Modeling the Spread and Control of Infectious Diseases: An example on Influenza Pandemic

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Prague, ISCB 2009

What is the definition of "pandemic"?

- From Greek words:

  pan + demos
  (All) (people)

- WHO definition

  "A disease epidemic occurs when there are more cases of that disease than normal. A pandemic is a worldwide epidemic of a disease. An influenza pandemic may occur when a new influenza virus appears against which the human population has no immunity"

Are influenza pandemics similar to each other?

1918 Pandemic (H1N1)

- Higher attack rates in young ages
- 99% of deaths in individuals <65 years

1957 Pandemic (H2N2)

- Much higher attack rates in school children
- <50% of deaths in individuals <65 years

1968 Pandemic (H3N2)

- Similar attack rates in all age groups
- <50% of deaths in individuals <65 years

Imply different approaches to mitigation

What are the characteristics of the current pandemic?

Novel H1N1 influenza

- greater disease burden on people younger than 25 years of age than older people.

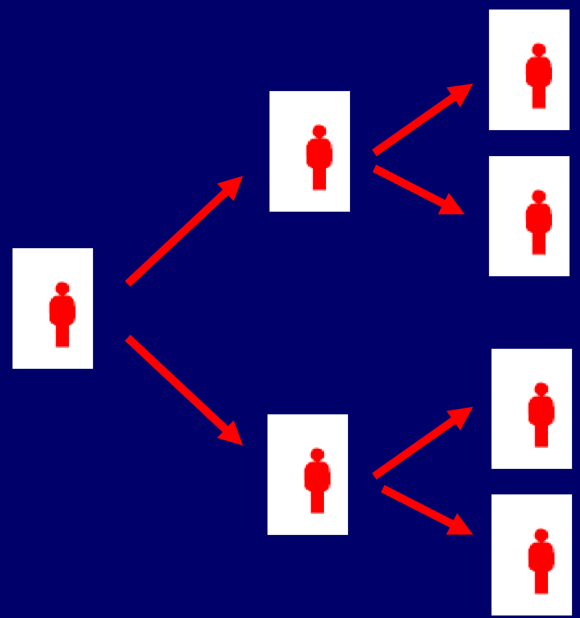
- Low mortality but individuals 25-49 years old more affected

How is containment achieved?

The spread of an infectious pathogen is characterised by
the basic reproduction number R_0

The average number of secondary cases generated by a single case in an entirely susceptible population

e.g. $R_0 = 2$



R_0 in influenza as compared to other infectious diseases

Measles	12-18
HIV	2-5
SARS	2-5
Influenza (1918) Influenza (1968) Influenza (2009)*	2-3 1.9 1.5

* Fraser et al, Science, May 2009

How is containment achieved?

If a pathogen is introduced in the population:

$R_0 > 1$: it will probably cause an epidemic

$R_0 < 1$: no epidemic

↓

Control policies aim at reducing $R_0 < 1$

What does R_0 depend from?

$$R_0 = D \times C \times p$$

- **D** → Duration of infectivity
  - Antiviral treatment
- **C** → Contact rate
  - Quarantine
  - School closure
  - Social distancing
- **p** → Probability of transmission per contact
  - Vaccination
  - Antiviral treatment
  - Antiviral prophylaxis

Approach to simulate influenza spread and assess the impact of control strategies

Stochastic individual-based simulation model

1. Generate a structured community to match the age-distribution, household size and number/size of schools (divided in 4 neighborhoods of equal size)

2. Make assumptions about the natural history of influenza (latent and infectious period)

3. Introduce influenza at day 0 by assigning a number of initial infective individuals

4. Use person-to-person transmission probabilities per day to simulate influenza spread

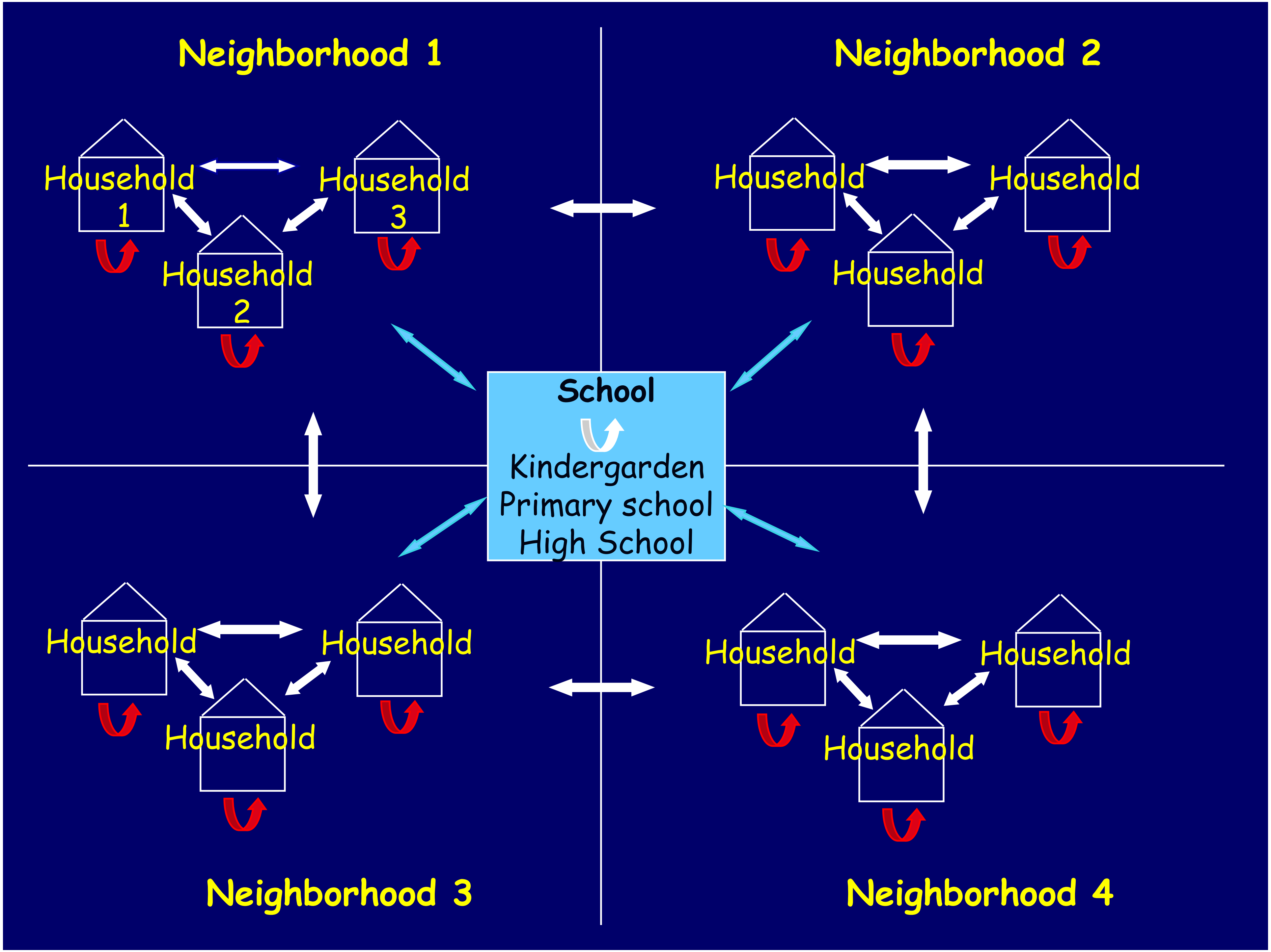
(Sypsa and Hatzakis, Eurosurveillance, 2009)

Model calibration

- Family transmission probabilities were taken from the literature (Longini *et al.* 1988; Addy *et al.* 1991)

- Illness attack rates based on the epidemic of novel H1N1 in La Gloria, Mexico (April 2009) as observed in the absence of intervention

0-14 years	61%
15-64 years	30%
65+ years	22%
Overall	39%


Neighborhood 1
Neighborhood 2
Household 1
Household 3
Household 2
Household
Household
Household
School
Kindergarden
Primary school
High School
Household
Household
Household
Household
Household
Household
Neighborhood 3
Neighborhood 4

Probability of infection

e.g. susceptible school child on day *t*

$I_h(t)$, $I_s(t)$, $I_n(t)$, $I_c(t)$: number of infective individuals within household, school, neighborhood and community, respectively

p_h, p_s, p_n, p_c : probability of infection within household, school, neighborhood and community, respectively

Probability of infection

Susceptible school child on day *t*

1. Escape probability

$Q(t) = (1 - p_h)^{Ih(t)} (1 - p_s)^{Is(t)} (1 - p_n)^{In(t)} (1 - p_c)^{Ic(t)}$

2. Infection probability

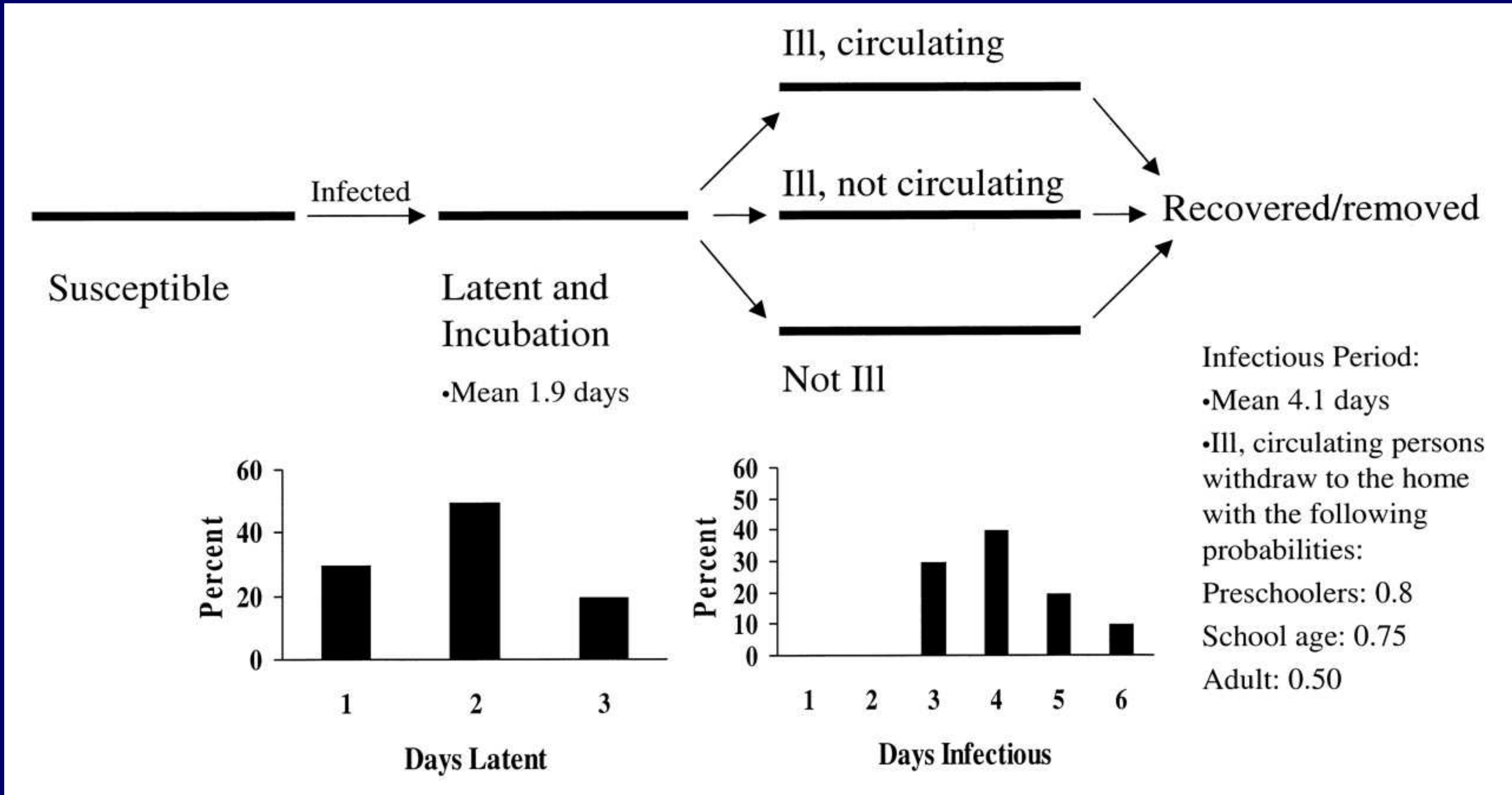
   $P(t) = 1 - Q(t)$

3. Generate random number [0,1]

4. If random number < $P(t) \Rightarrow$ child becomes infected

5. Repeat for every susceptible on day *t*

Natural history of influenza



Longini et al. Am. J. Epidemiol. 2004

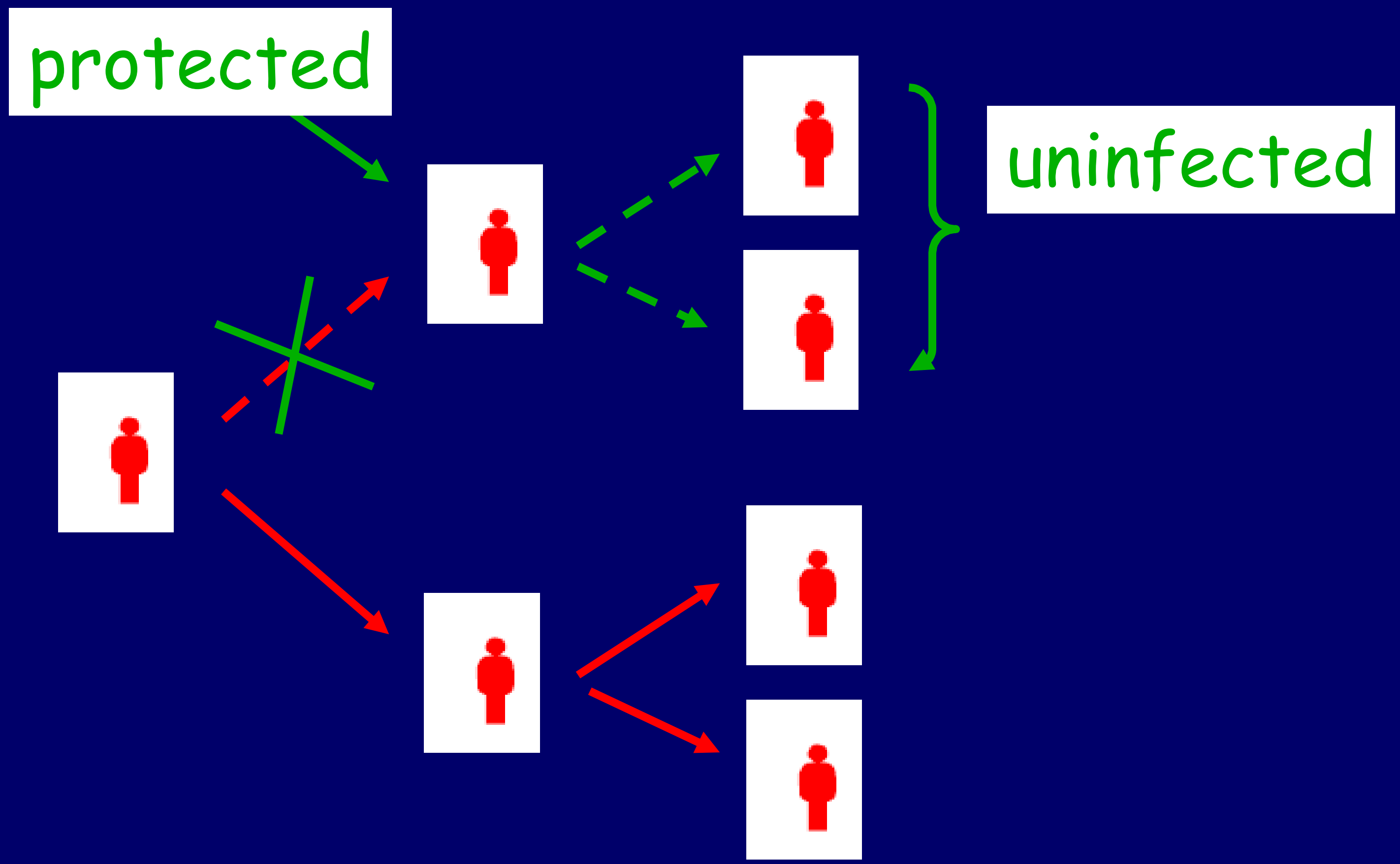
Data on H1N1 and from volunteer challenge studies suggest shorter latent period (assumed=1 day)

Interventions

	Treatment of symptomatic cases (Threshold: 0.05%)	Isolation of symptomatic cases (Threshold: 0.05%)	TAP (Threshold: 0.05%)	Social distancing (Threshold: 1%)	School closure (Threshold: 1%)
	% ascertainment of symptomatic cases / % compliance with receiving treatment	% compliance with staying home	% compliance with receiving prophylaxis	% reduction in community contacts	% of schools closing / % compliance of children with staying home
Scenario 0 (No intervention)	-	*	-	-	-
Scenario 1 (Treat and isolate)	80% / 100%	90%	-	-	-
Scenario 2 (Treat anc isolate, TAP)	80% / 100%	90%	100%	-	-
Scenario 3 (Social distancing)	-	-	-	50%	-
Scenario 4 (School closure)	-	-	-	-	100% / 60%
Scenario 5 (Treat and isolate, Social distancing)	80% / 100%	90%	-	50%	-
Scenario 6 (Treat and isolate, School closure)	80% / 100%	90%	-	-	100% / 60%
Scenario 7 (Treat and isolate, School closure, Social distancing)	80% / 100%	90%	-	50%	100% / 60%

Modeling the impact of interventions

- Indirect effects



Modeling the impact of interventions

- Antiviral treatment
  - Antiviral efficacy for infectiousness

    $AVE_I = 1 - \varphi$

- Antiviral prophylaxis
  - Protective efficacy

    $AVE_S = 1 - \theta$
  - Given infection, antiviral efficacy for infectiousness

    $AVE_I = 1 - \varphi$
  - Given infection, antiviral efficacy for illness

    $AVE_D = 1 - \psi$

e.g. for a susceptible school child on antiviral prophylaxis

- $AVE_S = 1 - \theta$, $AVE_I = 1 - \varphi$

- Ih(t), Is(t), In(t) , Ic(t): number of infected individuals in household, neighborhood, school , community who <u>do not receive antiviral treatment</u>

- Ihav(t), Isav (t), Inav (t) , Icav (t): number of infected individuals in household, neighborhood, school , community <u>on antiviral treatment</u>

e.g. for a susceptible school children on antiviral prophylaxis

- Escape probability

$$Q(t) =$$

Escape prob. from infected persons
<u>not on treatment</u>

$$(1 - \theta p_h)^{Ih(t)} (1 - \theta p_n)^{In(t)} (1 - \theta p_s)^{Is(t)} (1 - \theta p_c)^{Ic(t)}$$

$$(1 - \theta \varphi p_h)^{Ihav(t)} (1 - \theta \varphi p_s)^{Isav(t)} (1 - \theta \varphi p_n)^{Inav(t)} (1 - \theta \varphi p_c)^{Icav(t)}$$

Escape prob. from infected persons
<u>on treatment</u>

Modeling the impact of interventions

Home isolation of symptomatic cases / of children during school closure

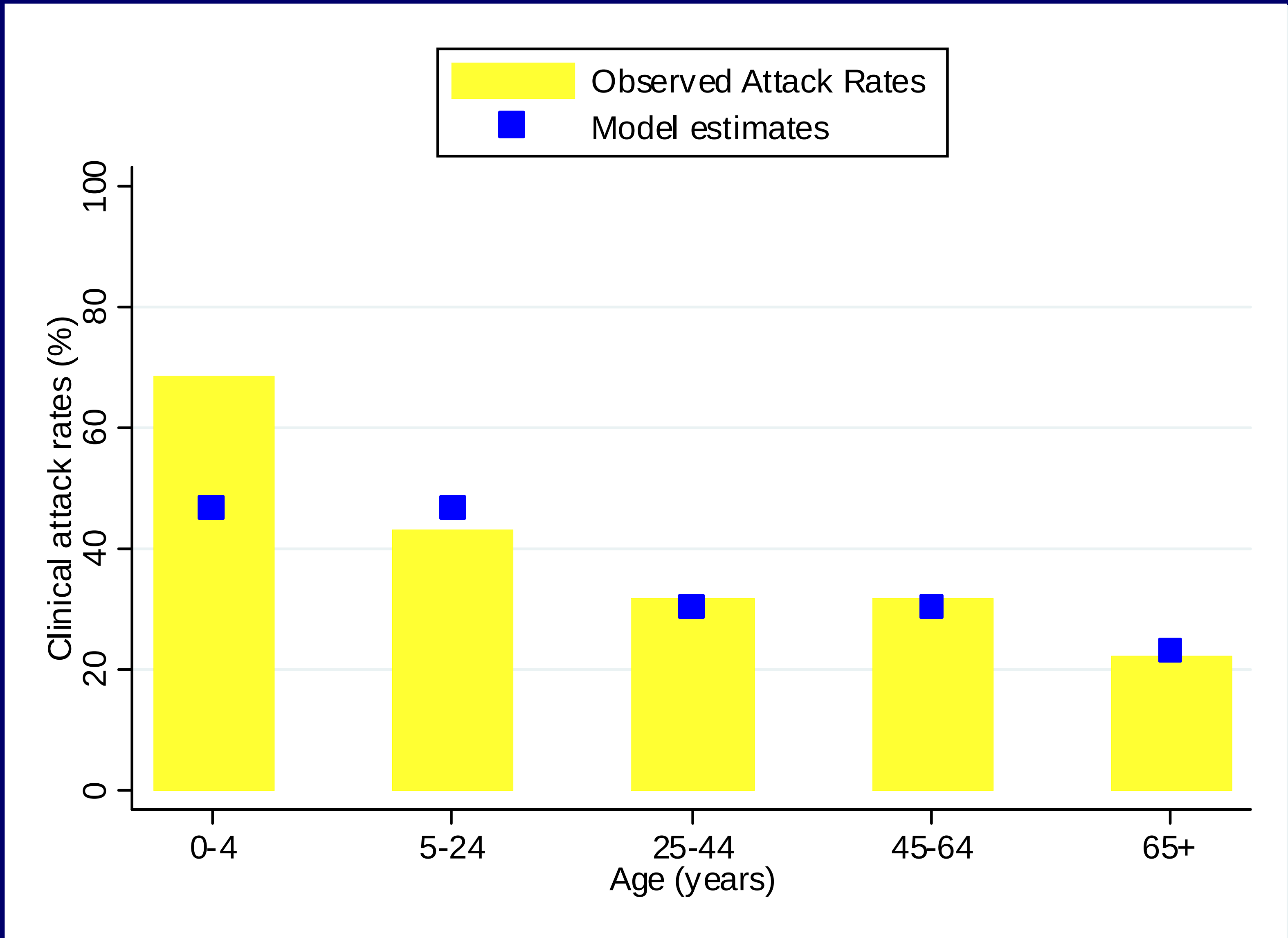
- the compliant proportion stayed at home
- non-compliant individuals continued circulation at neighborhood and community as usual

- During school closure: $Is(t)=0$

Model validation

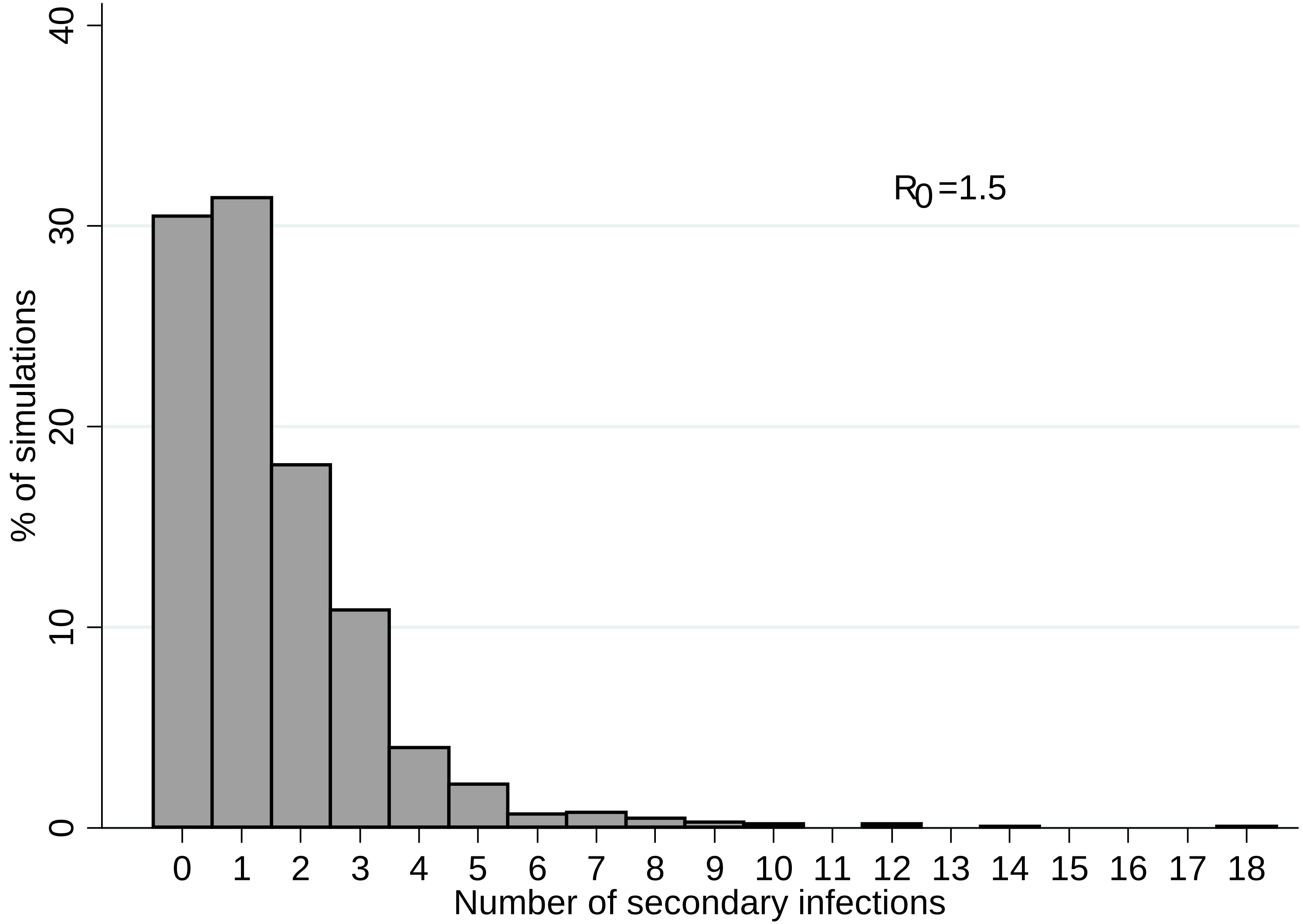
- Check whether the model reproduces key epidemiological parameters of the novel H1N1:
  - Age-specific attack rates
  - R_0
  - Household contact secondary attack rates

Age-specific attack rates observed in LaGloria and model predictions



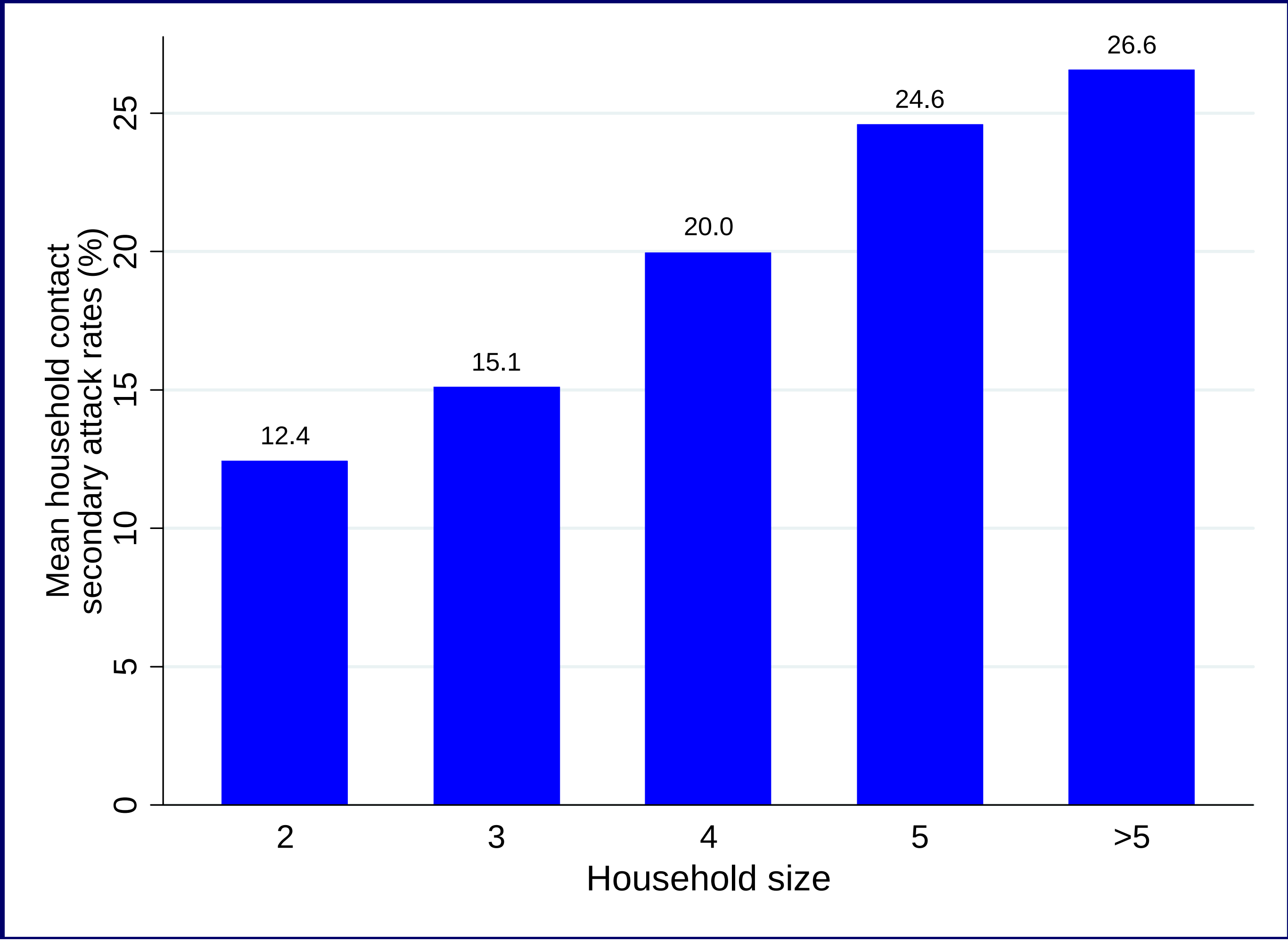
R_0 and model predictions

R= 1.58 (Fraser et al, Science 2009)



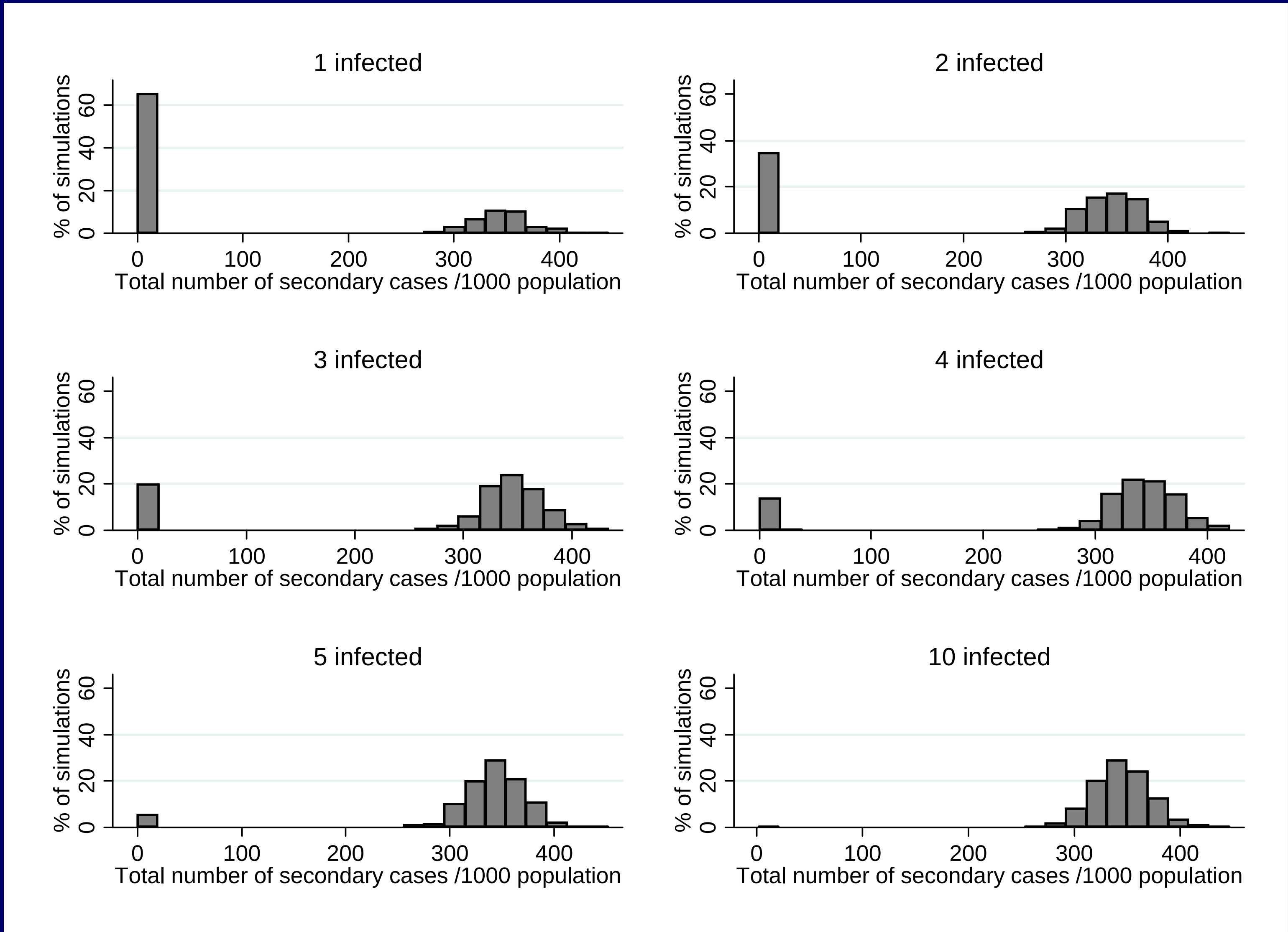
Reported household contact secondary attack rates and model predictions

23% for USA (Ferguson N, SAGE meeting 2009)
22%-33% (WHO, Weekly Epidemiological Record, 2009)

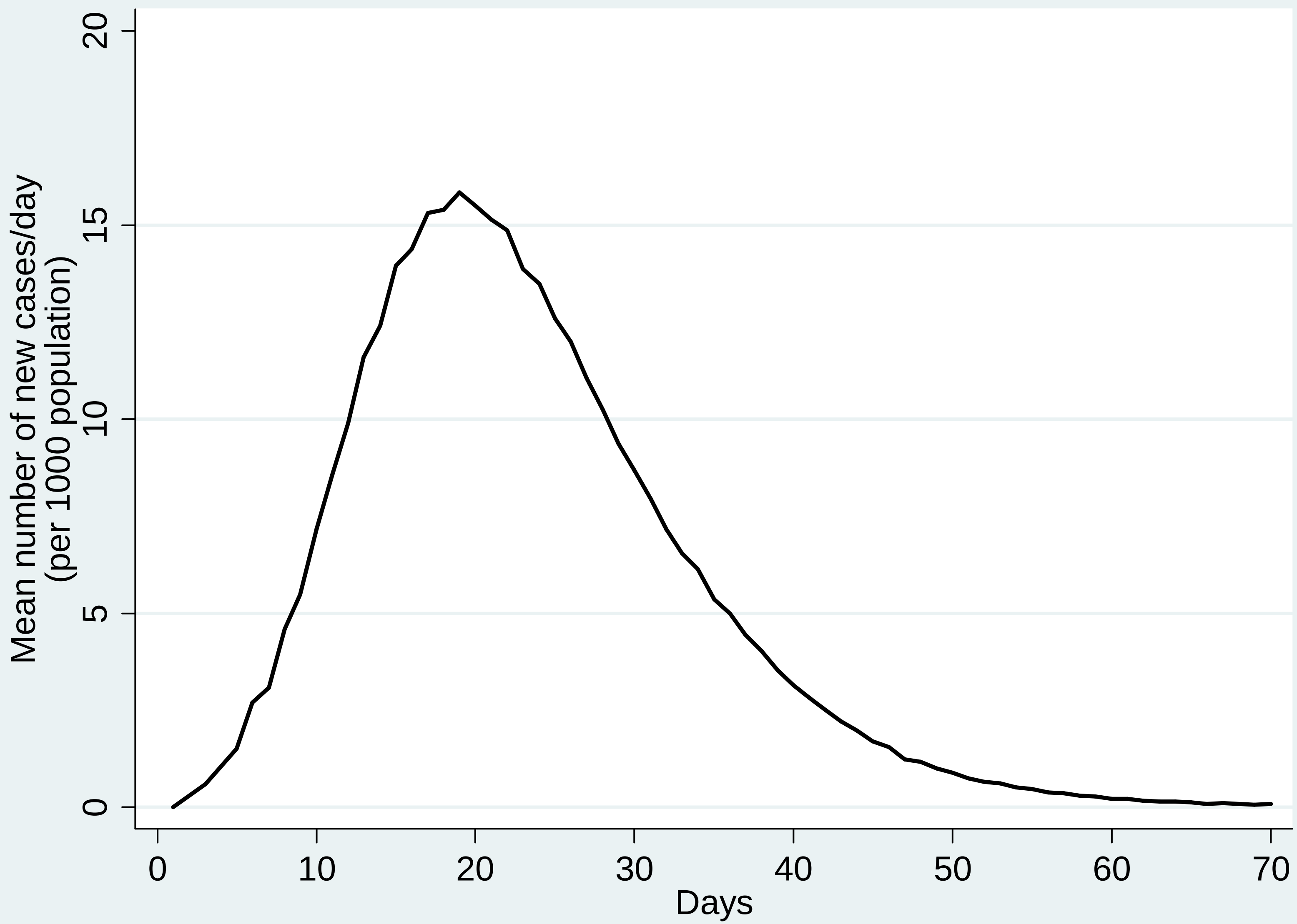


Results

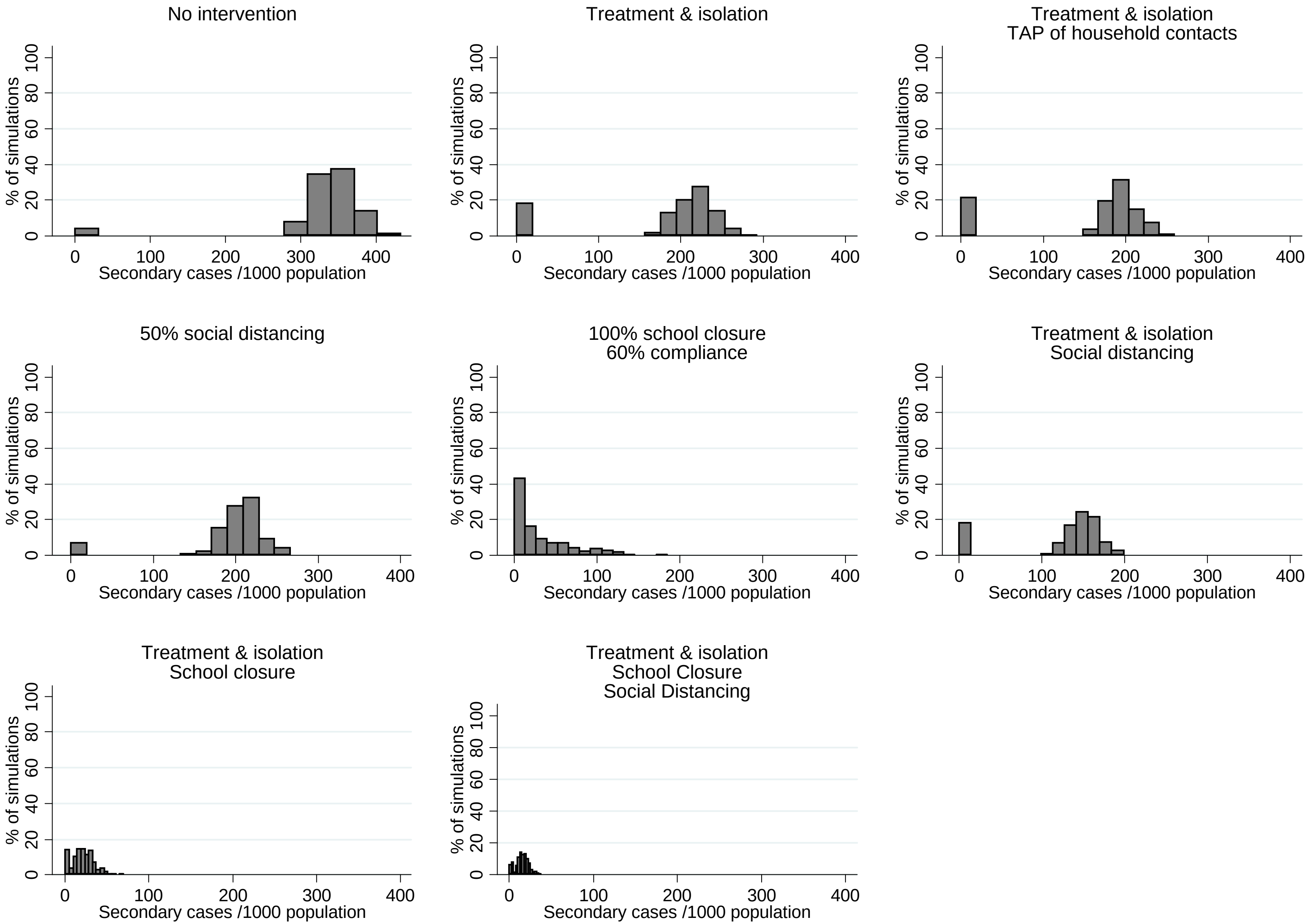
Probability of an outbreak in the absence of intervention according to the initial number of infected individuals



H1N1 epidemic curve in the absence of intervention



Distribution of the total number of secondary symptomatic cases by intervention



Discussion

Limitations of our analysis:

- Small community model
  - Predicted peak and duration do not apply for the whole country BUT an epidemic in a country occurs in subpopulations or regions at different times
- Workplaces not modeled
- After initial infected persons seeded inot the population, the community remains "isolated"

Discussion

- School closure needs further analysis
  - Proactive vs. reactive school closure
  - Contact behavior of pupils during school closure
  - Duration of school closure etc....

- Closing schools more effective when R_0 is low and attack rates are high among children (Glass & Barns, Epidemiology, 2007)

Discussion

- Given key epidemiological characteristics of a pandemic, stochastic simulation models are an attractive method to simulate the spread (predict duration, peak etc) in a community with a specified structure (age distribution, schools etc)

- Powerful tool for gaining insight into how the dynamics of an epidemic are affected by interventions.