1.00
Total	1,506	0.17	

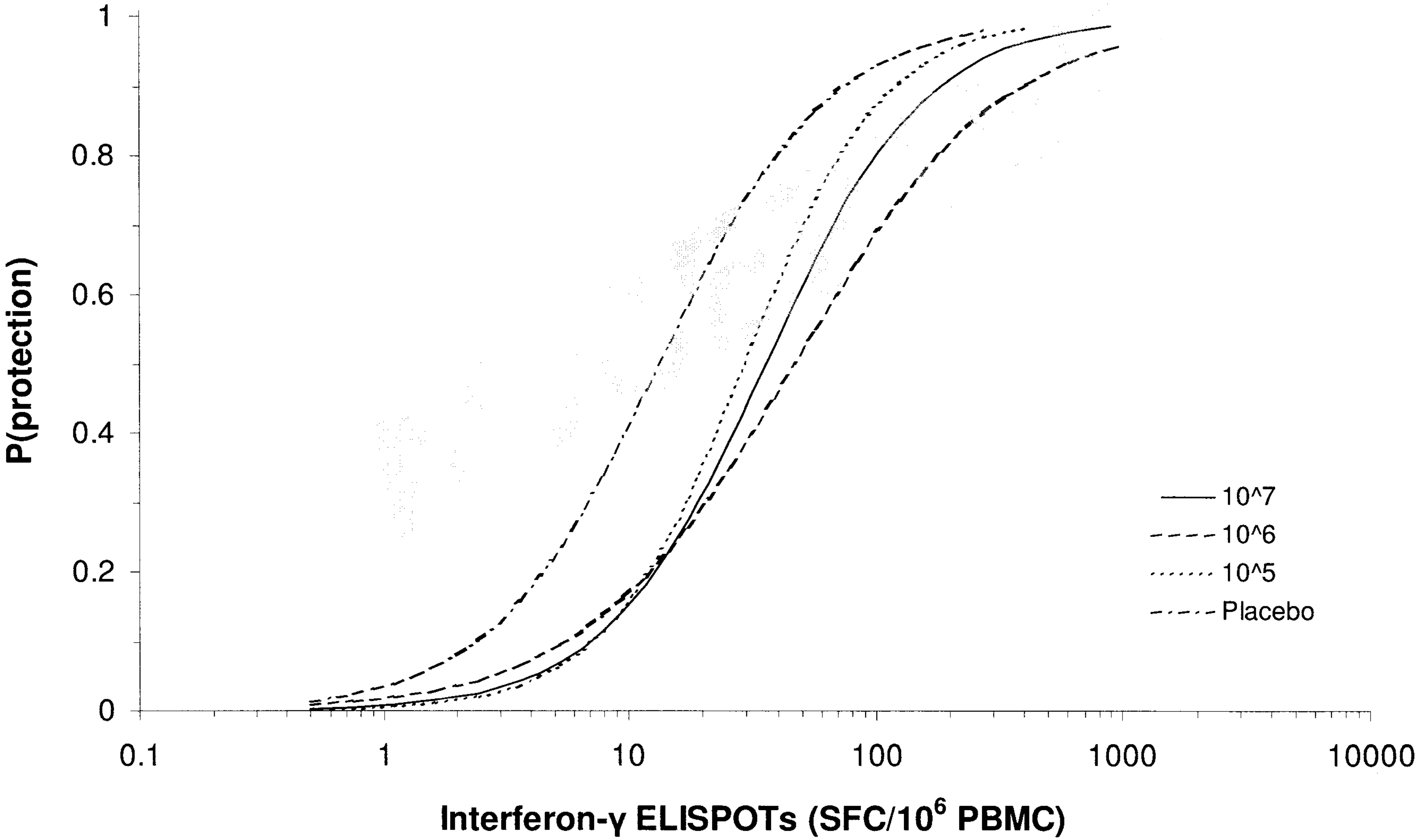
* Source: Longini, *et al. AJE*, **128** (1988)

Cell Mediated Immunity Gamma Interferon*



*Source: Forrest, et al., Clin. Vaccine Immunol. (April, 2008 on line)

Cell Mediated Immunity Vaccine and Naturally Induced*



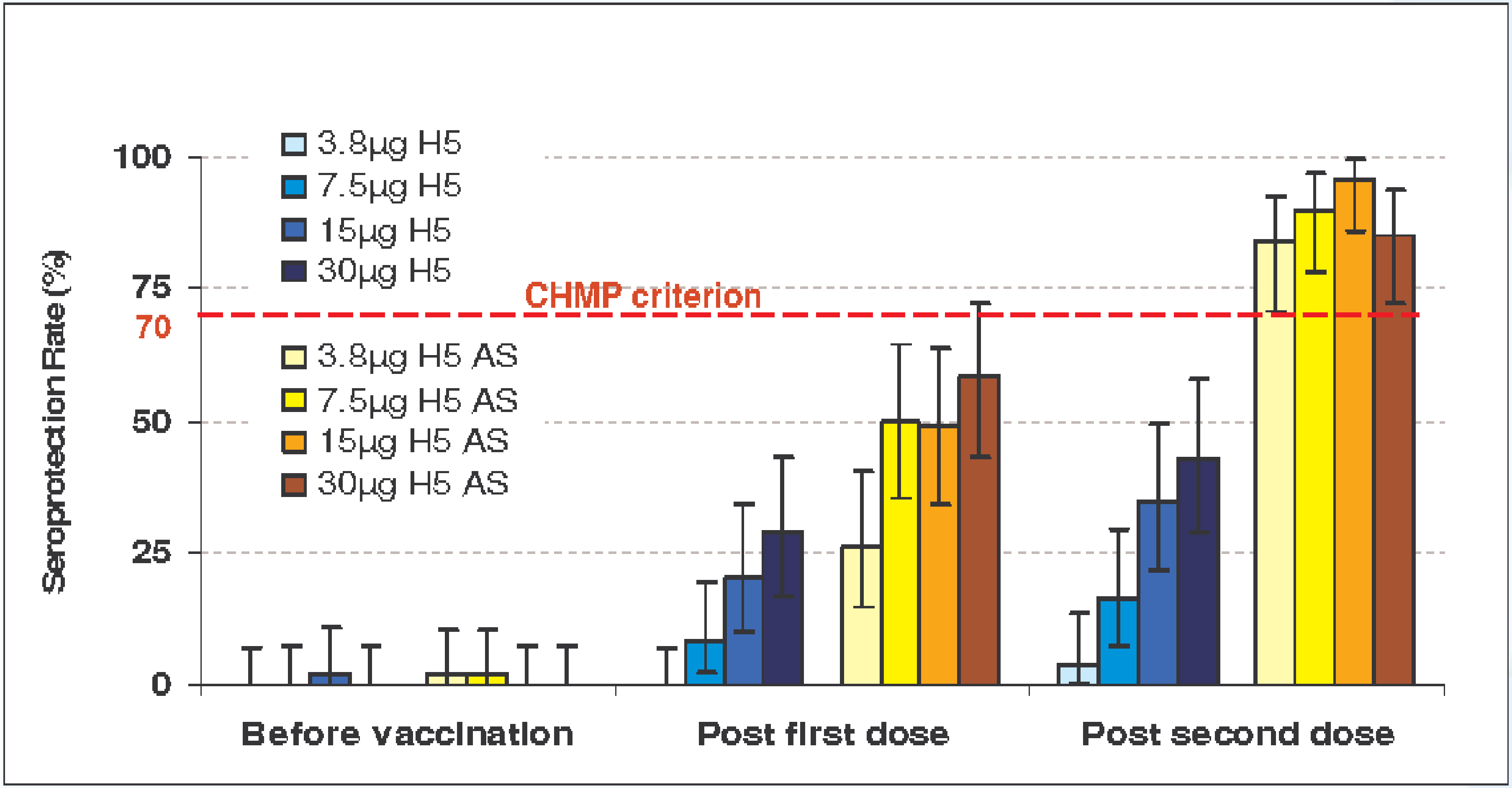
*Source: Forrest, et al., Clin. Vaccine Immunol. (April, 2008 on line)

GSK Pandemic Influenza Vaccine*

- Split, inactivated, adjuvanted with AS03
  - Requires two doses (3 weeks apart) in humans
  - Antigen-sparing properties (3.8 μg/dose)
  - Broad seroprotective heterologous response
  - Safe

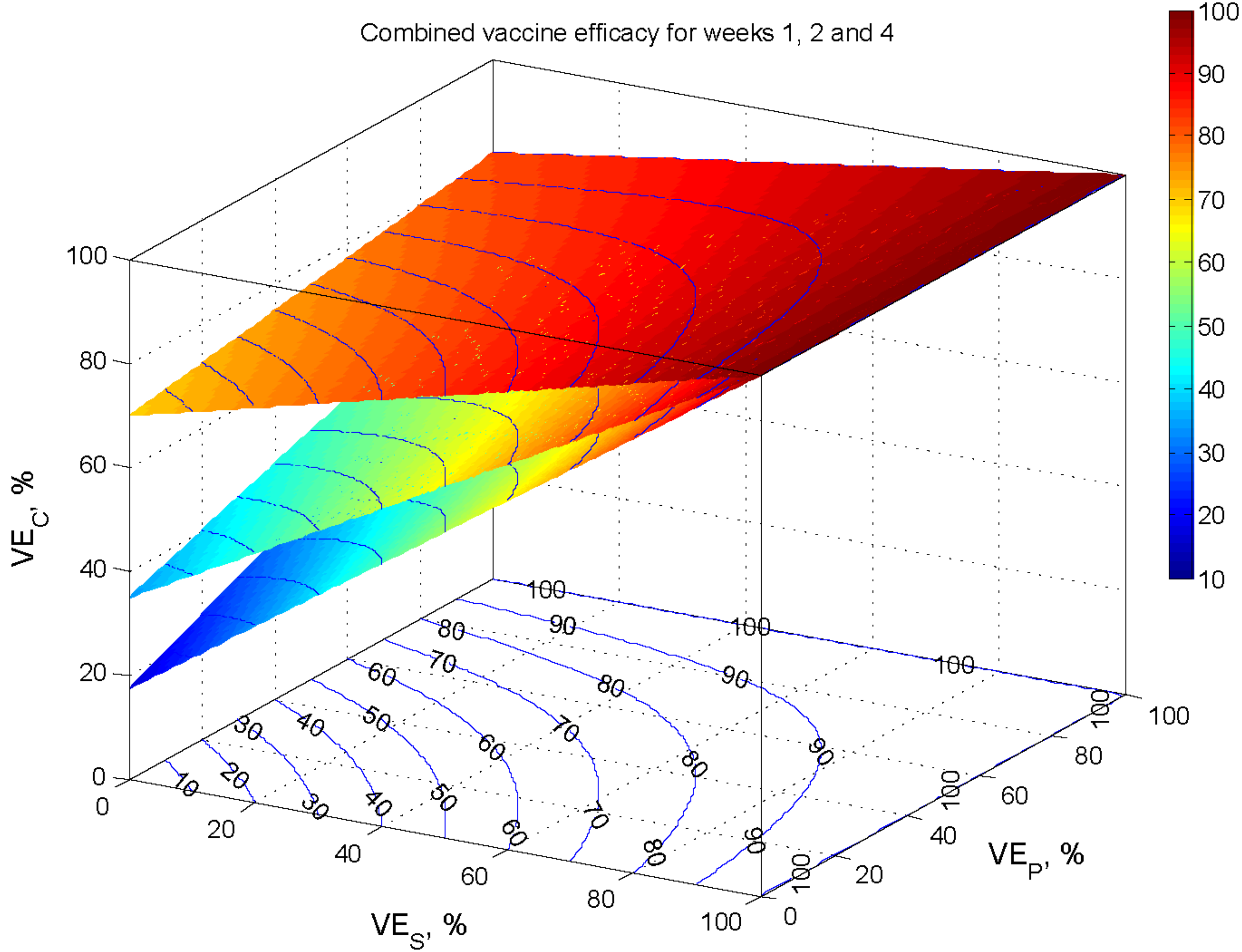
*Leroux-Roels, et al. Lancet 370, 580-589 (2007)

Antigen Sparing for Protection After 2nd Dose*



*Source: Roland Sanger, GSK

What we conclude at this point about VE parameters for heterologous virus



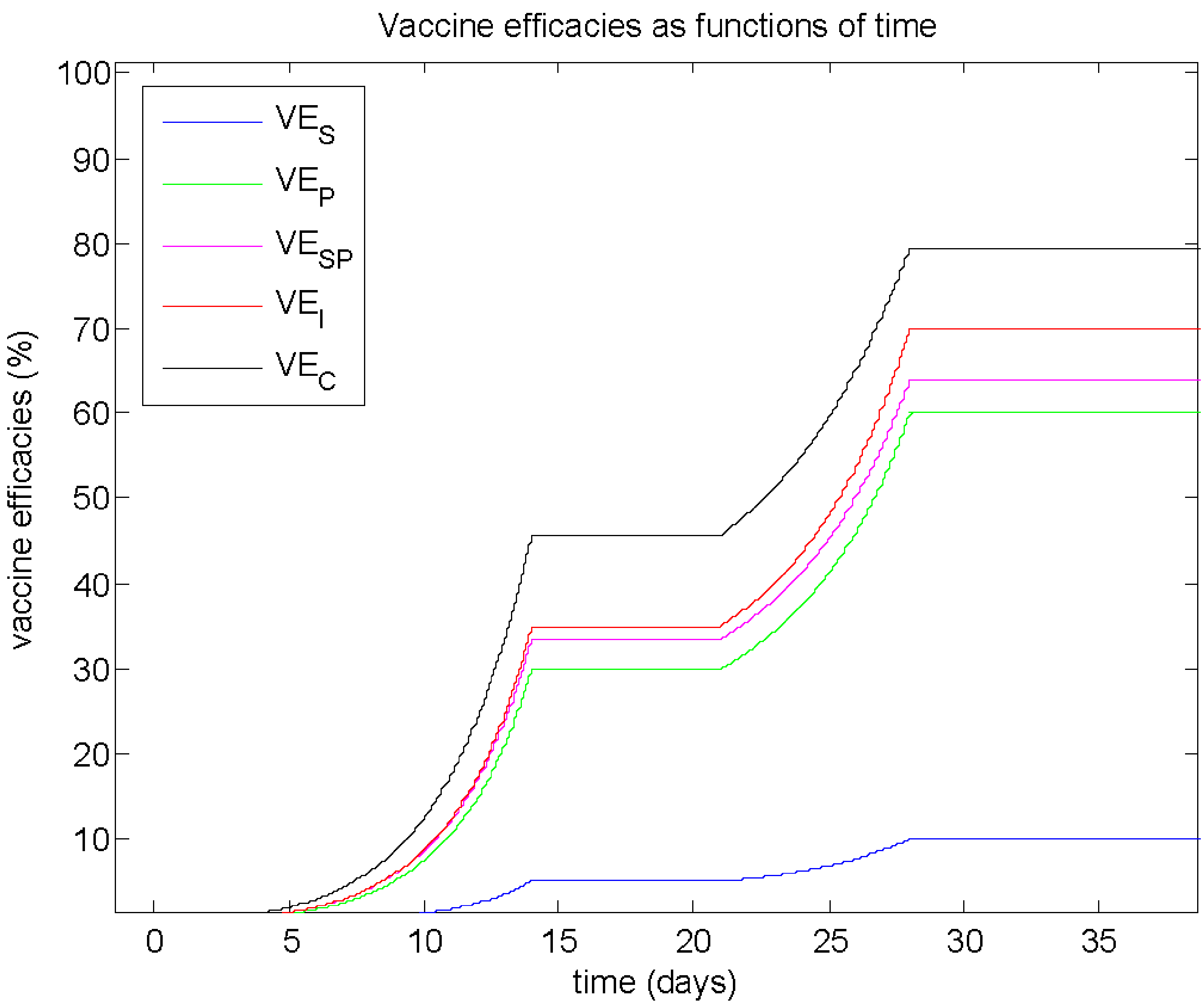
Combined vaccine efficacy for weeks 1, 2 and 4
VE_C, %
VE_S, %
VE_P, %
0
20
40
60
80
100
10
20
30
40
50
60
70
80
90
100

VE Parameters

- Based on clinical studies in humans
  - Overall: VE_{SP} = 60 – 70%
    - Get ≤ ½ way there after 1st dose
- Based on ferret challenge studies
  - VE_I = 0.70
  - e.g., viral shedding in the URT: (throat or nasal swab) 26.1% of treatment group, 91.7% of controls
    - $VE_I = 1 - (26.1/91.7) = 0.72$

Modeled Vaccine Efficacy

t	0	14	21	28
$VE_S(t)$	0	0.05	0.05	0.10
$VE_P(t)$	0	0.30	0.30	0.60
$VE_{SP}(t)$	0	0.34	0.34	0.64
$VE_I(t)$	0	0.35	0.35	0.70
$VE_C(t)$	0	0.46	0.46	0.79


Vaccine efficacies as functions of time
VE_S
VE_P
VE_{SP}
VE_I
VE_C
vaccine efficacies (%)
time (days)
100
90
80
70
60
50
40
30
20
10
0
5
10
15
20
25
30
35

Antiviral efficacies used in the model: Oseltamivir or zanamivir*

- Antiviral efficacy of reducing susceptibility to infection: **AVE_S = 0.30**
- Antiviral efficacy of reducing illness given infection: **AVE_P = 0.60**
- Antiviral efficacy of reducing illness with infection: **AVE_{SD} = 0.72**
- Antiviral efficacy of reducing infectiousness to others: **AVE_I = 0.62**
- Resistance could become a problem
  - Transmissibility of resistant strains
  - e.g., Norway, 66% A(H1N1) strains resistant to oseltamivir, February, 2008; US, 98% resistant to oseltamivir, January, 2009

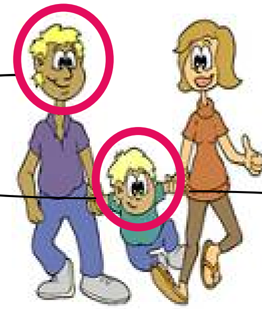
*data from Welliver, *et al*. *JAMA* (2001); Hayden, *et al. JID* (2004); analysis from Yang, Longini, Halloran, *Appl Stat* (2006); Halloran, *et al. Am J Epidemiol* (2007).

TAP

CONTACTS
Household
Household cluster
Preschool/daycare
School
Workplace

xx% ascertainment

xx% school



xx% household + HH cluster

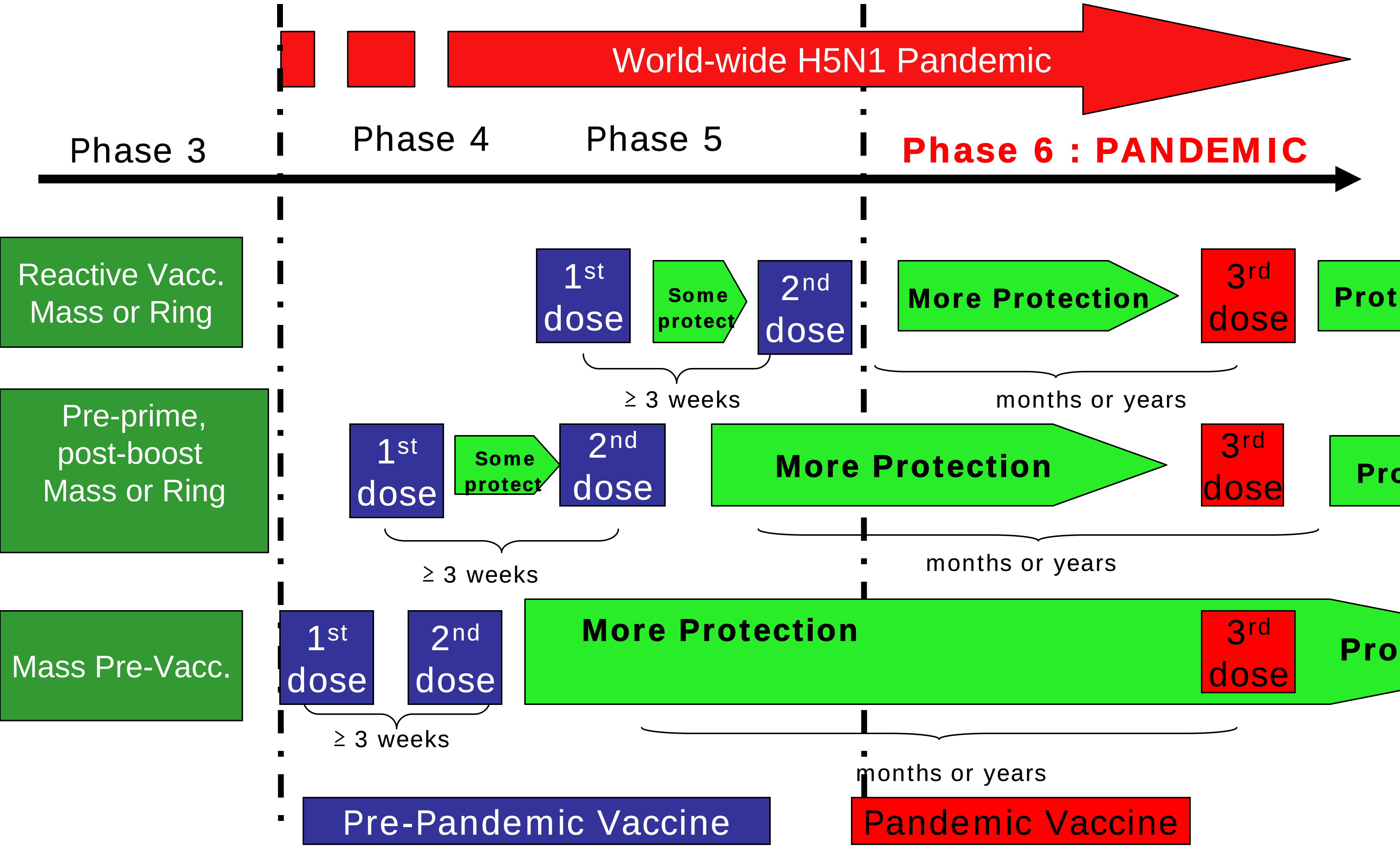
xx% workplace

xx% preschool

TAP: Targeted antiviral prophylaxis using neuraminidase inhibitors (oseltamivir/zanamivir)

Large-Scale, Individual-based, Stochastic Simulation Models

Vaccination Strategy Timing



Pre-pandemic Vaccination Strategies

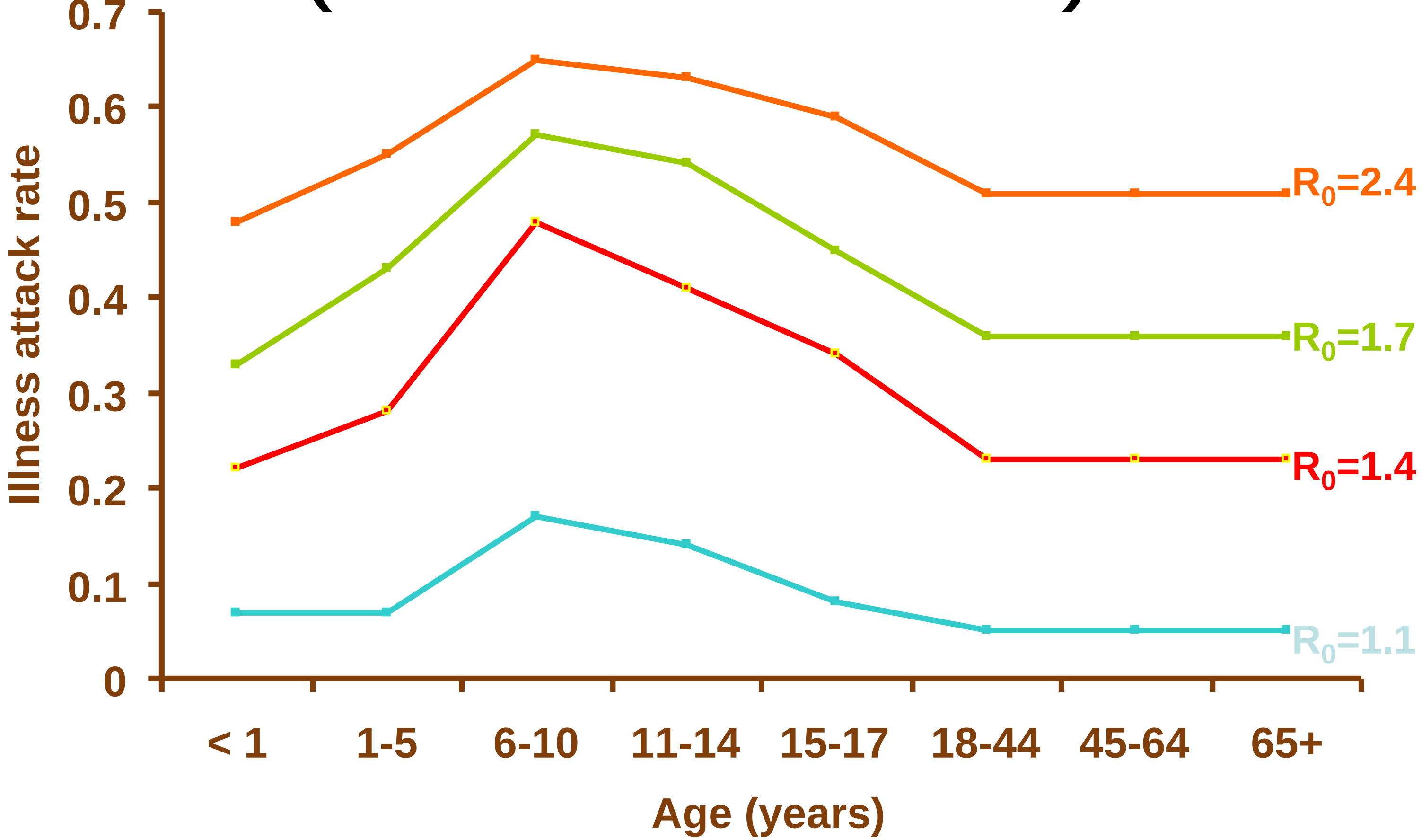
- Mass pre-vaccination
  - Two doses starting at least four weeks before initial case
- Reactive mass vaccination
  - Begin vaccinating x days after first case in a geographic region
- Ring vaccination
  - Begin vaccinating x days after first case in ring, then in a ring after each subsequent case
- Pre-prime, post-boost vaccination
  - One dose at least three weeks before the initial case, begin vaccinating x days after the first case with mass or ring reactive

Basic Reproductive Number Pandemic Influenza

For pandemic influenza: $1 < R_0 \leq 2.4$

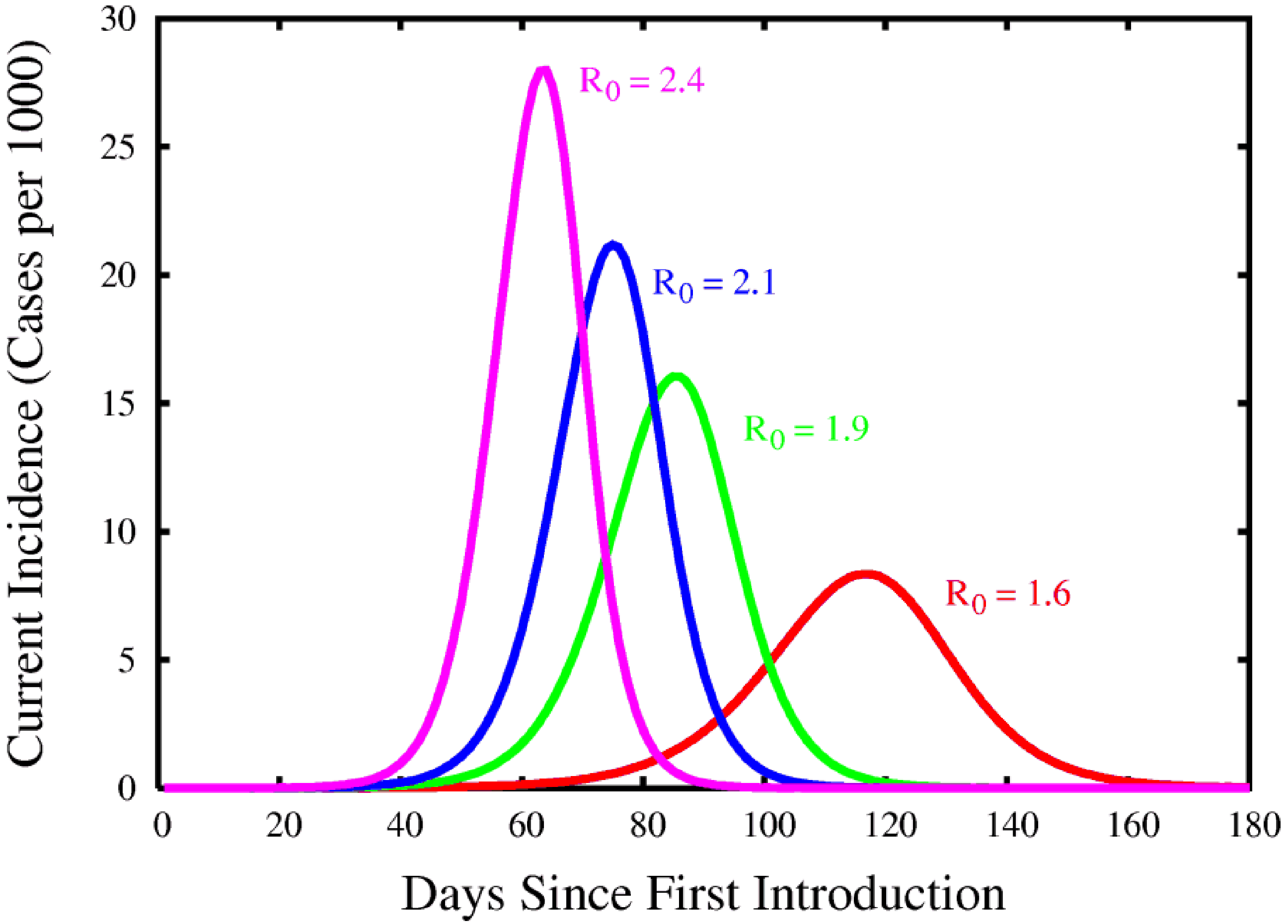
- A(H3N2) 1968-69, $R_0 \approx 1.7$
- A(H1N1) 1918, second wave, $R_0 \approx 2.0$
- New variant, early spread: $1 < R_0 \leq 1.6$
  - Estimate of R_0 = **1.14** (95% CI, 0.61-2.14) for A(H5N1) in Northern Sumatra, Indonesia
    - Yang, et al. *Emer Inf Dis* **9**, 1348-1353 (2007).

The influenza attack rate is influence by age and R_0 (no intervention)



Longini et al. Science 2005; 309: 1083-1087

The higher R_0, the earlier and the higher the peak incidence of the pandemic



Germann et al. PNAS 2006; 103 (15): 5935-5940

Goal of Modeling:

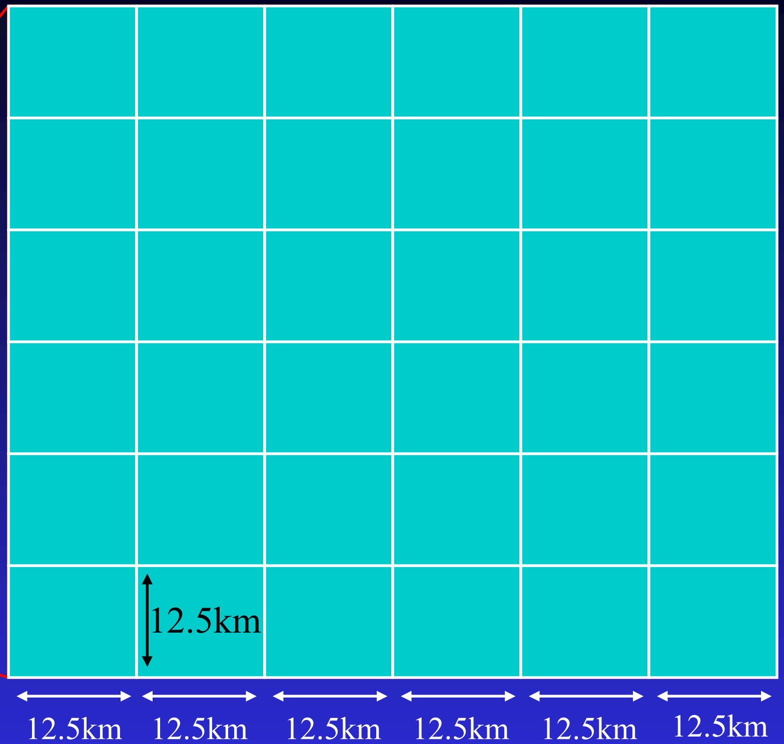
- Contain a reassorted or mutated strain of influenza at the source
- Avian A(H5N1) is the most likely virus
- Source could be in SE Asia

Rural population of 500,000 in Thailand

Population matched to non-municipal area household-size and age distributions.*

Avg. household size 3.6.

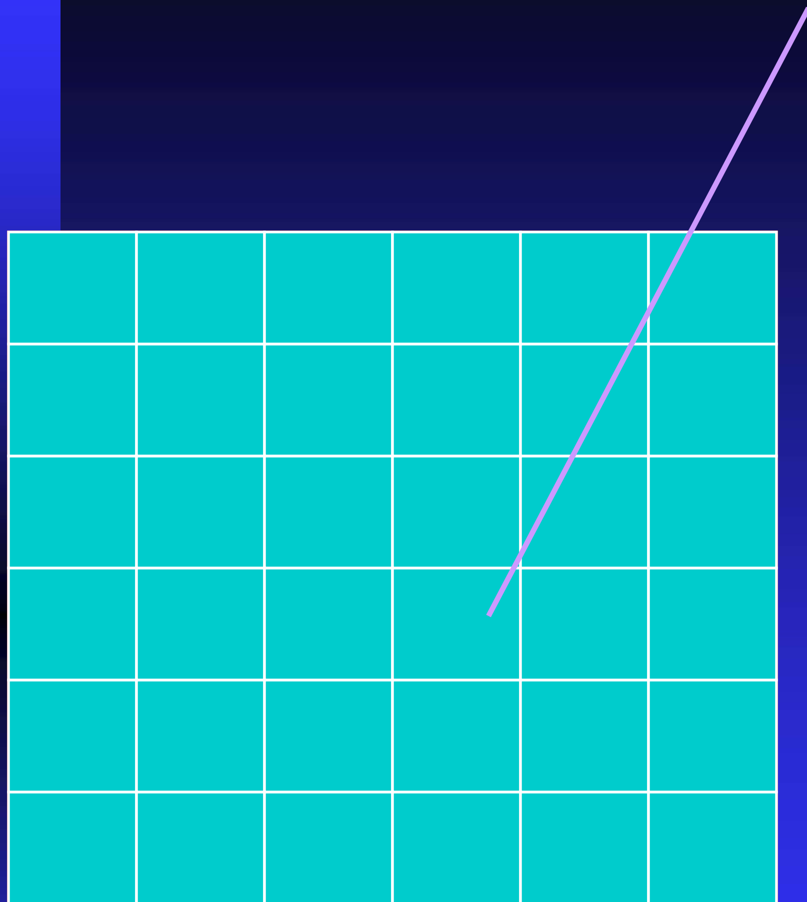
*Population and Housing Census 2000 data used where available (www.nso.go.th); other National Statistical Office reports and tables used as necessary.



Population Characteristics

- 36 localities each of size ~14,000
- Total area: 75 km X 75 km = 5,625 km^2
- Population density ~89/km^2

Localities Characteristics



- ~ 28 villages, each of size ~ 138 households, ~ 500 people
- Villages are clustered

Within village clusters:

- Household are clustered
- Small & large playgroups
- Elementary, lower-secondary and upper-secondary school mixing groups
- Social groups
- Work groups

Household composition

Household Size Distribution (Non-municipal Areas)

# Persons	% of Households
1	7.3%
2	15.3%
3	24.1%
4	29.8%
5	17.6%
6	3.0%
7	1.5%
8	0.7%
9	0.3%
10+	0.3%

Age distribution

Age Distribution (Non-municipal Areas)

No.	Age (Yrs)	%
1	< 6mos	0.9%
2	6mos - 4 yrs	8.2%
3	5-10	11.0%
4	11-14	5.5%
5	15-17	5.5%
6	18-44	44.4%
7	45-64	18.3%
8	65+	6.3%

What we incorporate from the Nang Rong District study*

- 310 villages under study
- Village size average ≈ 100 households
- Main mixing groups under study
  - Households
  - Villages
  - Hiring tractors
  - Temples
  - Elementary schools
  - Secondary schools
  - Workplaces

*Faust, et al., *Soc Net* (1999)

Nang Rong District*

- Close clusters of villages
  - Temples
    - 36% of villages
    - link villages aver 1.48 km apart
  - Elementary schools
    - 31% villages
    - link villages ave 2.11 km apart

*Faust, et al., *Soc Net* (1999)

Nang Rong District*

- Wider clusters of villages
  - Tractor Hiring
    - 41% villages involved
    - link villages ave 5.28 km apart
  - Labor movement
    - link villages ave 4.77 km apart
  - Secondary schools
    - 5.5% villages
    - link villages ave 5.26 km apart

*Faust, et al., *Soc Net* (1999)

Nang Rong District*

- Percent of villages with no ties outside of district
  - Tractor Hiring 74%
  - Temple Sharing 99%
  - Elementary schools 95%
  - Secondary schools 13%
  - Labor movement 87%

*Faust, et al., *Soc Net* (1999)

Children’s Playgroups

Small Playgroups:

-children 6 months - 4 years

-average size: 4

Larger Playgroups:

-children 6 months – 4 years

-average size: 22

Schools

Elementary schools:

-Children 5-10yrs old from village cluster

-2 schools per community, avg. size 117

Lower-secondary schools:

-Children 11-14yrs old from various localities randomly assigned to schools based on travel distribution

-1 school per community, avg. size 95

-17% of lower-secondary school age children do not attend school*

*Population and Housing Census 2000 data used where available (www.nso.go.th); other National Statistical Office reports and tables used as necessary.

Schools

<u>Upper-secondary schools:</u>

-Children 15-17yrs old from various localities, randomly assigned based on travel distribution

-1 school per community, avg. size 69

-42% of higher-secondary-age children do not attend school*

*Population and Housing Census 2000 data used where available (www.nso.go.th); other National Statistical Office reports and tables used as necessary.

Work groups

<u>Work Groups:</u>

-Consist of adults and children 11-17 who are not attending school.

-82% of adults are in the labor force*

-average group size: 25

-group members are randomly assigned and come from various localities, according to travel distribution

*Population and Housing Census 2000 data used where available (www.nso.go.th); other National Statistical Office reports and tables used as necessary.

Social groups

Social Groups:

-All individuals are members of two social groups.
-average group size: 100
-members are randomly assigned and come from various localities, according to travel distribution

*Population and Housing Census 2000 data used where available (www.nso.go.th); other National Statistical Office reports and tables used as necessary.

Hospital

- One centrally located 40-bed community hospital serving the 36 localities[1]
  - Age-specific hospitalization rates from '93-'94 Hong Kong physician sentinel data[2] used to select cases for hospitalization
  - If hospital is full, flu cases selected for hospitalization withdraw to "holding center" instead
    - One holding center of size 100 in each locality
  - If both hospital and holding centers are full, flu cases selected for hospitalization withdraw to the home instead
  - Staff of 125 persons works at the hospital

1. Thailand Health Profile 1999-2000, pp.279-291. http://www.moph.go.th/ops/thealth_44/

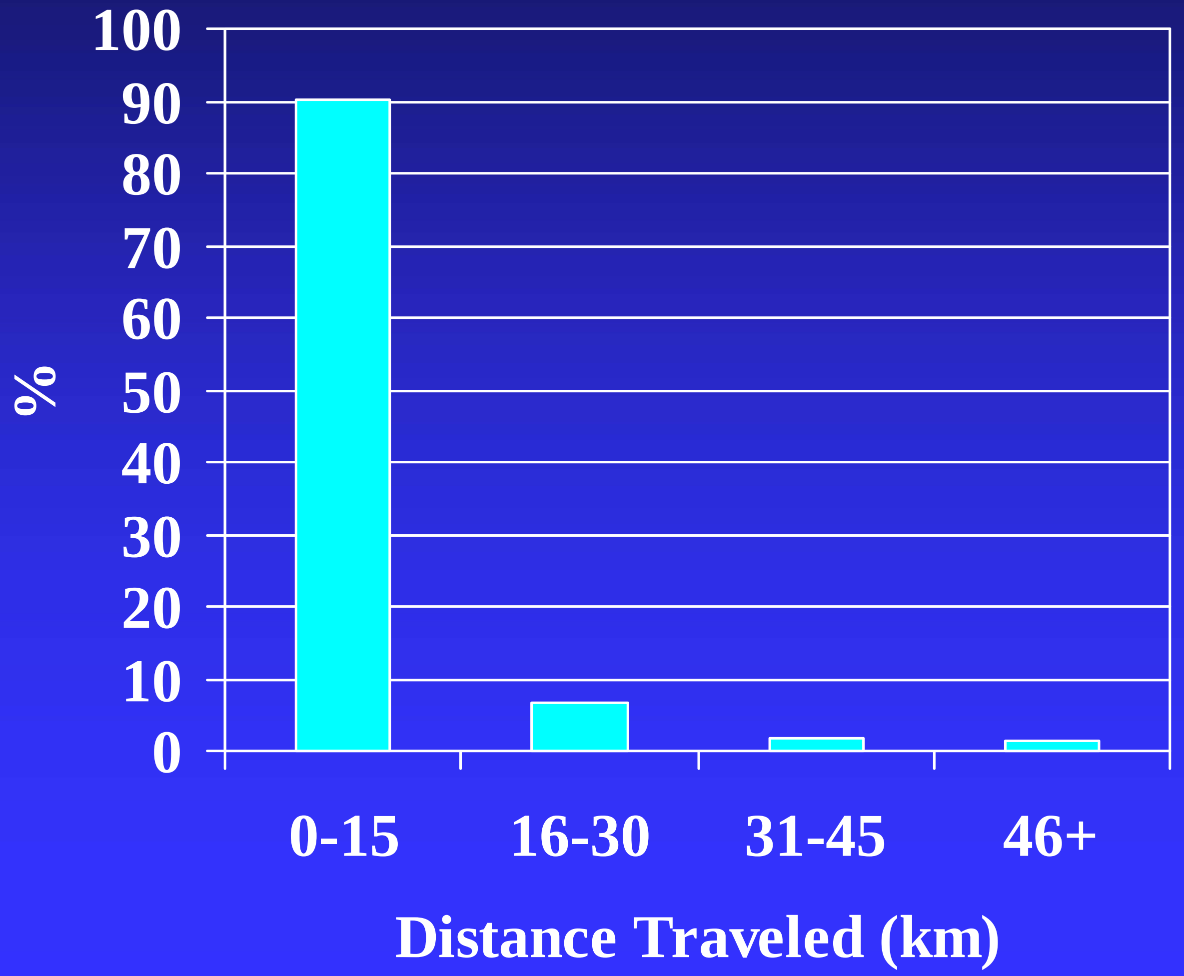
2. Fitzner et al, *Hong Kong Med J*, 1999

Hospitalization probabilities for a flu-like illness*

Age	Prob
<1	0.0023
2-4	0.0025
5-17	0.0008
18-64	0.0007
65+	0.0015

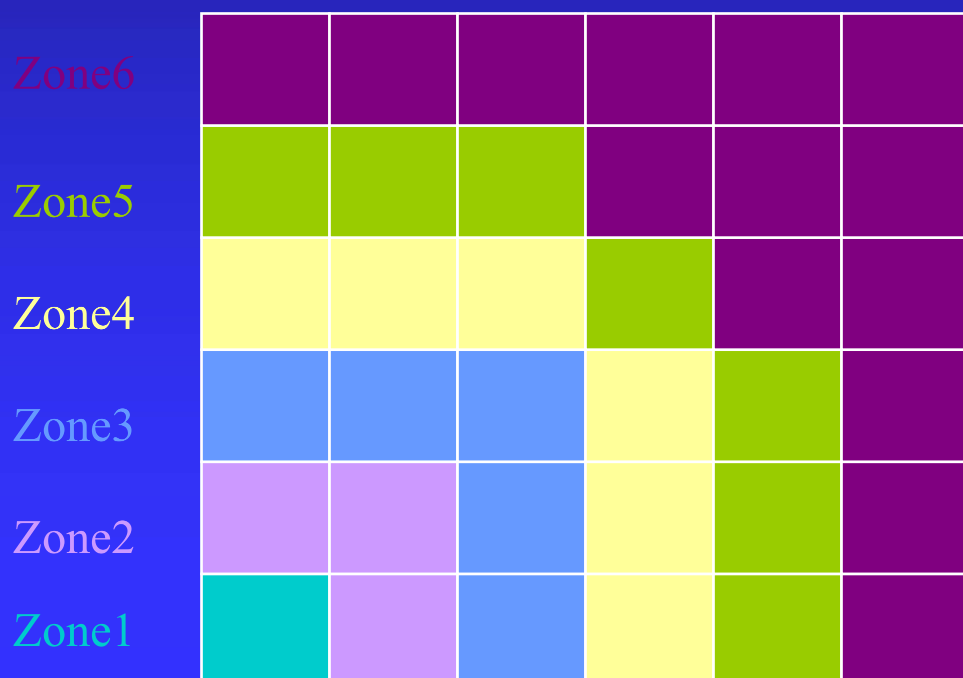
*Fitzner et al, *Hong Kong Med J*, 1999

Distribution of travel distance to work, school and social groups



Secondary school, work and social group assignment

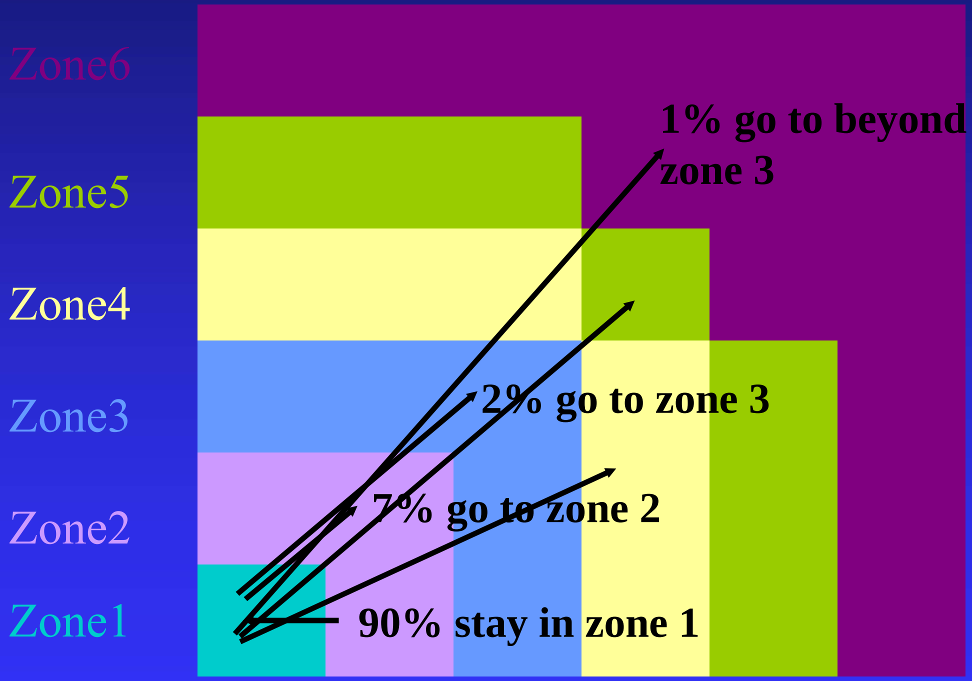
- Subpopulations are linked by secondary schools, work groups and social groups
- For residents of each subpopulation, Secondary school, work group and social group subpopulation is selected according to distance distribution shown below (using subpopulation 1 as an example)



Zone	%
1	90
2	7
3	2
4-6	1

Distribution of travel distance to work, school and social groups*

For residents of subpopulation 1:



Zone	%
1	90
2	7
3	2
4-6	1

Population Movement Outside of Area

- Individual migration probability for rural Thailand is on the order of 1/10,000 per day*
- Modeled individual level short term trip probability is on the order of 1/1,000

*Guest, et al. *Asian and Pacific Migration J* (1994)

Other parameters

- Transmission probability: *x* varies
- Household and household cluster contact probabilities doubled when schools or other local groups are closed.
- 100 simulations per scenario
- Results averaged over simulations where at least one additional case occurs

Basic Reproductive Number: R_0

Average number of people that a (one) ***typical*** infected person infects over the course of his or her infectious period in ***completely susceptible*** population.

- $R_0 > 1$ for sustained transmission
- For pandemic influenza: $1 < R_0 \leq 2.4$
  - A(H3N2) 1968-69, $R_0 \approx 1.7$
  - A(H1N1) 1918, second wave, $R_0 \approx 2.0$
  - New variant, early spread: $1 < R_0 \leq 1.6$

Model calibration

	Illness Attack Rate		
	Asian A(H2N2) 1957-58	Modeled Pandemic Strain	HK-Like ’68-69
Young Children	35%	32%	34%
Older Children	62%	45%	35%
Adults	24%	29%	33%
Overall	33%	33%	34%

Social Connectivity

Transmission

- *c* daily adequate contact probability
  - c(n-1) average mixing group degree
- *x* transmission probability given adequate contact
- y relative susceptibility
- $p = cxy$ overall transmission probability

Infection Probability Each Day

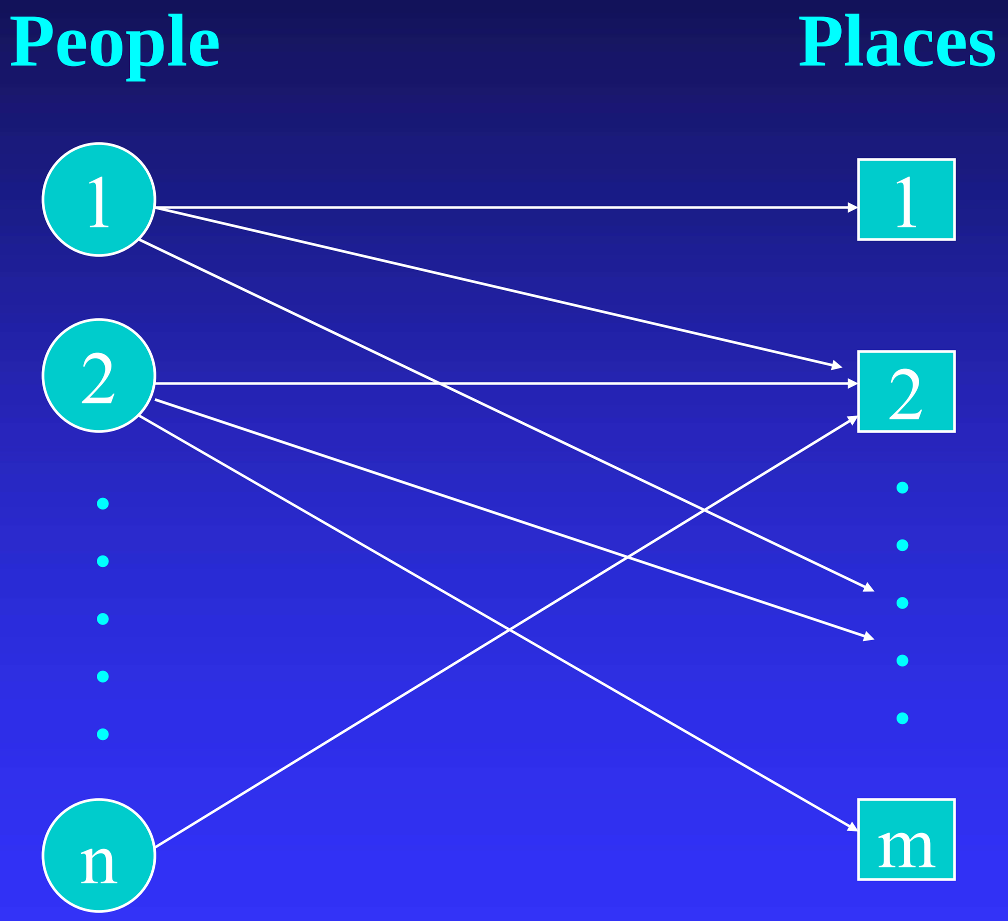
- *e.g.*, susceptible person on antivirals on day *t*
- AVE_S = 1 - 🖹 , AVE_I = 1 - ☠
- Sequence of Bernoulli trials
- Escape probability

  $Q(t) = (1 - \text{🖹}p_1)^{I1(t)}\,(1 - \text{🖹}p_2)^{I2(t)}\,(1 - \text{🖹}p_3)^{I3(t)}\ldots\ldots$

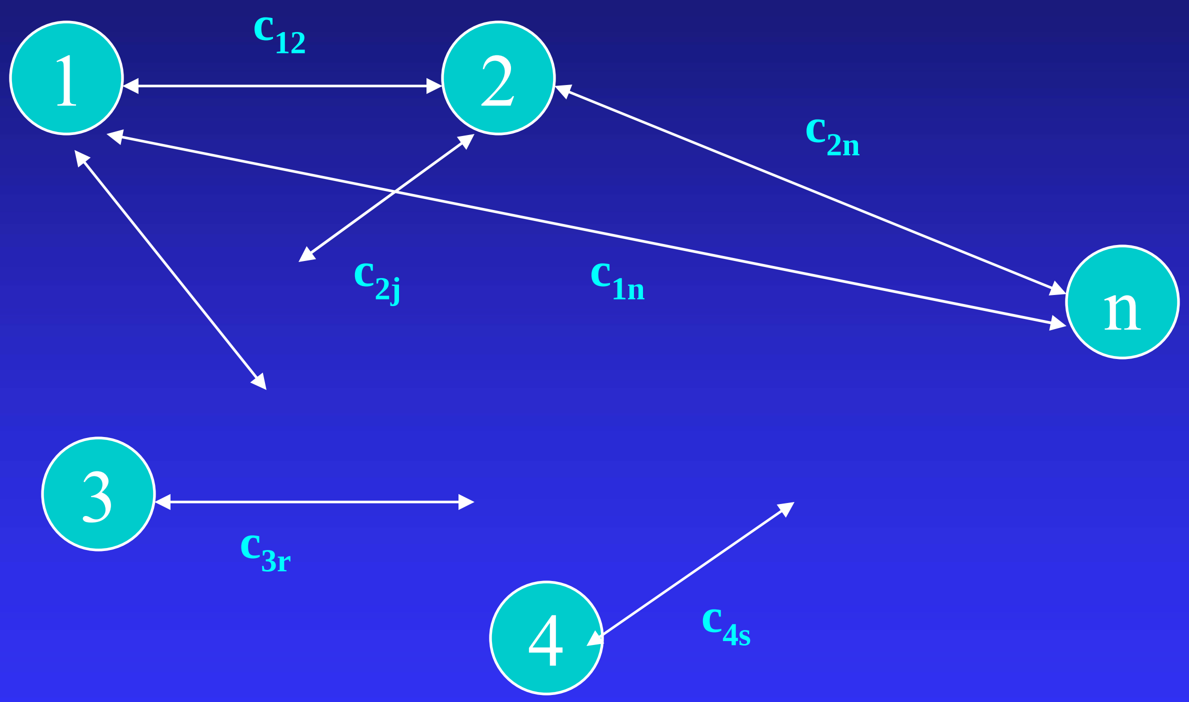
  $(1 - \text{🖹☠}p_1)^{Iav1(t)}\,(1 - \text{🖹☠}p_2)^{Iav2(t)}\,(1 - \text{🖹☠}p_3)^{Iav3(t)}\ldots\ldots$

- Infection probability
  - $P(t) = 1 - Q(t)$
- Generate random number [0,1]
- Repeat for every susceptible on day *t*

Bipartite Graph



Weighted Person-to-Person Graph



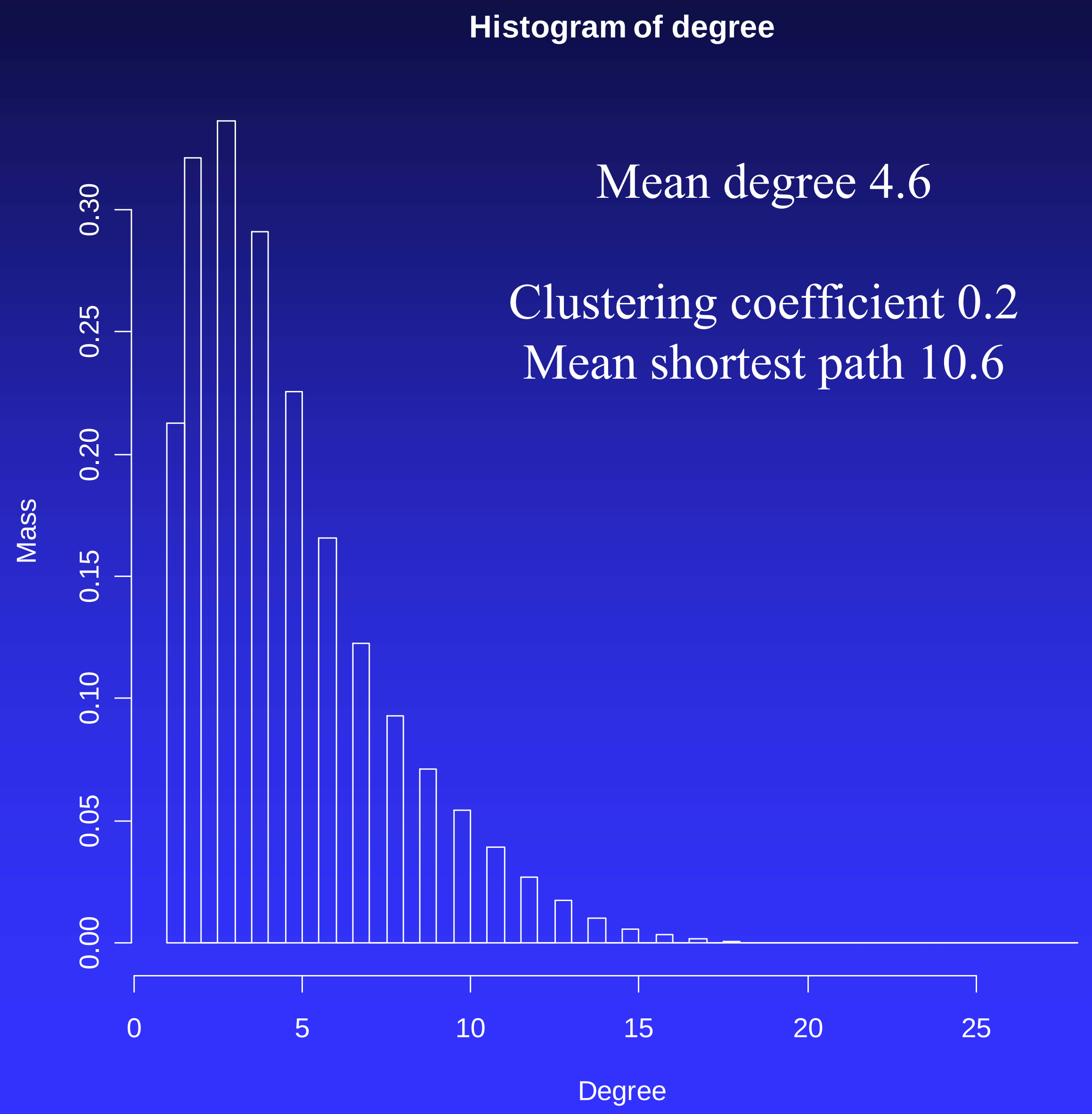
Daily contact probabilities adults by mixing group

Contact group	Children					Adults
	Pre-School		School			
	Small Playgroup	Large Daycare	Elementary	Middle	High	
Small playgroups	0.35					
Large playgroups		0.25				
Elementary school			0.062			
Middle school				0.062		
High school					0.062	
Family						
Child	0.60	0.60	0.60	0.60	0.60	0.30
Adult	0.30	0.30	0.30	0.30	0.30	0.40
Neighborhood Cluster						
Child	0.15	0.15	0.15	0.15	0.15	0.08
Adult	0.08	0.08	0.08	0.08	0.08	0.10
Hospital						
Flu ward						
Worker-worker						0.01250
Patient-worker	0.01000	0.01000	0.01000	0.01000	0.01000	0.01000
Patient-visitor	0.01000	0.01000	0.01000	0.01000	0.01000	0.01000
Other wards						0.00250
Workgroup						0.08
Social Groups	0.0018	0.0018	0.0020	0.0020	0.0020	0.0040

Average Daily Contact Degree, by Mixing Group

	Children					
	Pre-School		School			
Contact group	Small Playgroup	Large Daycare	Elementary	Middle	High	Adults
Small playgroups	0.98					
Large playgroups		5.2				
Elementary school			7.2			
Middle school				5.9		
High school					4.2	
Family						
Child	0.37	0.37	0.37	0.37	0.37	0.72
Adult	0.48	0.48	0.48	0.48	0.48	0.56
Neighborhood Cluster						
Child	0.56	0.56	0.56	0.56	0.56	0.75
Adult	0.38	0.38	0.38	0.38	0.38	0.84
Hospital						
Flu ward						
Worker-worker						1.9
Patient-worker	-	-	-	-	-	-
Patient-visitor	-	-	-	-	-	-
Other wards						1.4
Workgroup						1.9
Social Groups	0.20	0.20	0.27	0.27	0.27	0.95

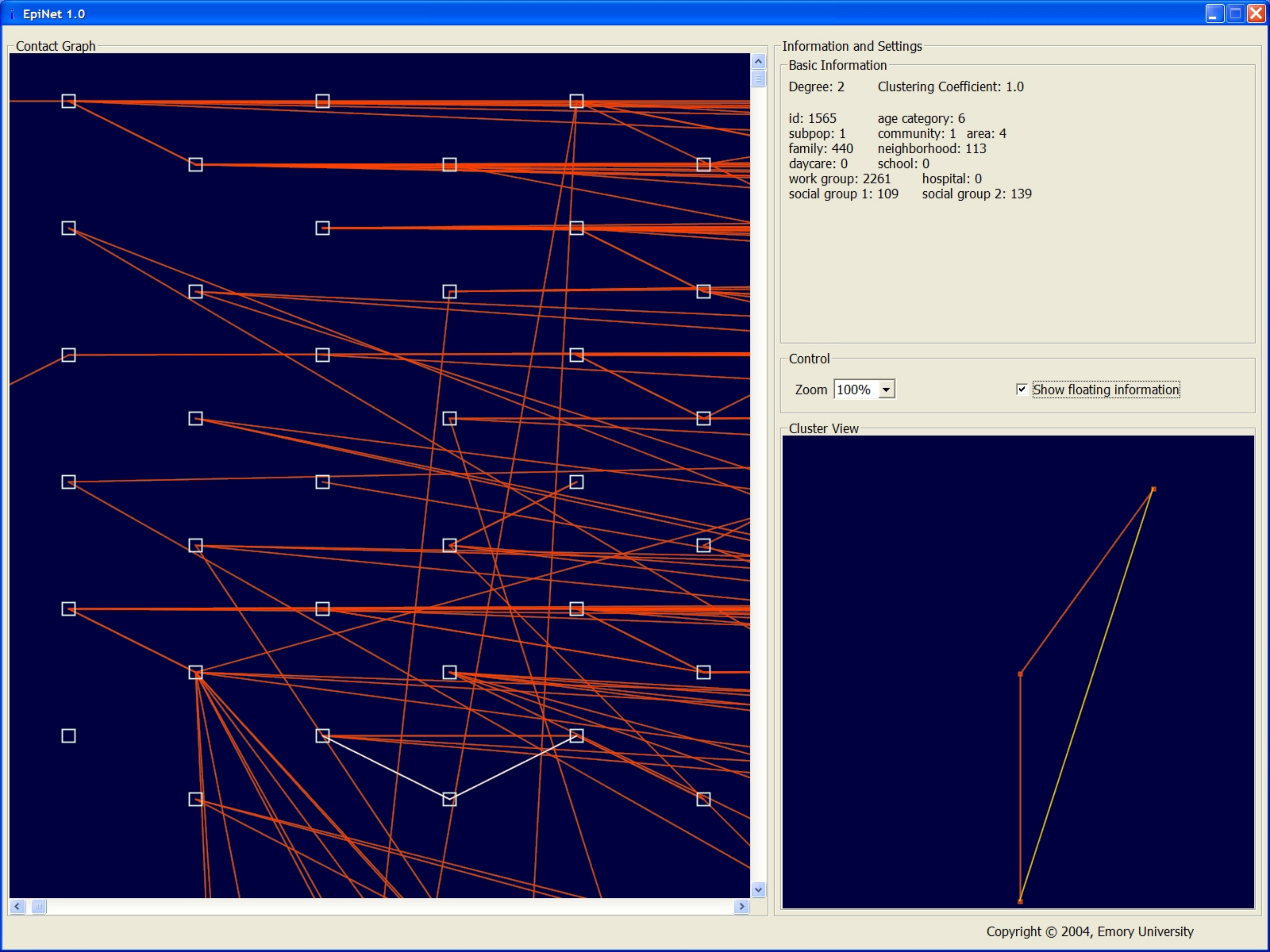
Degree Distribution

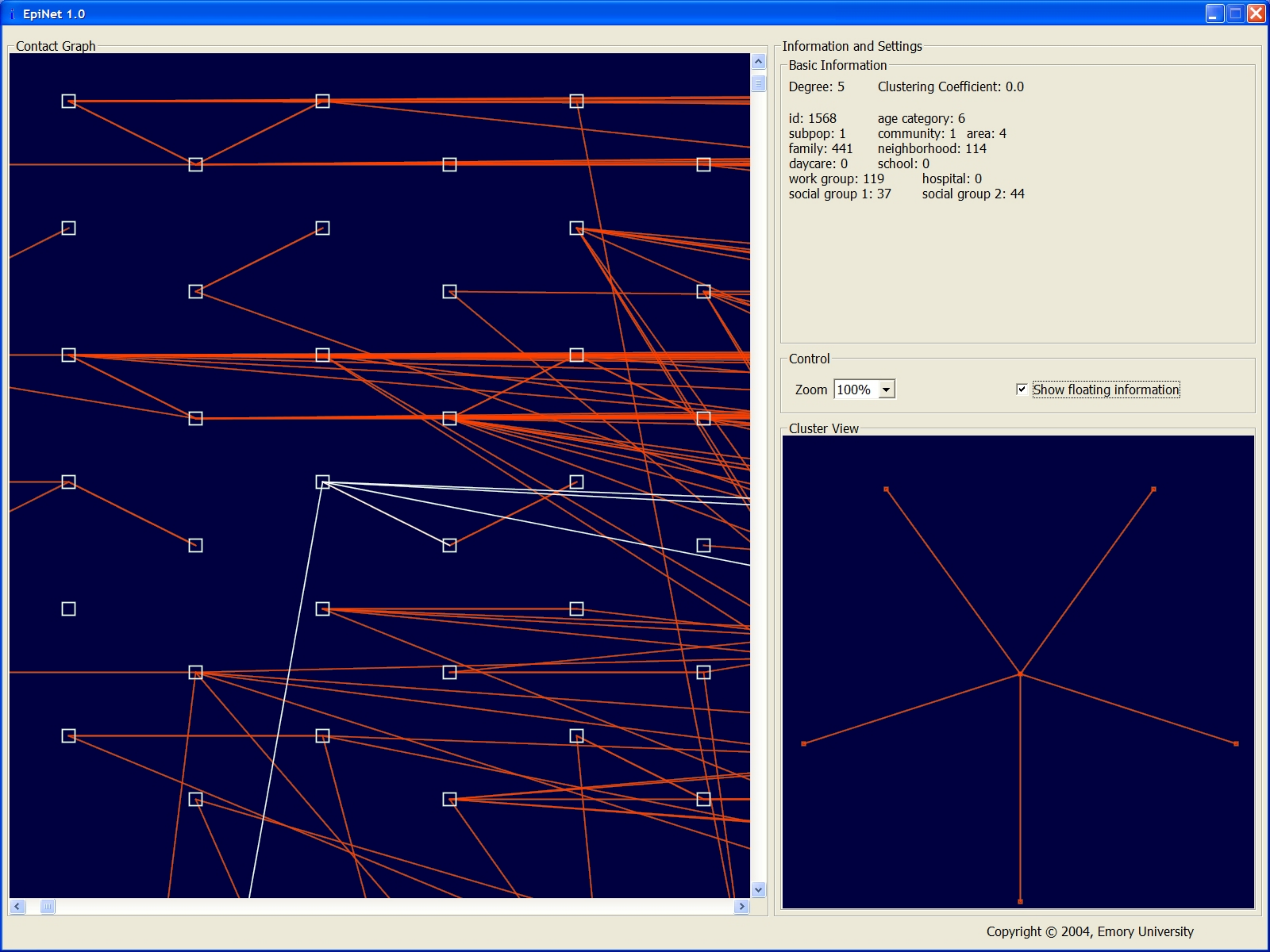


Mean degree 4.6

Clustering coefficient 0.2

Mean shortest path 10.6


EpiNet 1.0
Contact Graph
Information and Settings
Basic Information
Degree: 2
Clustering Coefficient: 1.0
id: 1565
age category: 6
subpop: 1
community: 1 area: 4
family: 440
neighborhood: 113
daycare: 0
school: 0
work group: 2261
hospital: 0
social group 1: 109
social group 2: 139
Control
Zoom 100%
Show floating information
Cluster View
Copyright © 2004, Emory University


EpiNet 1.0
Contact Graph
Information and Settings
Basic Information
Degree: 5
Clustering Coefficient: 0.0
id: 1568
age category: 6
subpop: 1
community: 1 area: 4
family: 441
neighborhood: 114
daycare: 0
school: 0
work group: 119
hospital: 0
social group 1: 37
social group 2: 44
Control
Zoom 100%
Show floating information
Cluster View
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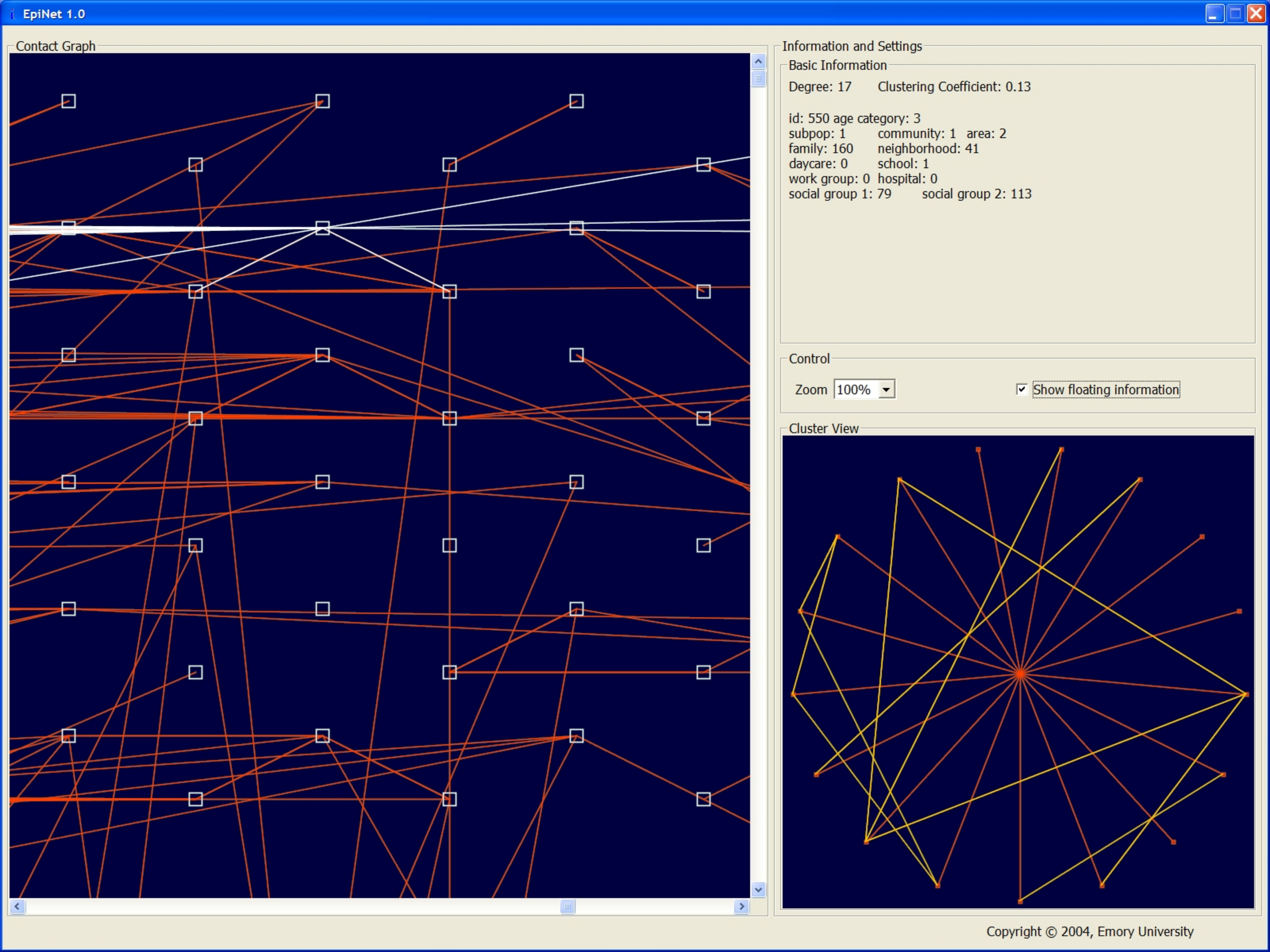

EpiNet 1.0
Contact Graph
Information and Settings
Basic Information
Degree: 17
Clustering Coefficient: 0.13
id: 550 age category: 3
subpop: 1
community: 1
area: 2
family: 160
neighborhood: 41
daycare: 0
school: 1
work group: 0
hospital: 0
social group 1: 79
social group 2: 113
Control
Zoom
100%
Show floating information
Cluster View
Copyright © 2004, Emory University

Average Contact Matrix

				From				
age group	< 6 m	6 m - 4	5 – 10	11– 14	15 -17	18-44	45-64	65+
< 6 m	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
6 m - 4	1.0	3.9	1.0	1.0	1.0	1.1	1.1	1.1
5 - 10	1.1	1.1	7.5	1.1	1.1	1.1	1.1	1.1
To 11 - 14	1.0	1.0	1.0	5.9	1.0	1.0	1.0	1.1
15 - 17	1.0	1.0	1.0	1.0	4.2	1.0	1.0	1.1
18 - 44	1.3	1.4	1.4	1.4	1.4	2.2	2.1	2.4
45 - 64	1.1	1.1	1.1	1.1	1.1	1.4	1.4	1.4
65+	1.1	1.1	1.1	1.1	1.1	1.2	1.2	1.2

Estimated mean numbers of conversations per week, The Netherlands, 1986*

Age class	1-4	5-12	13-19	20-39	40-59	60+
0-4	12.3	2.3	1.3	2.5	1.2	0.8
5-12	2.7	23.8	2.8	3.0	1.8	1.0
13-19	2.0	3.6	25.2	5.7	4.2	1.7
20-39	11.5	11.6	16.9	25.1	16.4	8.3
40-59	3.6	4.7	8.5	11.2	13.9	7.5
60+	1.9	2.0	2.5	4.3	5.6	9.2

*Wallinga, et al., unpublished manuscript

Next Generation Matrix **R**

	From							
age group	0	1	2	3	4	5	6	7
0	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
1	0.11	0.40	0.11	0.11	0.11	0.11	0.11	0.11
2	0.11	0.11	0.77	0.11	0.11	0.11	0.11	0.11
To 3	0.11	0.11	0.11	0.61	0.11	0.11	0.11	0.11
4	0.11	0.11	0.11	0.11	0.43	0.11	0.11	0.11
5	0.14	0.14	0.14	0.14	0.14	0.22	0.22	0.25
6	0.12	0.12	0.12	0.12	0.12	0.14	0.14	0.15
7	0.11	0.11	0.11	0.11	0.11	0.12	0.12	0.12

Basic reproduction number $R_0 = 1.2$

Infection Transmission Process

Modeled natural history of influenza

Ill, circulating

0.67

Ill, not circulating

Infected

Recovered/removed

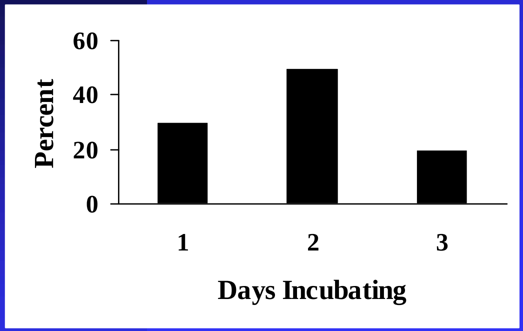
Susceptible

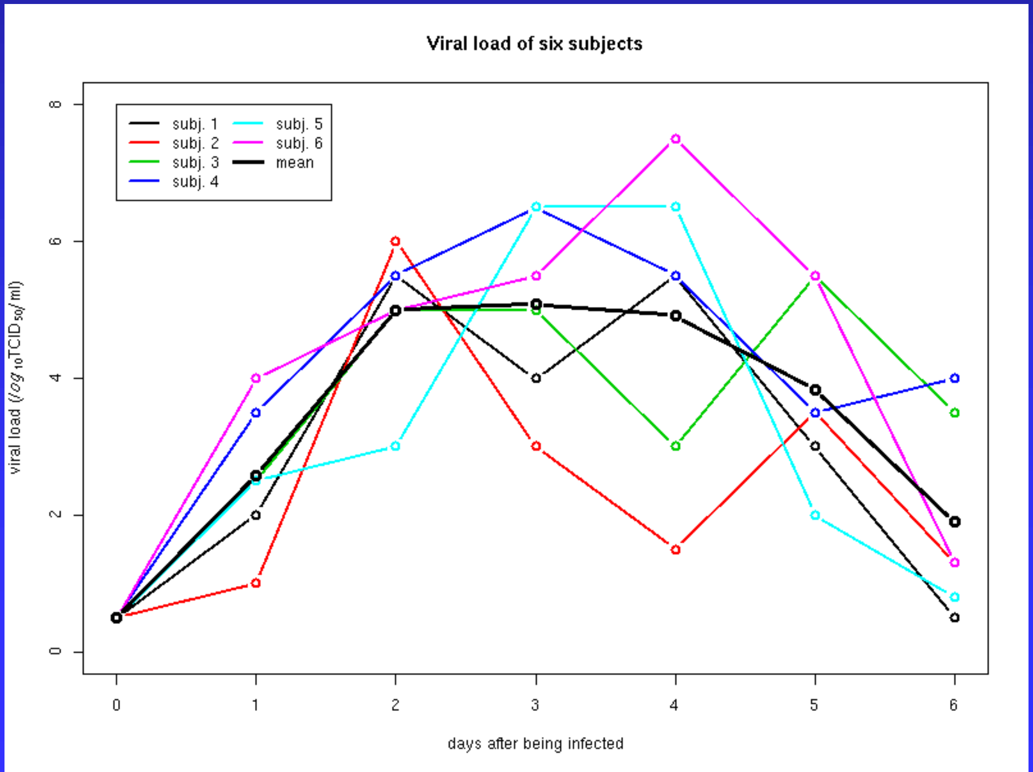
0.33

Incubation period: Mean 1.9 days

Not ill ½ infectious as ill

Serial interval: Mean 2.3 days



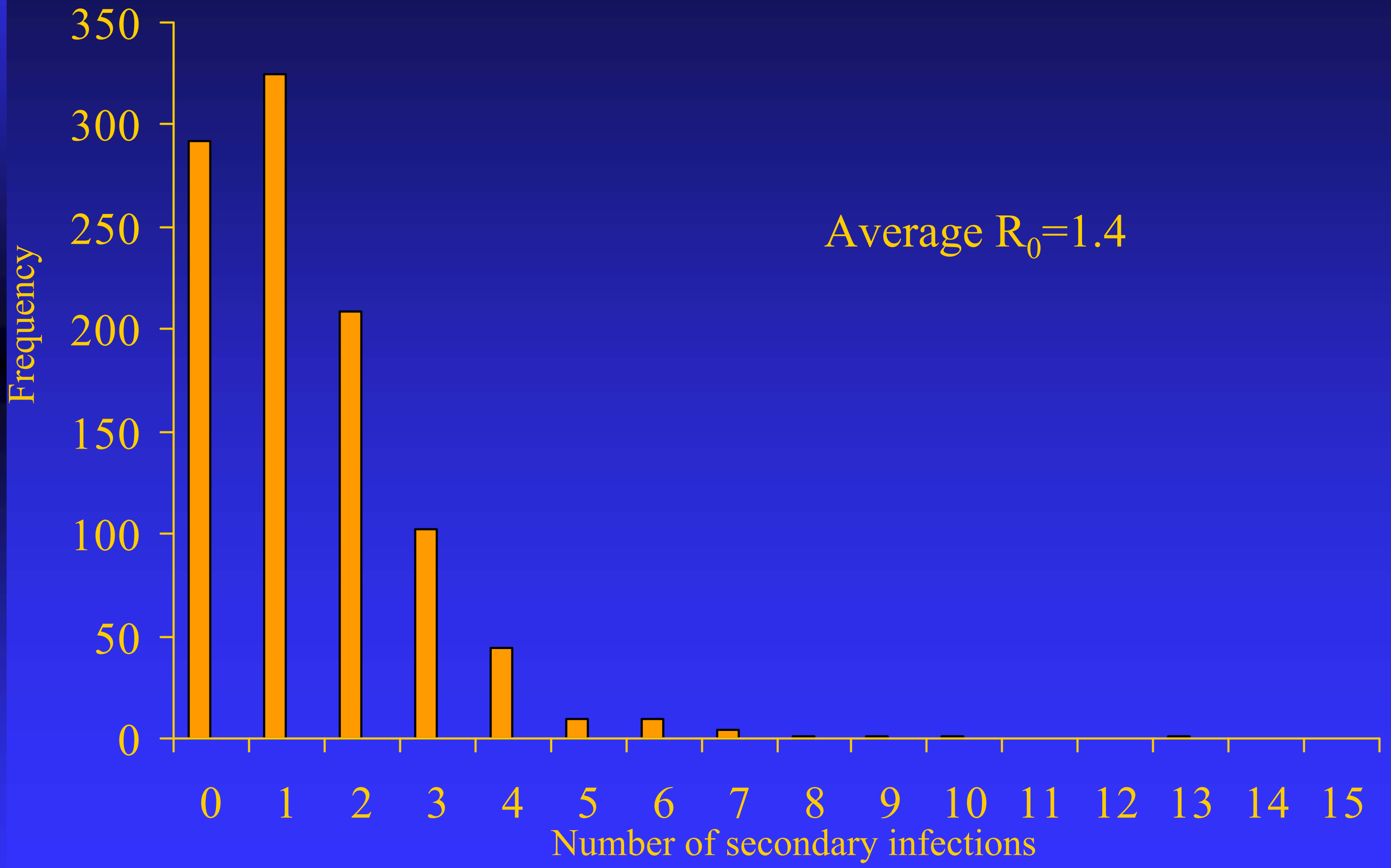


Use of Oseltamivir

- Each person to be treated is given a single course of Oseltamivir
  - 5 days of treatment
- Each person to be prophylaxed is given a single course of Oseltamivir
  - 10 days of prophylaxis

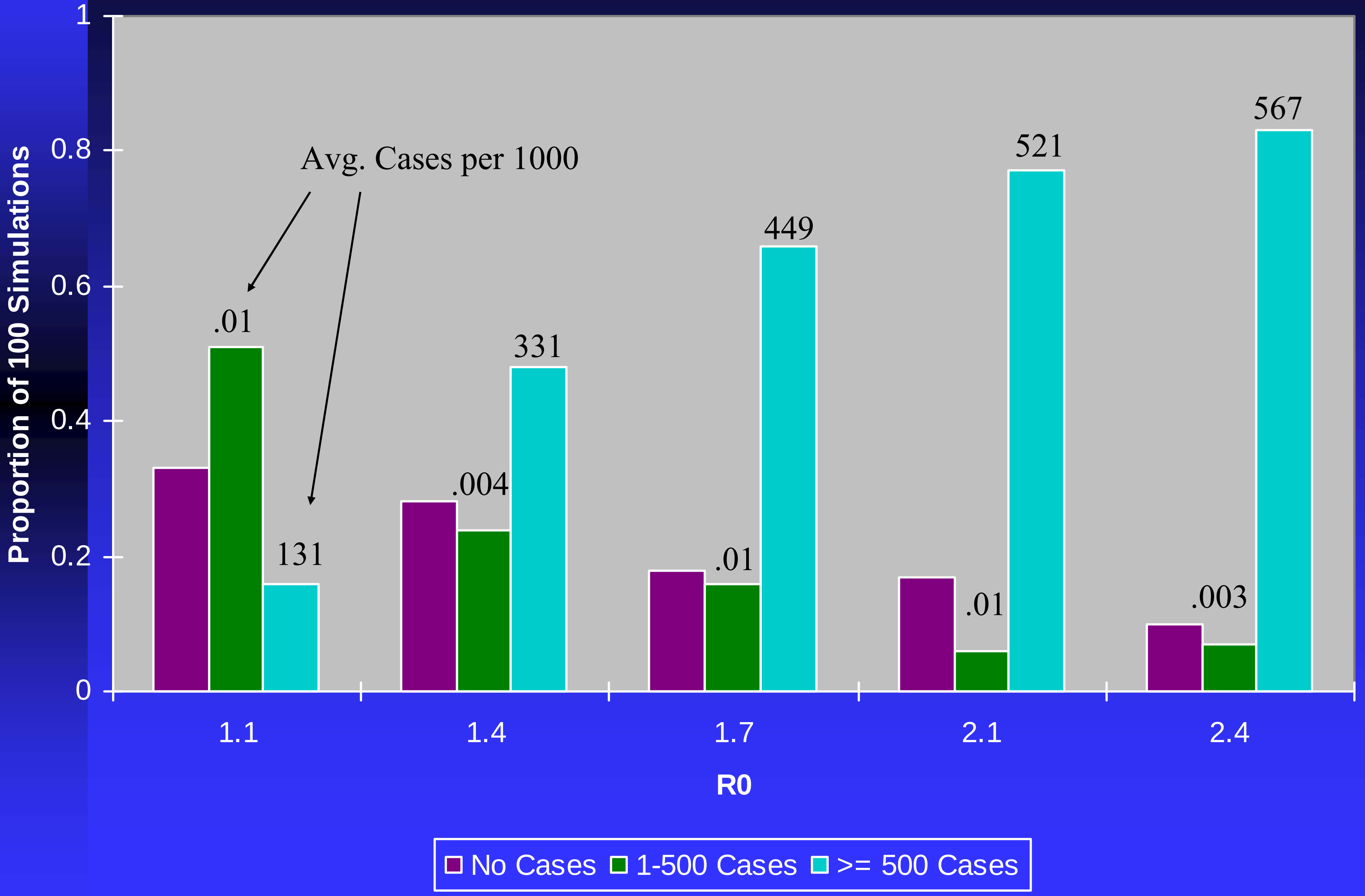
Some Results

R_0*: Number of people infected by a single initial infective



* Based on 1000 simulations

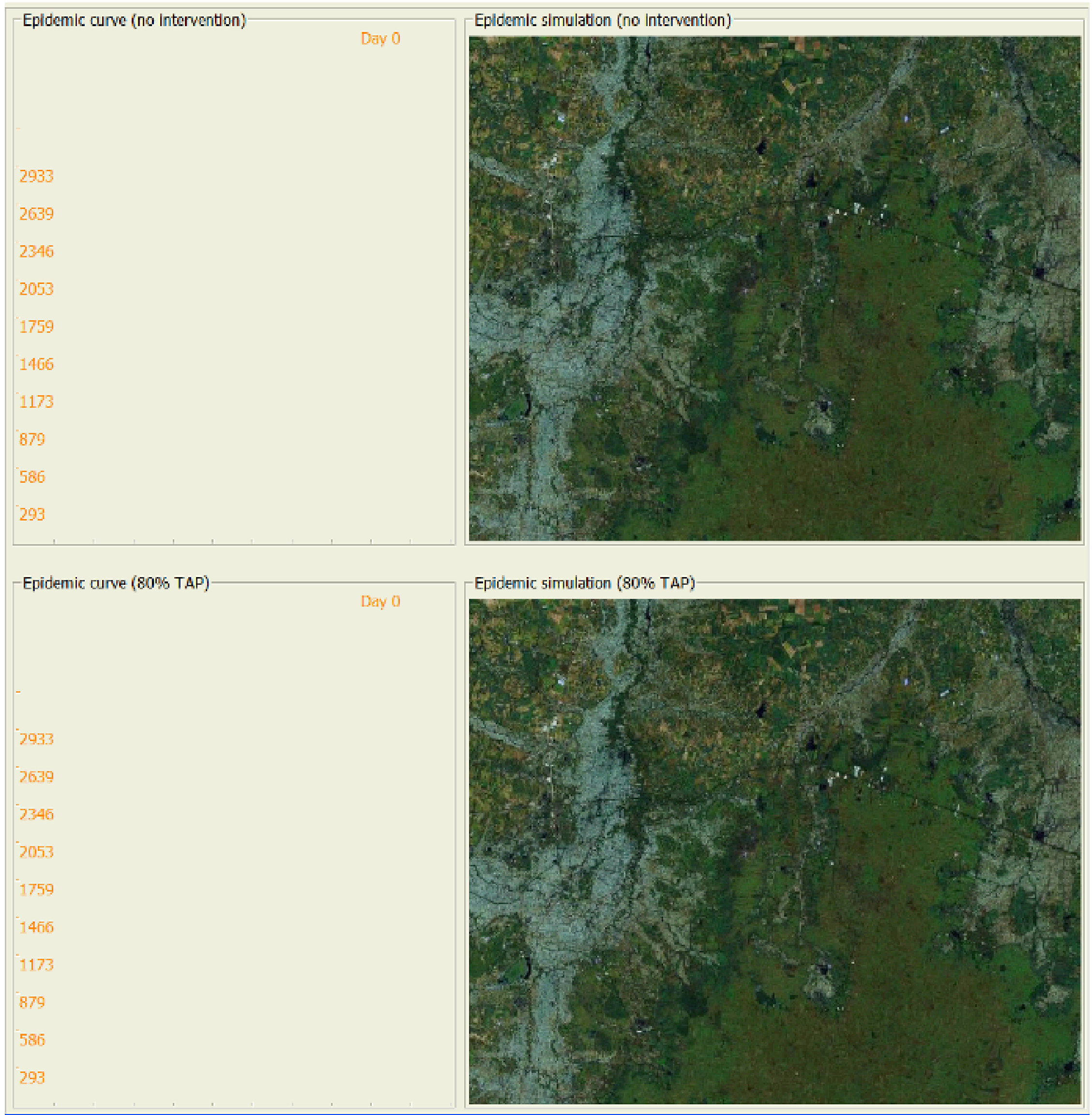
Probabilities and Epidemic Sizes: No Intervention



Simulated pandemic influenza outbreak
$R_0 = 1.4$

Without intervention

80% TAP



Longini et al. Science 2005; 309: 1083-1087

Simulated pandemic influenza outbreak

$R_0 = 1.7$

80% TAP

80% TAP
+ 50% Pre-vacc

Longini et al. Science 2005; 309: 1083-1087

Simulated pandemic influenza outbreak $R_0 = 1.7$

70% reactive vaccination

No intervention

Simulated pandemic influenza outbreak
$R_0 = 1.7$

70% reactive vaccination

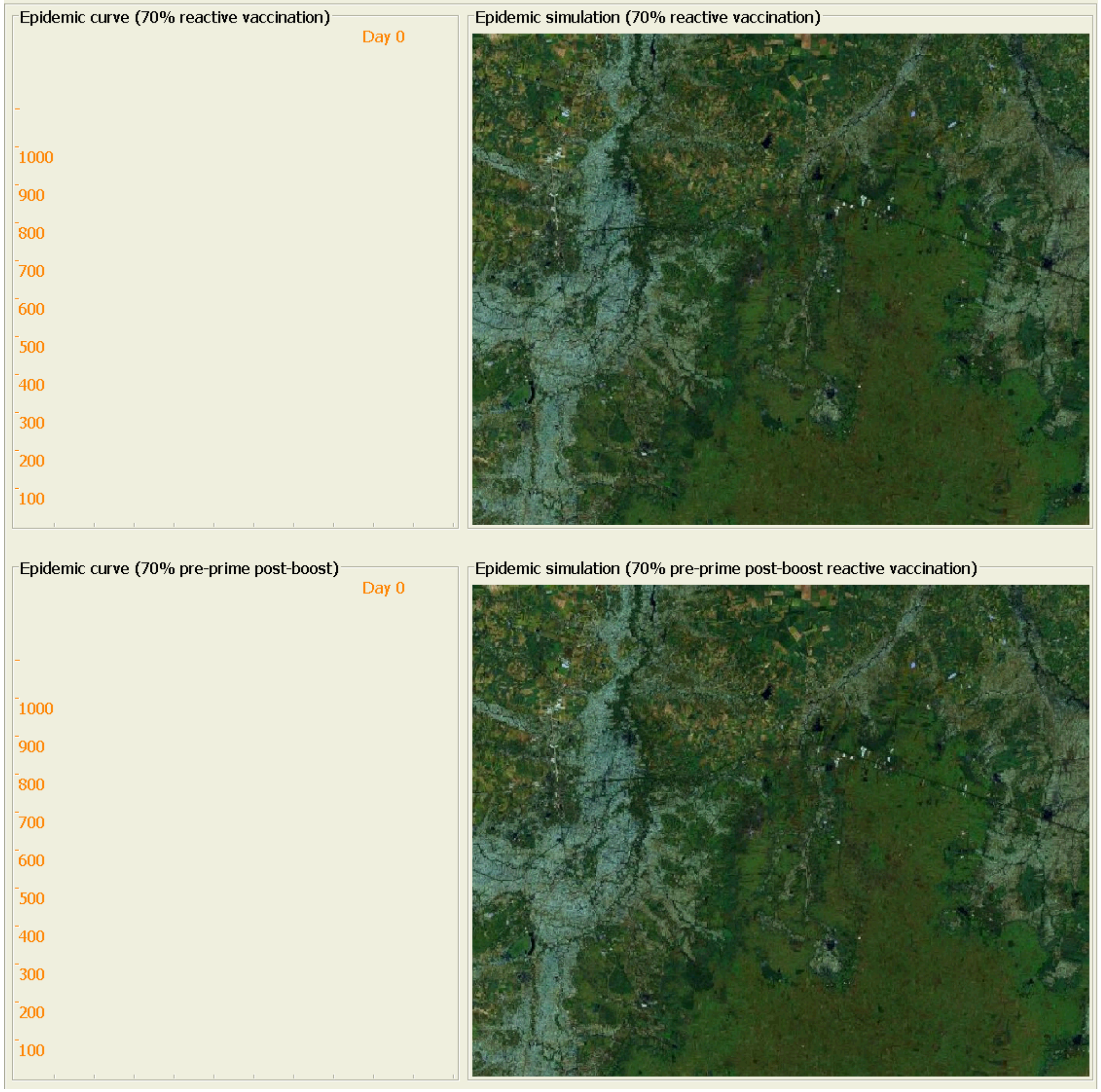
70% reactive vaccination
+ 80% TAP

Simulated pandemic influenza outbreak

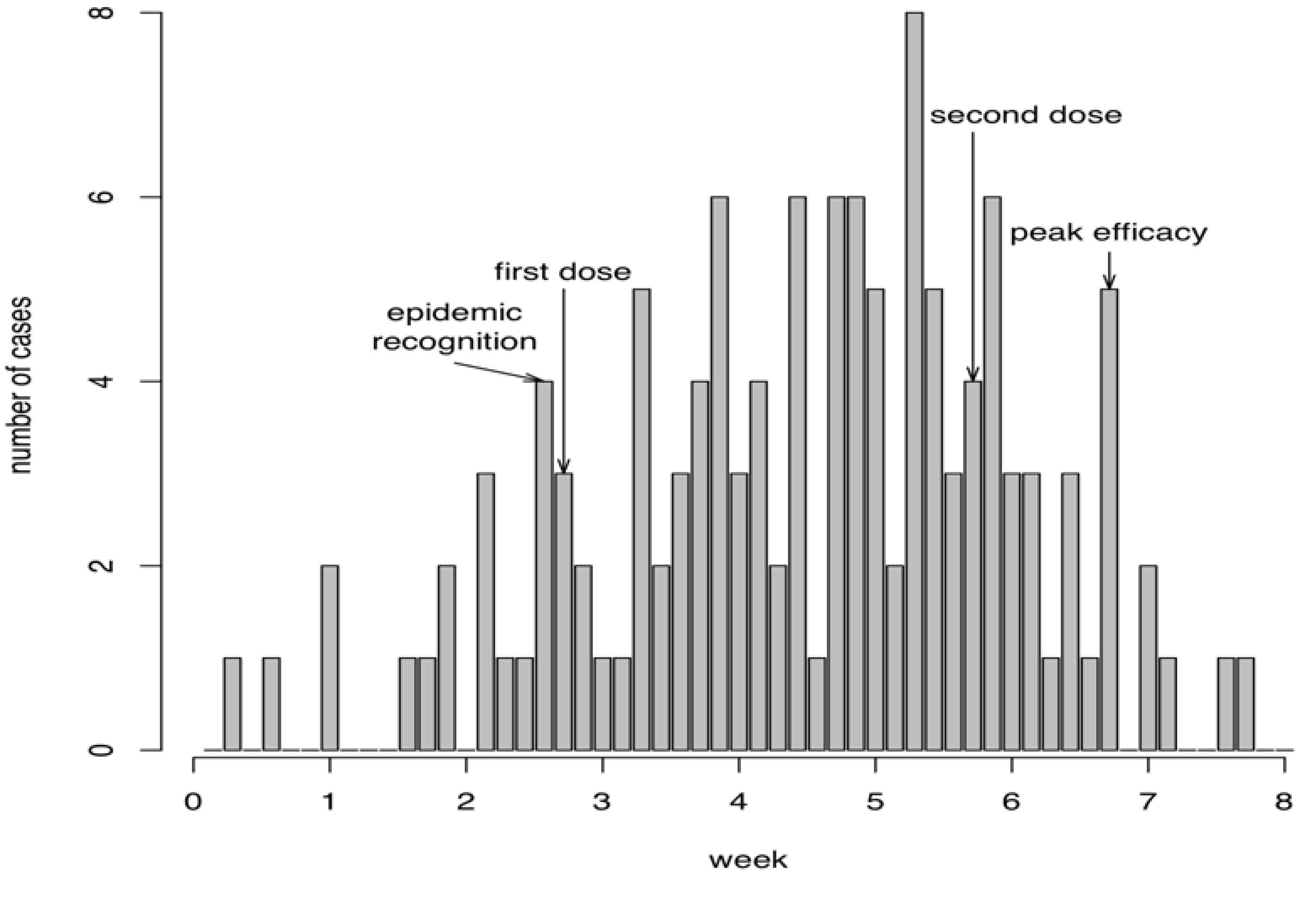
$R_0 = 1.7$

70% reactive vaccination

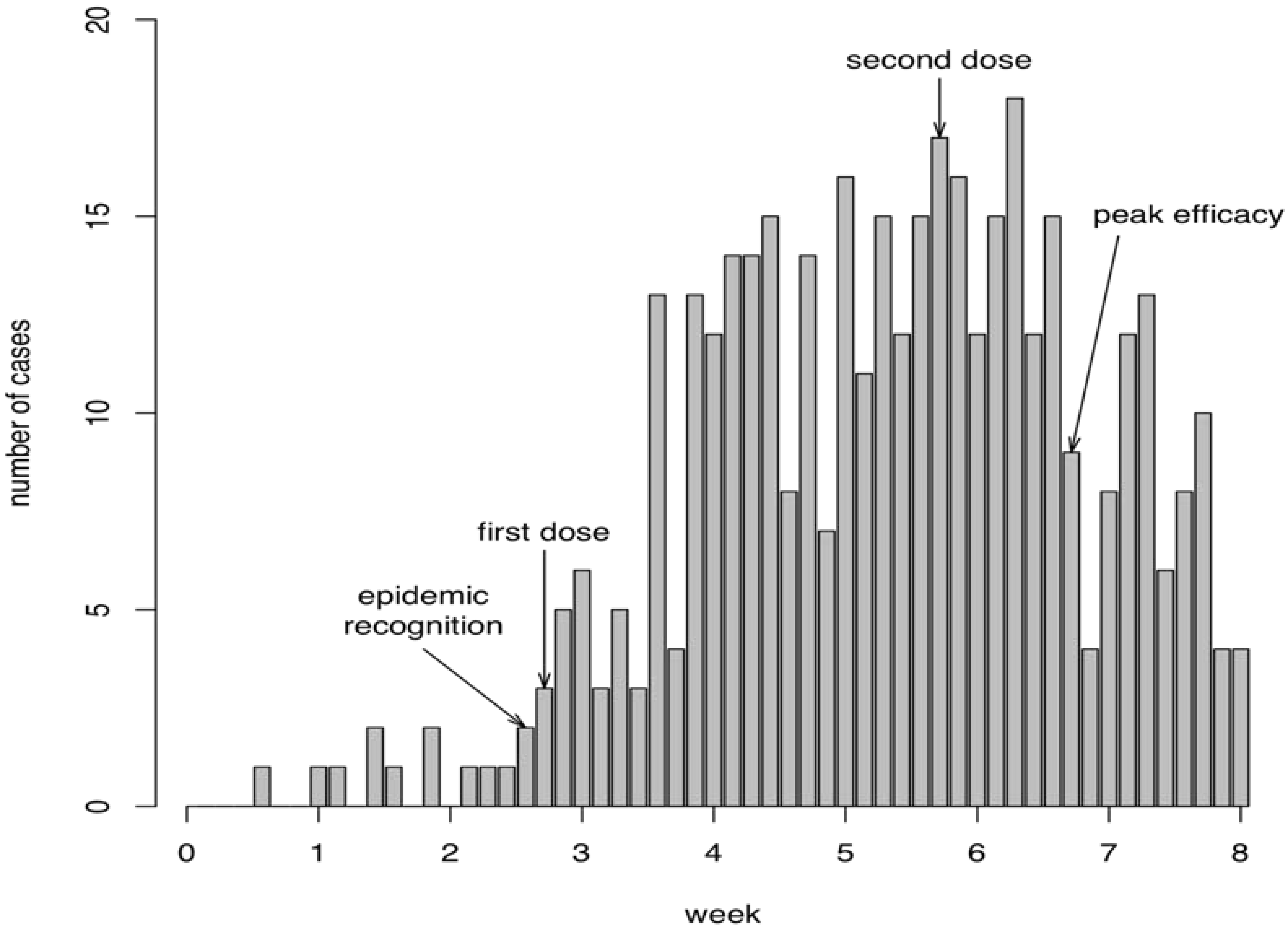
70% pre-prime post boost



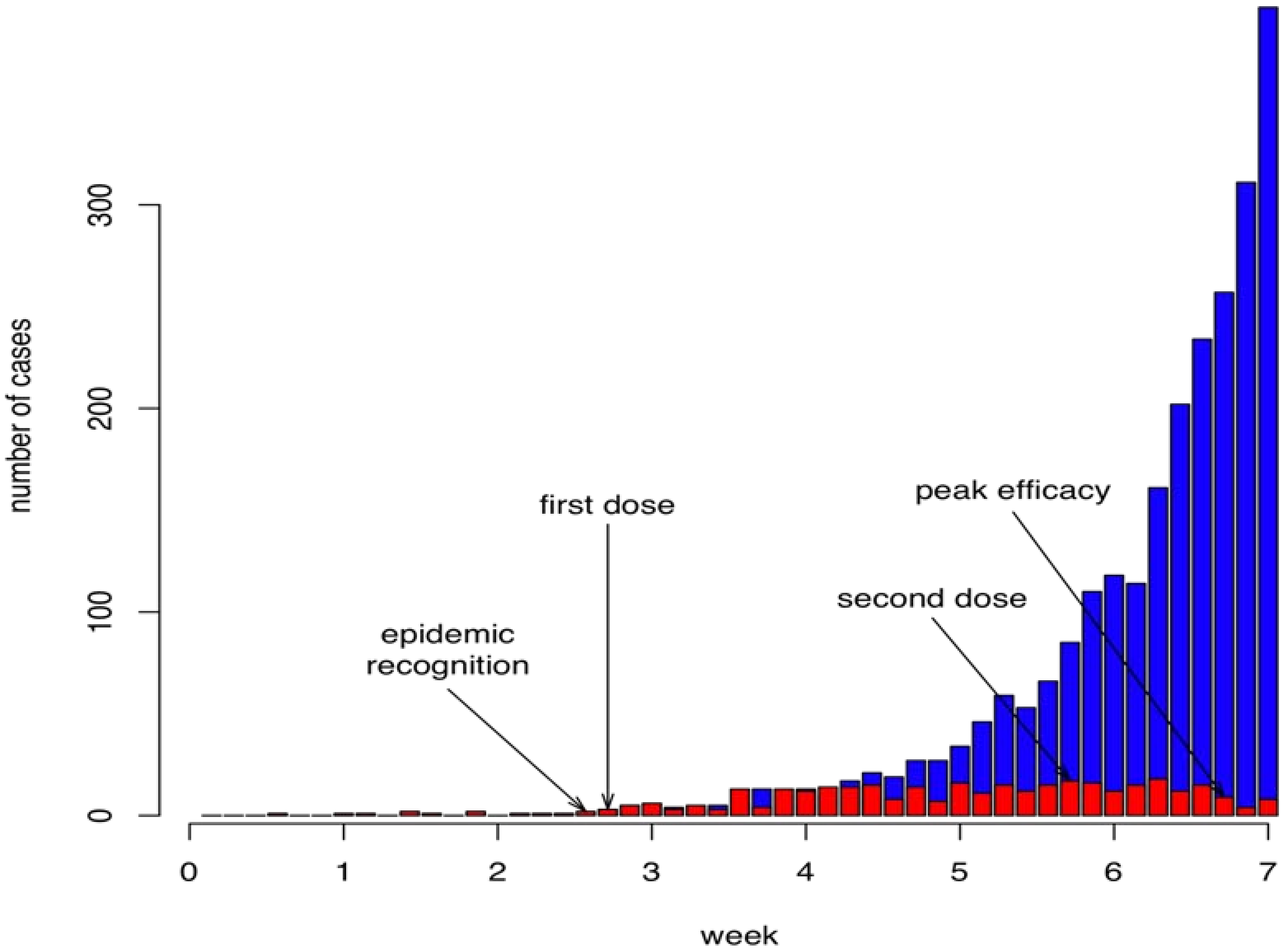
70% reactive vaccination R_0=1.2 intervention at day 18

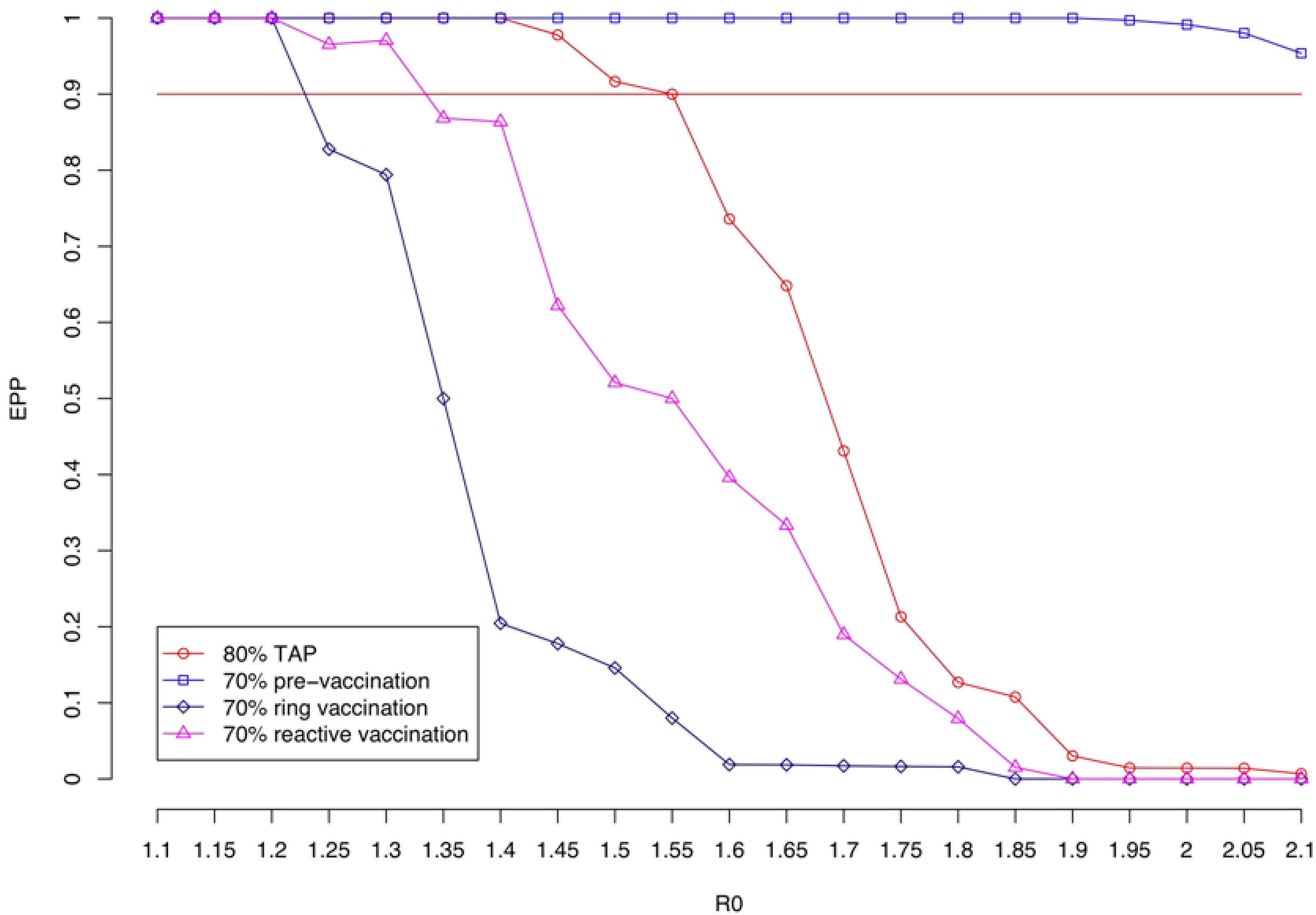


70% reactive vaccination R_0=1.7 intervention at day 18

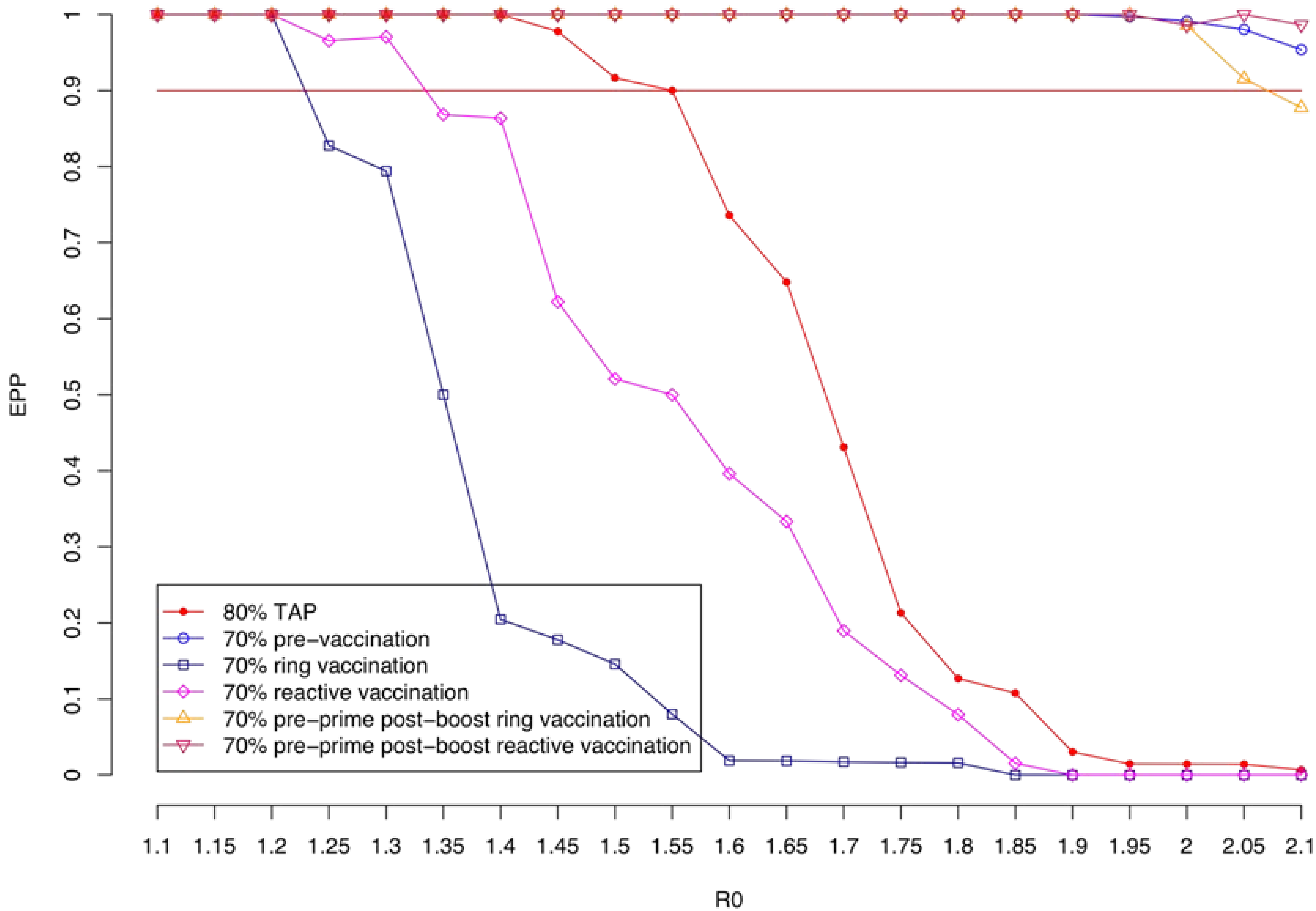


Comparison of epidemic size for 70% reactive vaccination and baseline at R_0=1.7





EPP
R0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
1.1 1.15 1.2 1.25 1.3 1.35 1.4 1.45 1.5 1.55 1.6 1.65 1.7 1.75 1.8 1.85 1.9 1.95 2 2.05 2.1
80% TAP
70% pre−vaccination
70% ring vaccination
70% reactive vaccination



EPP
R0
80% TAP
70% pre−vaccination
70% ring vaccination
70% reactive vaccination
70% pre−prime post−boost ring vaccination
70% pre−prime post−boost reactive vaccination
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
1.1
1.15
1.2
1.25
1.3
1.35
1.4
1.45
1.5
1.55
1.6
1.65
1.7
1.75
1.8
1.85
1.9
1.95
2
2.05
2.1

Largest R_0 with 90% EPP for each scenario

Scenarios	R_0
50% pre-vaccination	1.6
70% pre-vaccination	2.1
70% ring vaccination	1.2
70% reactive vaccination	1.3
80% TAP	1.6
80% TAP + 70% pre-vaccination	2.1
80% TAP + 70% ring vaccination	1.8
70% pre-prime post-boost ring vaccination	2.1
70% pre-prime post-boost reactive vaccination	2.1

Conclusions: Containment

- TAP alone is sufficient for $R_0 \leqslant 1.6$
- Yearly pre-vaccination with pre-pandemic vaccine would be best, but obviously impossible
- Reactive mass vaccination is somewhat better than ring vaccination
- Reactive vaccination would only work for $R_0 \leqslant 1.3$
- TAP + reactive vaccination would work for $R_0 \leqslant 2.1$
- Pre-prime, post boost vaccination would work for $R_0 \leqslant 2.0$
- Reactive and ring vaccination should be started no less than two weeks after the initial case

Conclusions

- Mitigation targeting with limited quantities of vaccine
  - Vaccination school children
  - High Risk
  - Essential workforce
- Probably the pre-prime, post boost vaccination strategy is more sure and robust than any other strategy