Health Technology II
Measures against large-scale epidemics：

(1st of 4 lectures)
Mathematical modeling of pandemics

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Goal of the class

To study the roles and the limitations of mathematical modeling in making pandemic-related policies.

Road Map

I) Introduction of Presenter (and Students)

II) Basic Backgrounds of the COVID-19

III) Mathematical Modeling

IV) Discussion

V) Next Week

Presenter's introduction

- 1st MD, PhD (health economics) among 300,000+ MDs in Japan

- Medical resident (orthopedic surgery) in Japan
  → MS (Harvard Univ.) PhD (Johns Hopkins Univ.) in US (since 1995)
  → worked for Stanford Univ. in CA, US federal agency Centers for Disease Control and Prevention (CDC) in GA, Univ. Rochester in NY., Univ. of California Davis in CA,
  → (Since April 2020) Kanagawa University of Human Services

- Research: Preventive behavior change ((a) Infectious Disease (esp. Flu Vaccine) and (b) Chronic disease prevention (esp. Diet and Physical Activity), Tele-health, Workforce supply, Long term care (dementia), Health insurance

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Basic Backgrounds of the COVID-19 (as of May 28, 2020)

(source: WHO website https://www.who.int/emergencies/diseases/novel-coronavirus-2019)

- Global impacts
  - 5.6 M Confirmed cases, 0.25M deaths
- Japan's case
  - 16,683 Confirmed cases, 867 deaths

- No vaccine/treatment confirmed

→ Primary prevention (to reduce infection risk)

- Behavior change to mitigate the negative impacts of COVID-19
  - Social distancing

- (Q for students) Other options?

Basic Measures against the COVID-19

- Primary prevention (to reduce infection risk)
  - Behavior change to mitigate the negative impacts of COVID-19
    - Social distancing (*Long-term* commitment like *obesity prevention*)
    - Vaccination (*One-time* commitment; Simple??: available after spring 2021?)

- Secondary prevention (if close contact w/ infected)
  - Detect early enough to improve outcome

- Tertiary Prevention
  - Treatment after infected & w/ serious symptoms

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III) Mathematical Modeling

-A) Goals

-B) Basic concepts of basic SIR model

-C) Data needed to construct SIR model

-D) More examples

IV) Discussion

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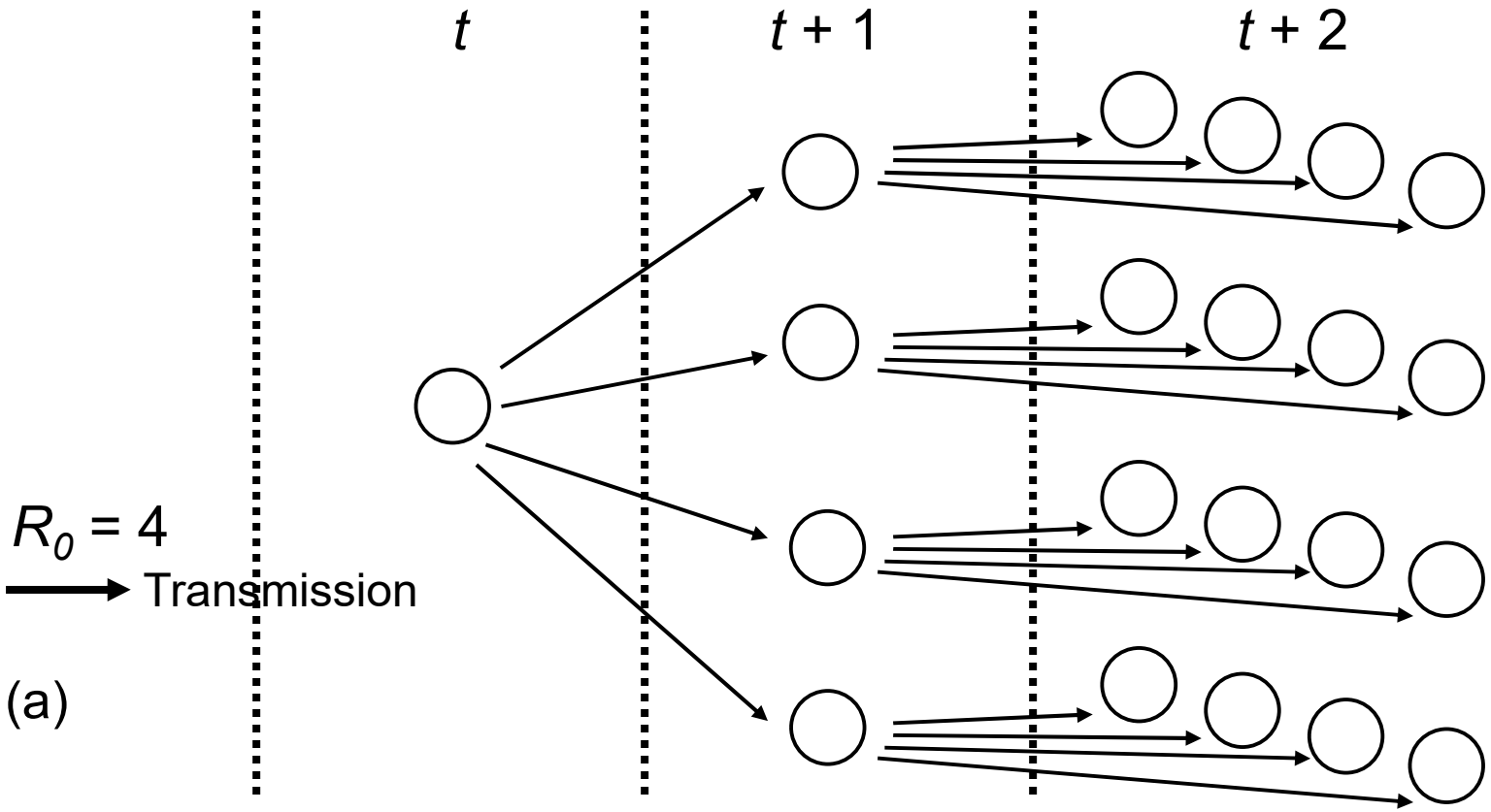
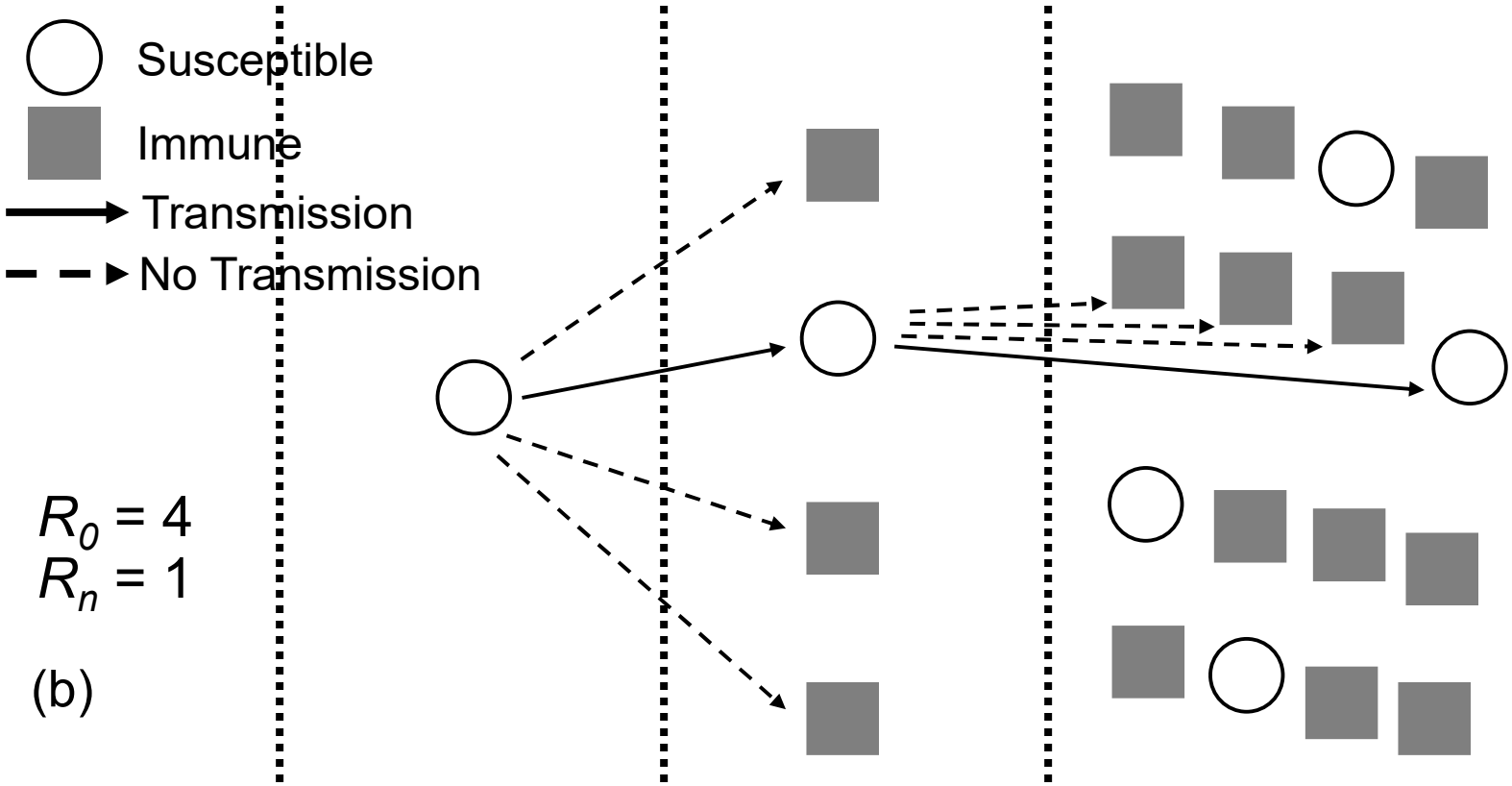
Goals of Mathematical Modeling 1 of 2

	Epidemic path/impacts	**Specific measures**
Evaluation	Past/Current Severity Ex. Reproduction number/rate	• Vaccination • Social distancing (Quarantine facilities; lock-down office, school, etc.) • Treatments (?) • Other measures (?) • (NOTE) In general, very difficult to evaluate specific measure effectiveness.
Prediction	Future Severity [absolute # of cases, % population] and Timing/Period [when] Ex. Infected, Clinic visits, Hospitalized, ICU use, Death -> Will help prepare resources	

Cartoon illustrating implications of a **basic reproduction number of R0=4.**
(a) If the population is entirely "susceptible," incidence increase exponentially, four-hold each generation (until the accumulation of immunes slows the process).
(source: Vyunncyky 2020, p.7)



Cartoon illustrating implications of a basic reproduction number of $R_0=4$.
(b) If 75% of the population is "immune", then only 25% of the contacts lead to successful transmissions and the net (or effective) reproduction number $R_n = R_0 \times$ (s: proportion of population) = 4x25% =1.
(source: Vyunncyky 2020, p.7)



What are the specific policy goals (x3) related to reproduction number? 1of 2

- Goal 1: The net/effective reproduction number Rn < 1

→ The infection will disappear (die down/out)

- Goal 2: Exceed Crude herd immunity threshold (CHIT)

= 1 – (1/R_0)

Ex. Previous slide

when R_0=4 & 75% is immune, Rn=1.

Namely, 75% is the crude herd immunity threshold

What are the specific policy goals (x3) related to reproduction number? 2 of 2

- Goal 3: Immunity by vaccination (or infection?)

→ Vaccination program's target is to vaccine the proportion of "crude herd immunity threshold" (e.g., at least 75% in the previous example) of the total population

- When vaccines are not available yet, what are the options?

  --> National policy to exceed Crude herd immunity threshold by infection?

  – Ex. (past) UK, Sweden and (where else?)

  – → Seriously failed so far,

    due to the collapse of health care (HC) system

    1) Patients beyond the capacity (= excess demand for HC)
    2) HC providers (eg MDs) become infected (= reduced supply of HC)

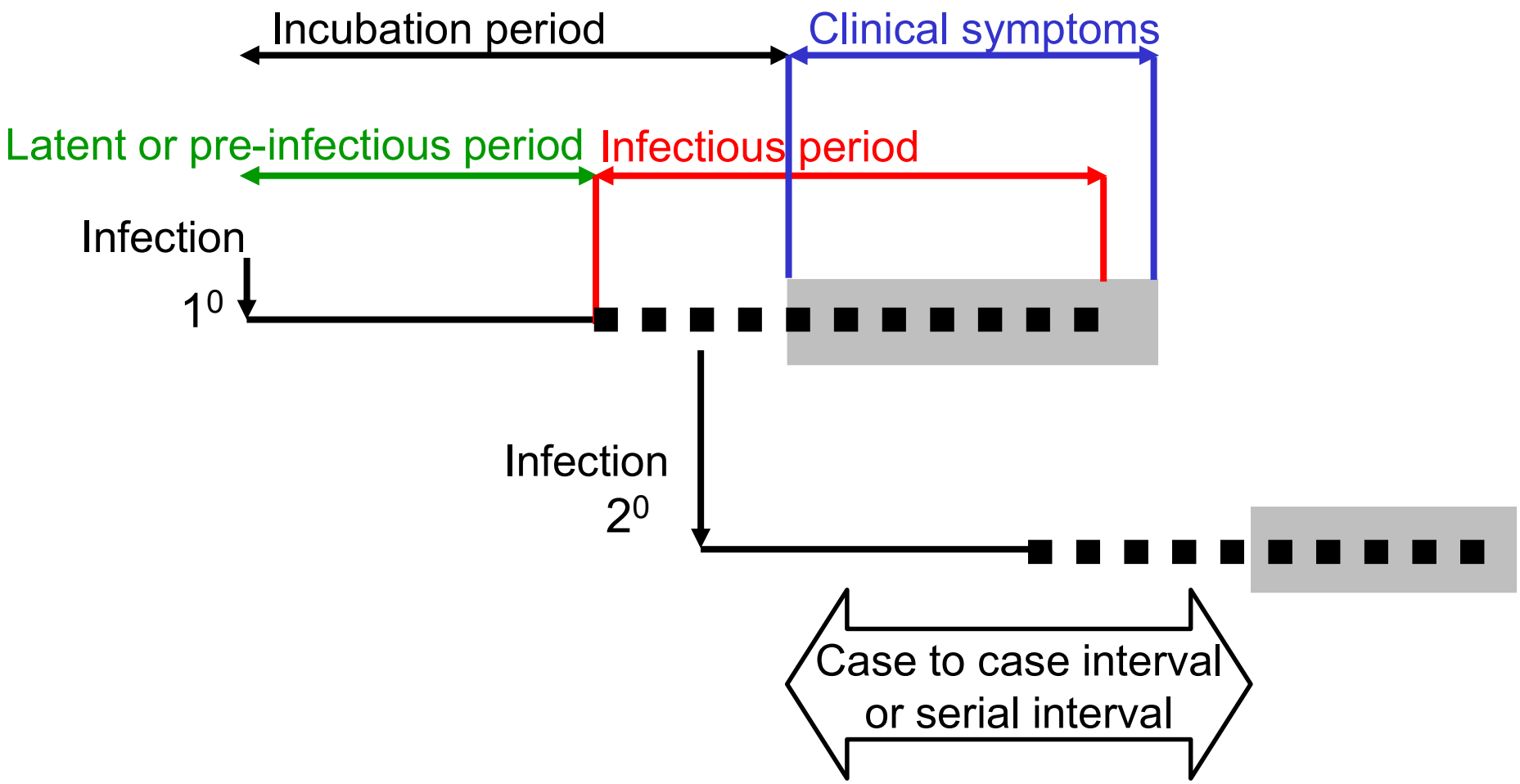
(source: Vyunncyky 2020, p.8)

Table 1.2 Approximate serial intervals, basicre reproduction numbers and implied crude herd immunity thresholds (calculated as 1-1/R_0) for common potentially vaccine-preventable diseases. Estimates drawn from [16, 12, 17, 18, 19, 20]. Adapted from Fine, 1993.[14]

Infection	**Serial interval (range)**	**R_0**	**Herd immunity threshold (%)**
Diphtheria	2-30 days	6-7	85
Influenza	2-4 days	2-4	50-75
Malaria	20 days	5-100	80-99
Measles	7-16 days	12-18	83-94
Mumps	8-32 days	4-7	75-86
Smallpox	9-45 days	5-7	80-85
Tuberculosis§	Months-years	-	-

§ R_0 and herd immunity threshold for tuberculosis are not well defined because of changes in contact over time and the long serial interval, as well as controversial issues over immunity and the extent of reinfection.

Summary of the definitions of the pre-infectious (latent), incubation and infectious periods for an infection. The dotted lines refer to the infectious period and the **shaded blocks refer to clinical disease**. (source: Vyunncyky 2020, p.3)

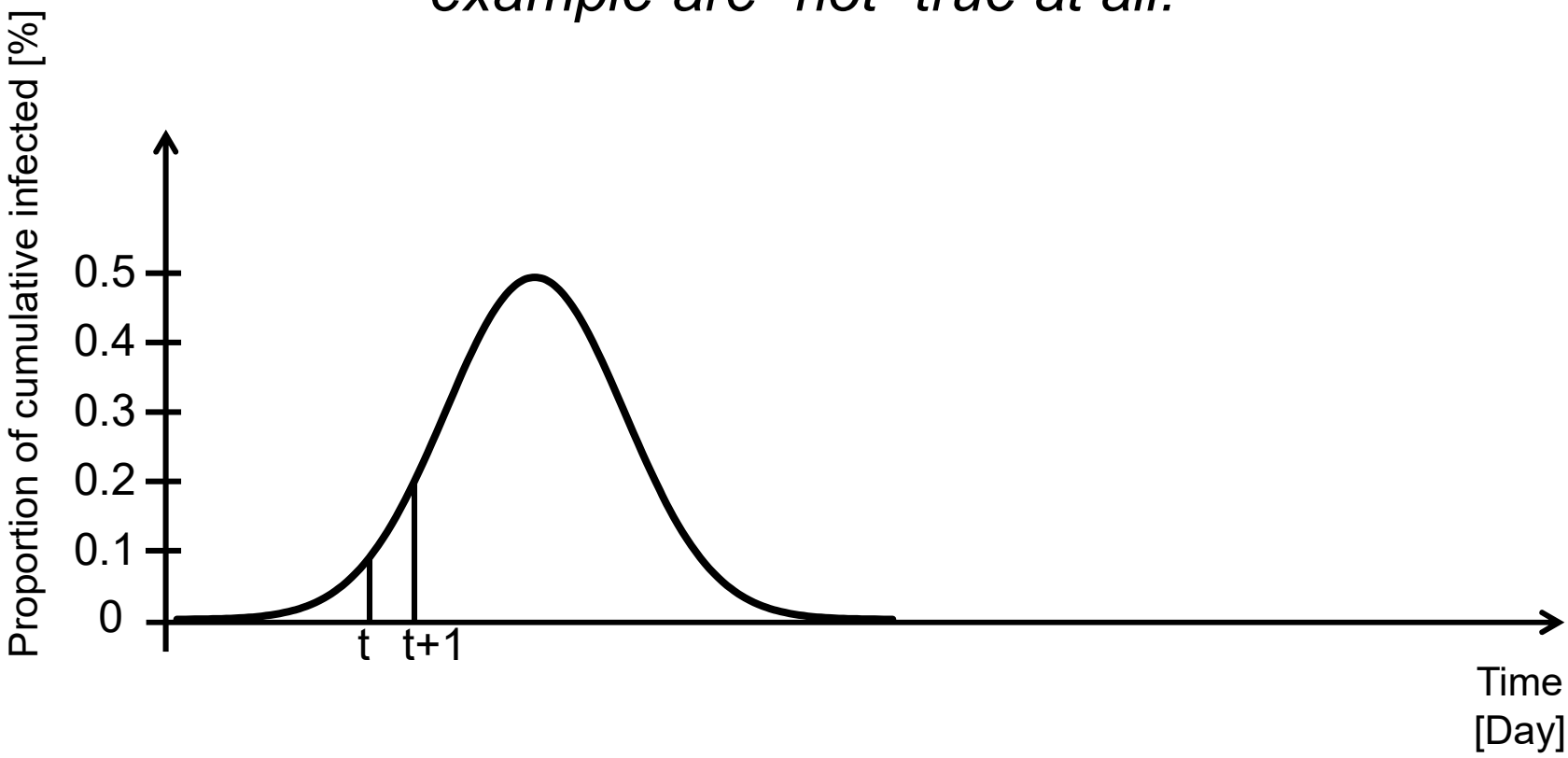


(*) Hypothetical illustration of an epidemic path

Y axis = Proportion of infected per day [% total population]

Ex. Y = 0.1% on Day=t, Y = 0.2% on Day=t+1

(*) please note that the numbers in this hypothetical example are "not" true at all.

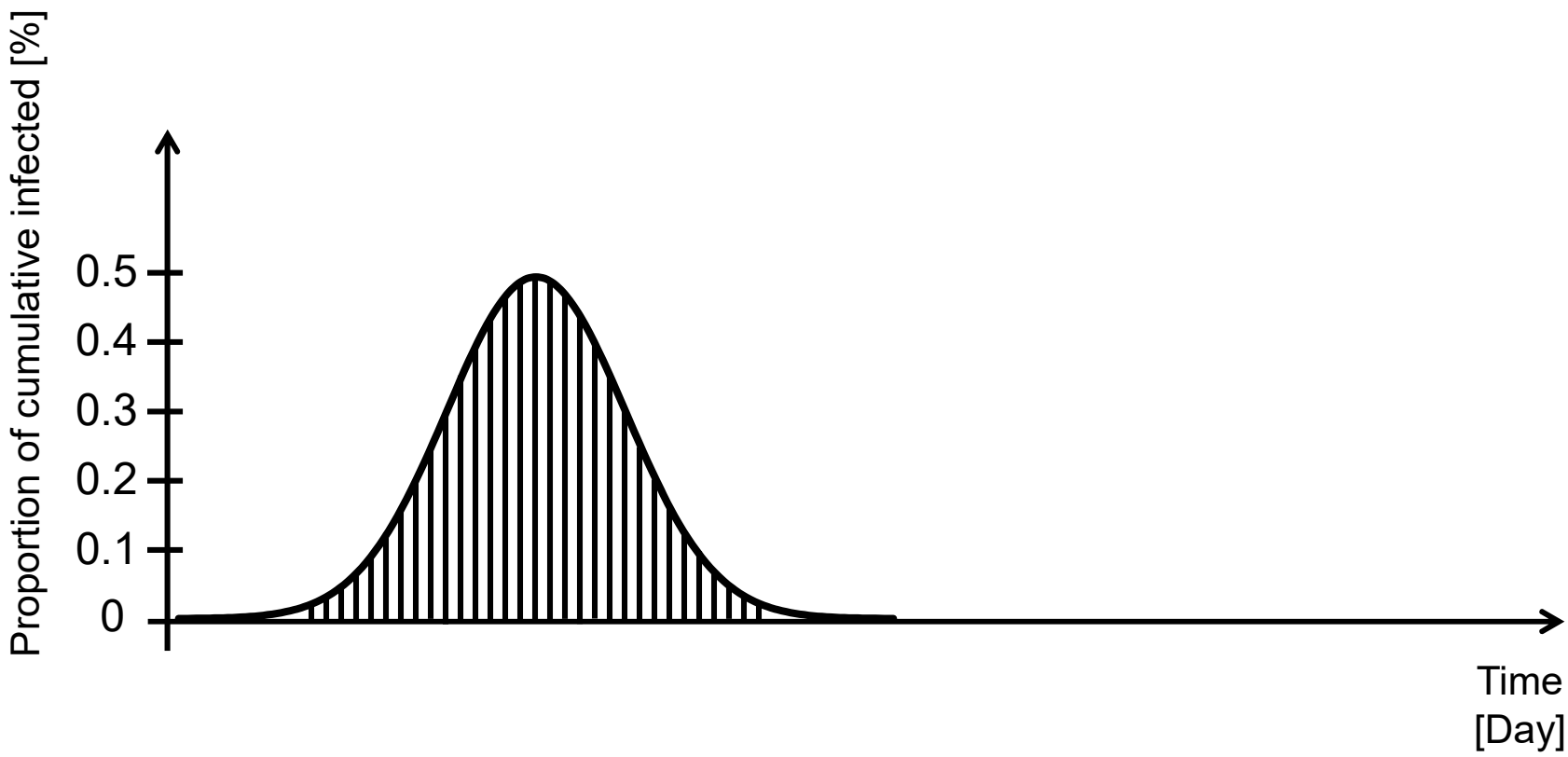


Hypothetical illustration of an epidemic path

Area under the curve (shaded area in Figure)

= Proportion of total infected [% total population]

= sum of Y (Day1) + Y (Day2) + …. + Y (Final Day of an epidemic)



Hypothetical illustration of an epidemic path

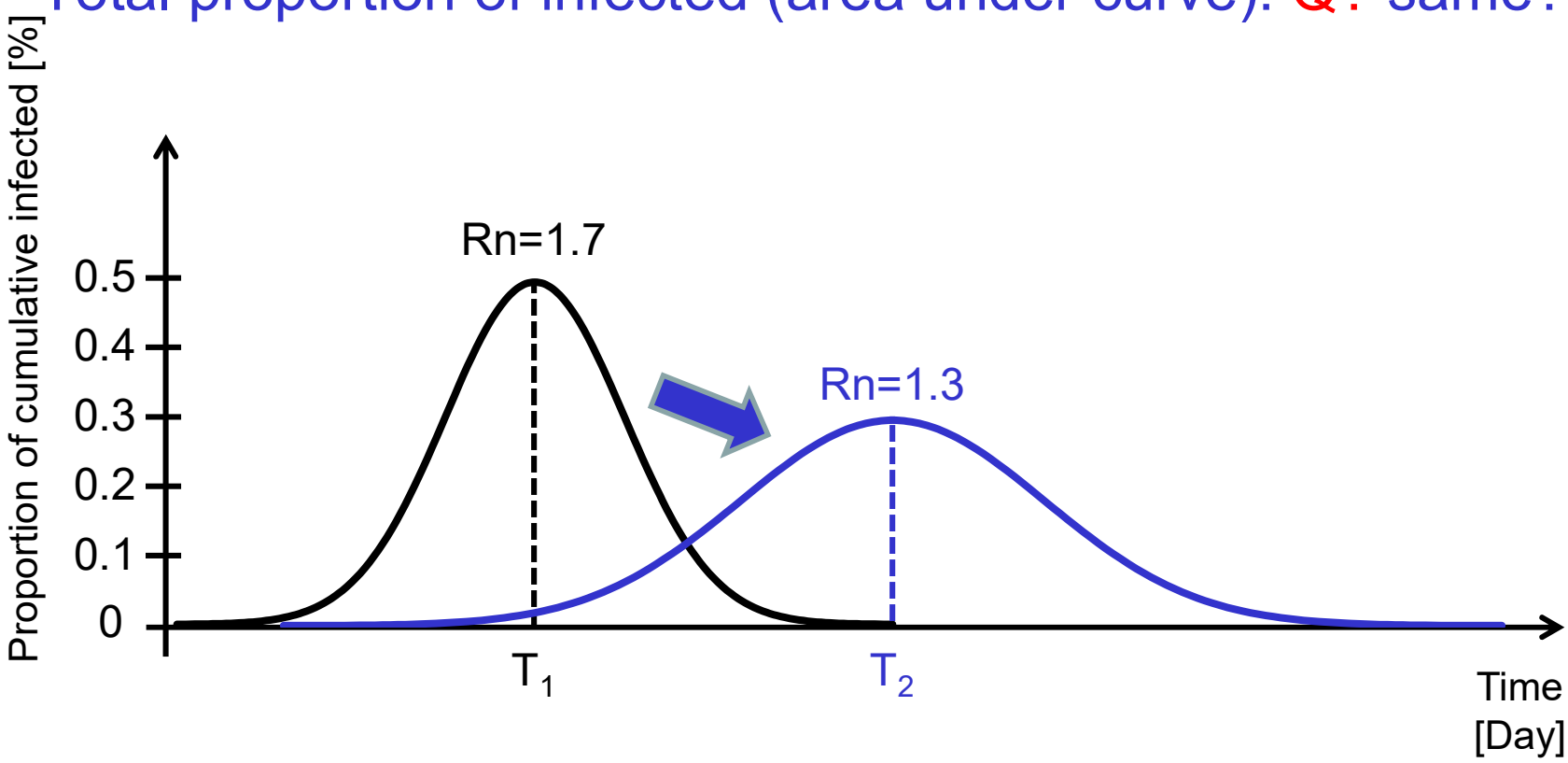
Primary policy goal is to ↓↓net reproduction number (Rn)

Upsurge-Speed: Slower in the lower-Rn-curve

Peak-Timing: Delayed in the lower-Rn-curve (T_2)

Peak-Level: Lower in the lower-Rn-curve

Total proportion of infected (area under curve): Q? same?



Hypothetical illustration of an epidemic path

Primary policy goal is to ↓↓reproduction number (Rn)

Assuming that Rn is constant, no vaccination available

Total proportion of infected (area under curve)

= Crude herd immunity threshold (CHIT)

= 23% (if Rn =1.3), being smaller than 41% (Rn =1.7)

(*Note: Numbers in the table below are "true."*)

Rn	Crude herd immunity threshold (CHIT)
1.1	9%
1.3	23%
1.5	33%
1.7	41%
2.0	50%
2.5	60%
3.0	67%

Hypothetical illustration of an epidemic path

Primary policy goal is to ↓↓reproduction number (Rn)

Peak-Level: Lower in the lower-Rn-curve

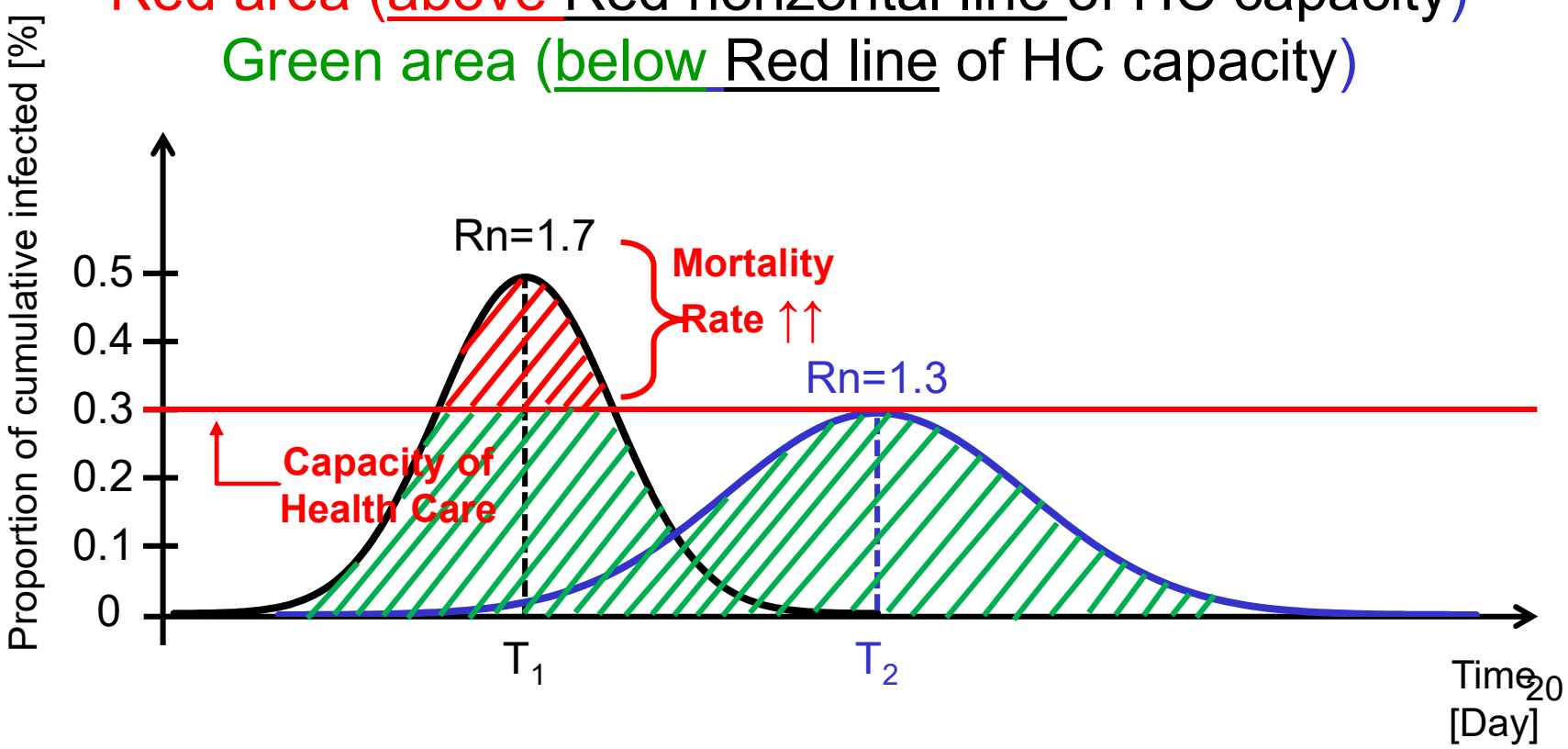
Assuming capacity of health care is 0.3% (eg ICU beds)

The collapse of health care (HC) system:

Mortality rate in Red area > Green area (→*Ethical issue*)

Red area (above Red horizontal line of HC capacity)

Green area (below Red line of HC capacity)



How to reduce the risk of health care (HC) system collapse?

- ↓↓ Reproduction number (RN): Demand Side
  - ↓ infection risk among high risk subpopulations (institutionalized, essential workers)

- ↑↑ Capacity of health care: Supply Side
  - Facility/Equipment: # of beds, respirators
  - Workforce: # of MDs, nurses, labo tech etc.
    - ↓ infection risk of health care workers

Goals of Mathematical Modeling 2 of 2

	Epidemic path/impacts	**Specific measures**
Evaluation	Past/ Current Severity Ex. Reproduction number/rate	• Vaccination • Social distancing (Quarantine facilities; lock-down office, school, etc.) • Treatments (?) • Other measures (?) • (NOTE) In general, it is very difficult to evaluate a specific measure's **unique** effectiveness.
Prediction	Future Severity [absolute # of cases, % population] and Timing/Period [when] Ex. Infected, Clinic visits, Hospitalized, ICU use, Death -> Will help prepare resources	

“Public Avoidance and the Epidemiology of novel H1N1 Influenza A”

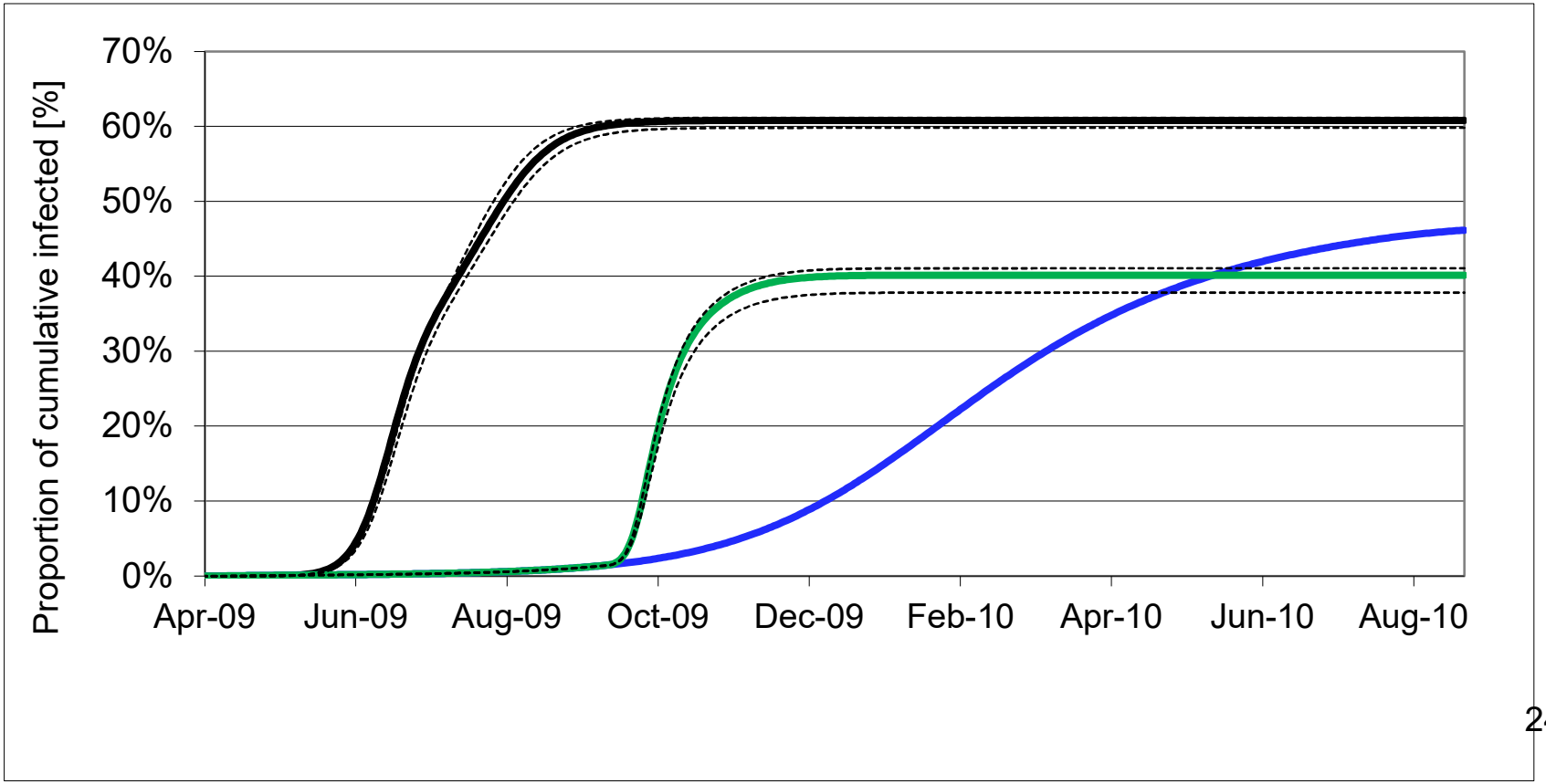
Byung-Kwang Yoo, et al.
National Bureau of Economic Research (NBER) (*)

Working Paper, 2010, (www.nber.org/papers/w15752).

(*) *NBER* is the nation's leading nonprofit economic research organization. 16 of the 31 American Nobel Prize winners in Economics and 6 of the past Chairmen of the President's Council of Economic Advisers have been researchers at the *NBER.*

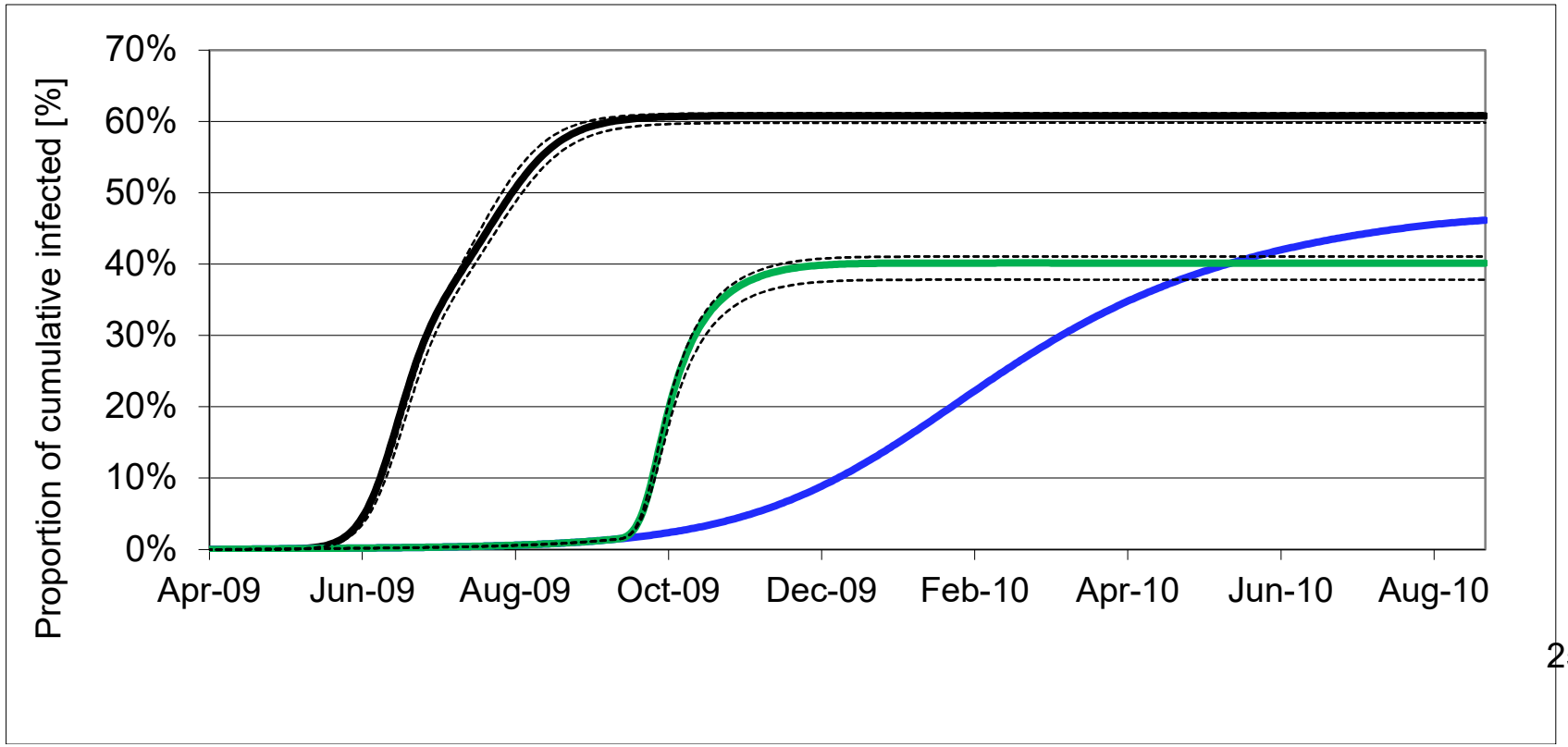
Example 1 of Prediction (Yoo et al. 2010)
Forecast US baseline H1N1 influenza pandemic path:
[Proportion of cumulative infected among total population [%]

3 Predictions of 3 colors based on 3 different scenarios
(due to uncertainties in model assumptions)



Example 2 of Evaluation (Yoo et al. 2010)
Forecast US baseline H1N1 influenza pandemic path:
[Proportion of cumulative infected among total population [%]

The Difference between (Black curve = Predicted a priori) and
(Green curve = Observed after Measure X is conduction) is
"the unique impact of Measure X (e.g., vaccination)"
[% infected↓ & Timing delayed]



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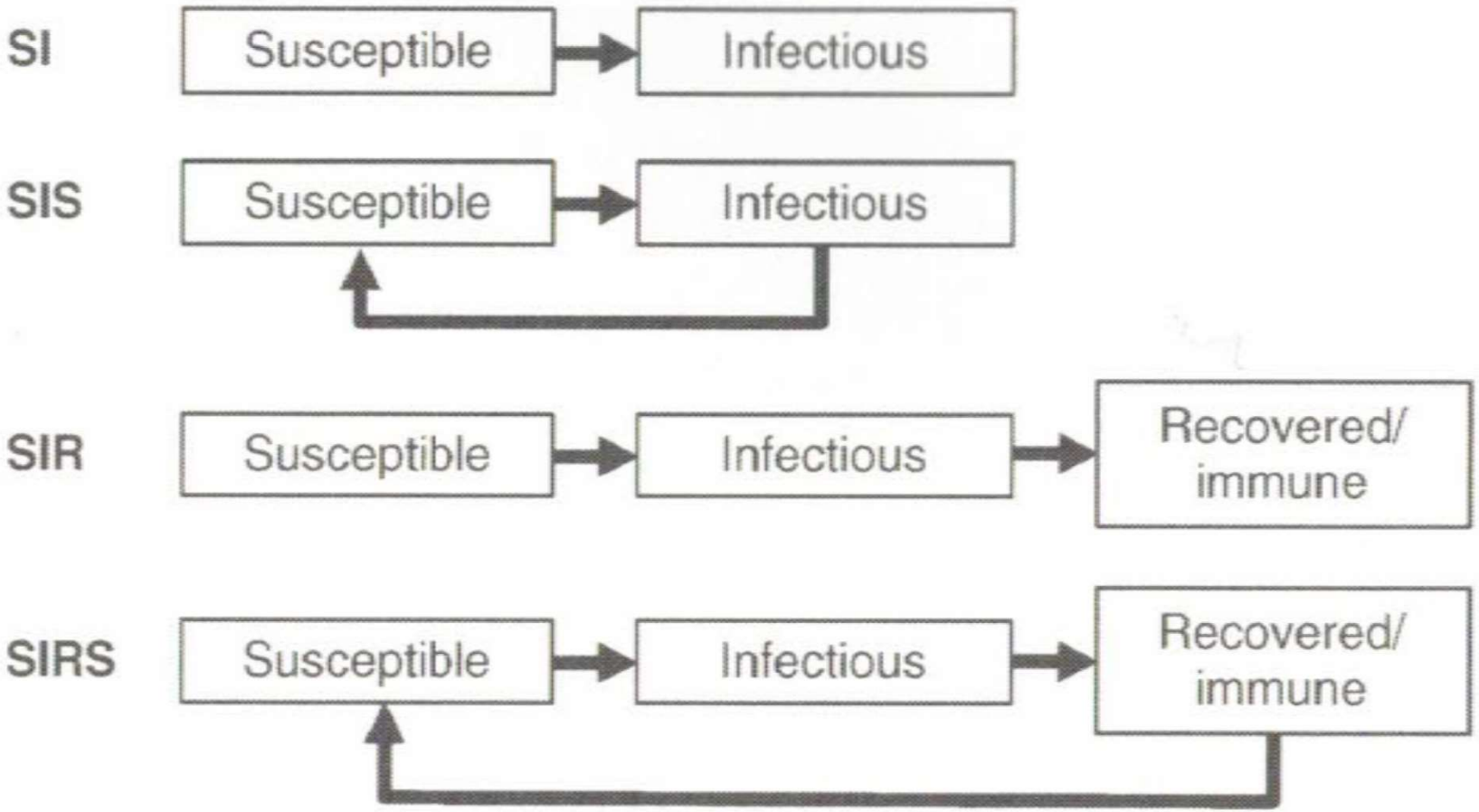
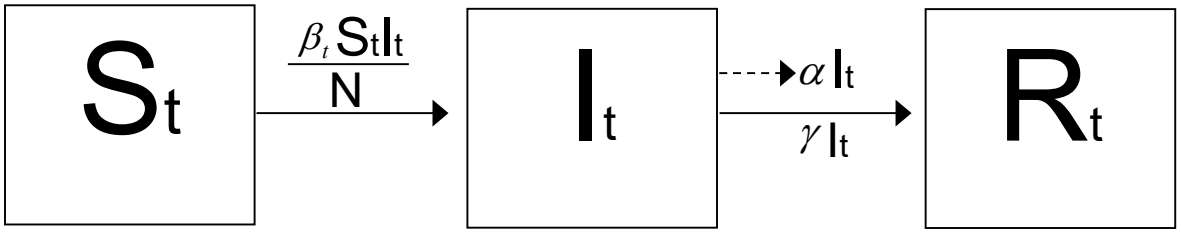
Common structures for models used to describe the transmission of infections.
(source: Vyunncyky 2020, p.16)



3 Compartment Model of Epidemic
Susceptible-Infected-Recovered (SIR) Model



S_t: the number of <u>susceptible</u> people on day t
I_t : the number of <u>infected</u> people on day t
R_t: the number of <u>recovered</u> (immune) people on day t
N: the total state population as of July 1, 2008

α = the case fatality rate β_t = the virus attack rate γ = the recovery rate

2 Components of Disease Attack Rate

Attack rate = product of 2 components

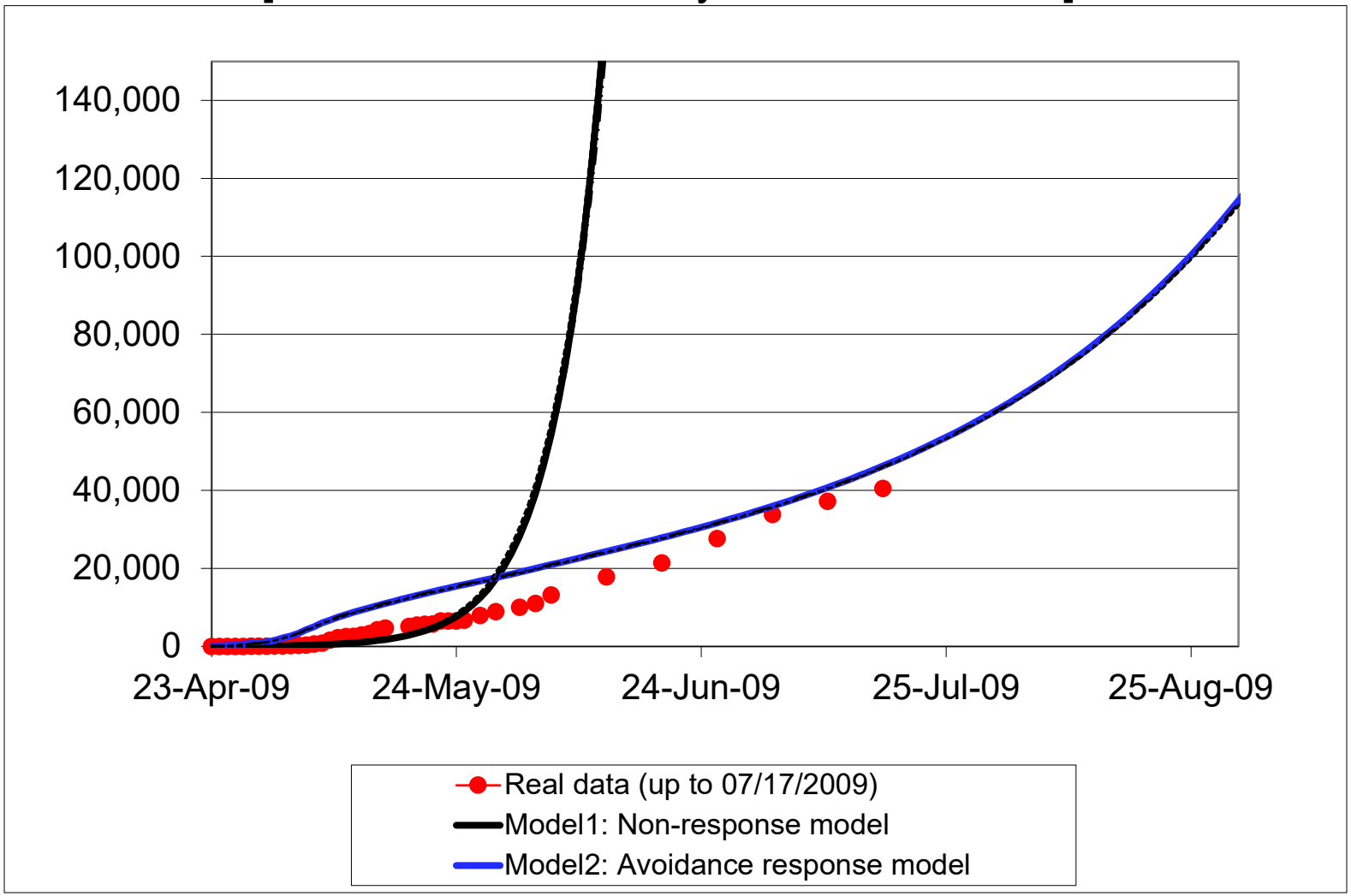
- constant baseline attack rate
  - "biological" transmission rate
  - Same as "basic reproduction number of R_0 in the earlier slide #10)"
- baseline contact frequency
  - differs among subgroups (eg, age, occupation)

Test Validity of Avoidance Response Model:

novel H1N1 influenza epidemic path in the U.S.

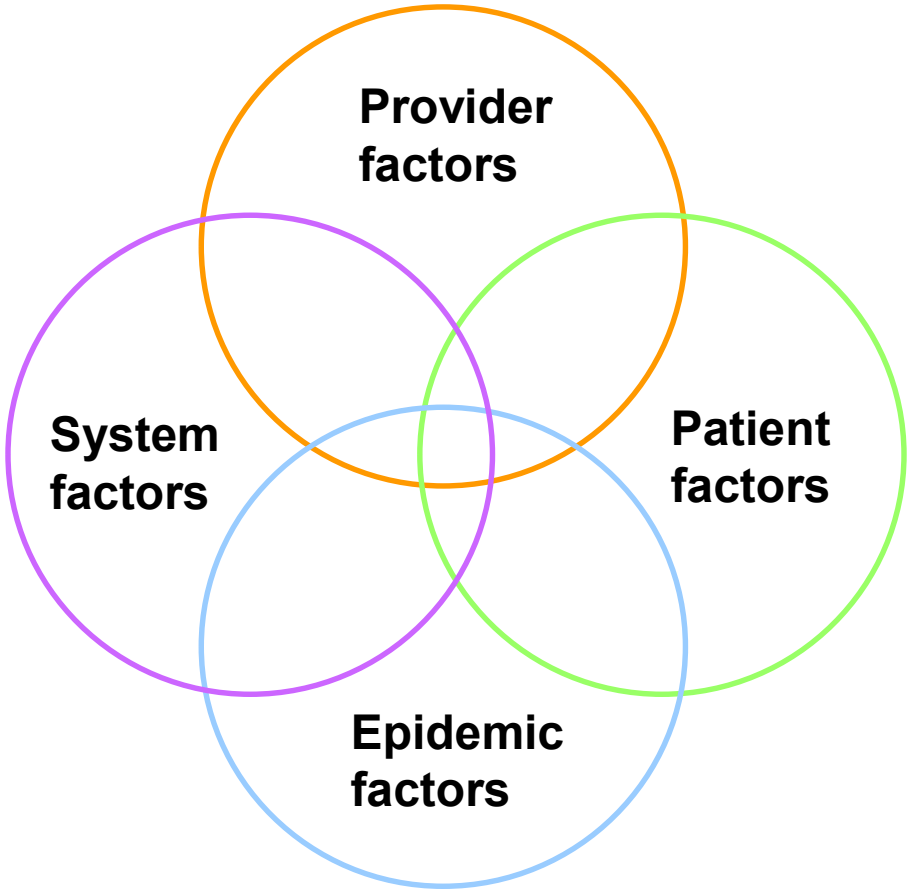
from April 23 to August 31, 2009 (day 86)

[Cumulative laboratory confirmed cases]



Conceptual Framework of Preventive Behavior: Case of Infectious Disease by Yoo (2011)*

Modified (CDC Task Force on Community Preventive Services, MMWR 1999)



(*) Yoo BK, "How to improve influenza vaccination rates in the U.S.," ***Journal of Preventive Medicine & Public Health,*** 2011 Jul;44(4):141-8 Web Link to PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21894062/

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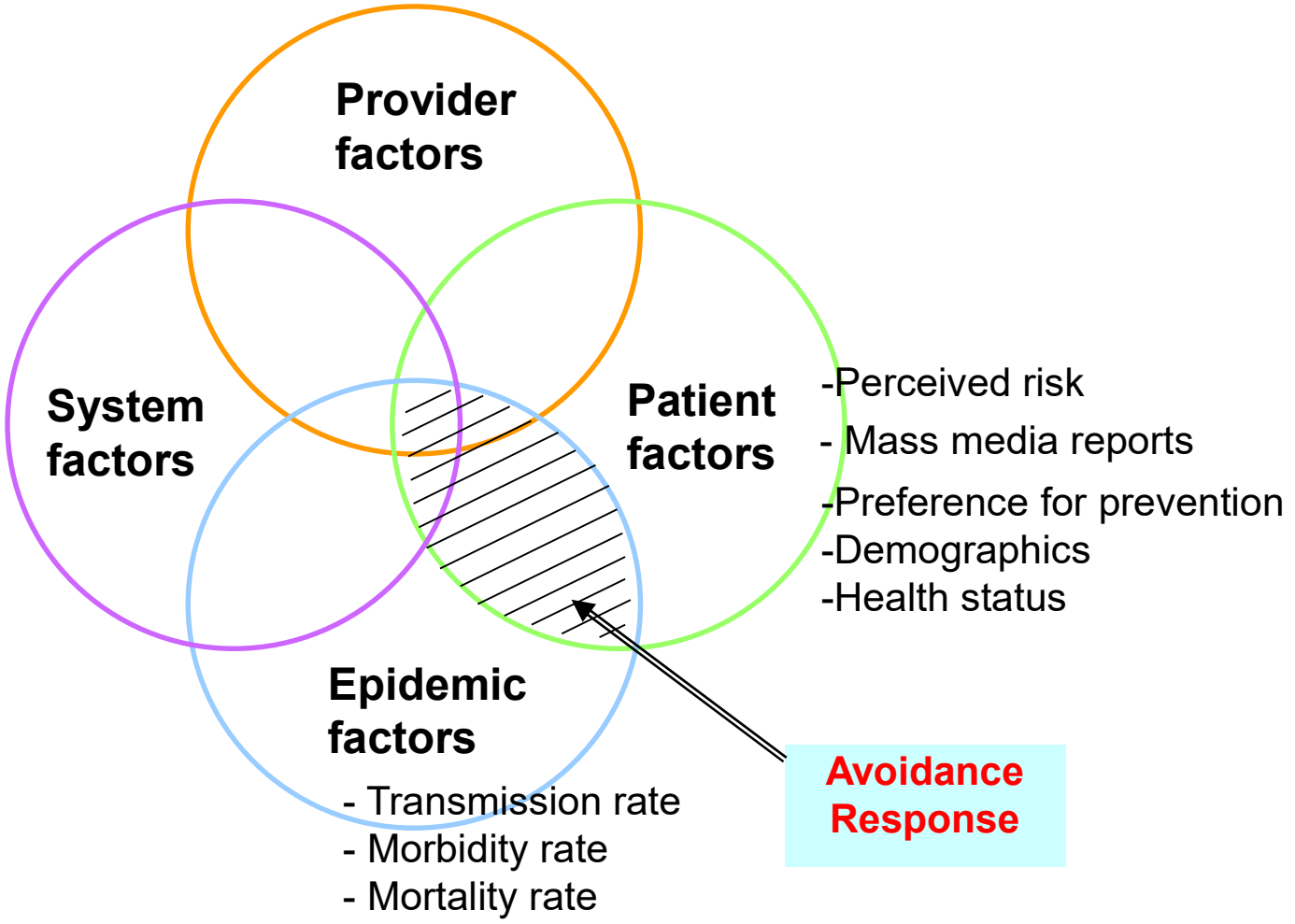
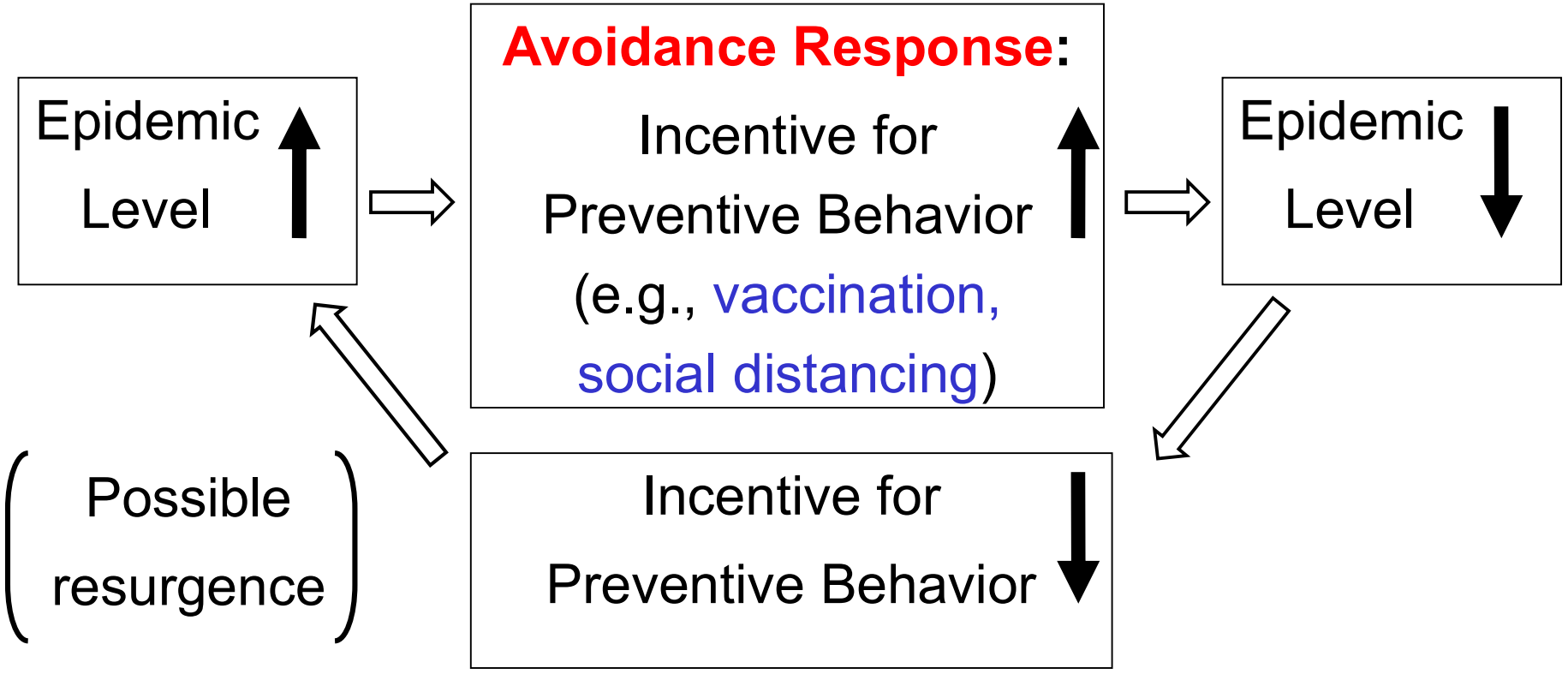


Mutual (cyclic) Interaction between Epidemic Level and Incentive for Preventive Behavior

(Philipson 1996)



3 Components of Disease Attack Rate

Attack rate = product of 3 components

- constant baseline attack rate
  - "biological" transmission rate
- baseline contact frequency
  - differs among subgroups (eg, age, occupation)
- *avoidance response* parameters (original)
  - influenced by the disease prevalence rate [past week, in residential state]

How to empirically measure attack rate and avoidance response?

- Original data from CDC website
  - State level, daily "*cumulative*" confirmed cases

  →Micro-simulation to obtain #s in S/I/R compartments in "*each day*" in each state (200 iterations)

  →Calculate "attack rate", varying daily for each state (panel data: β_{it}, i: 50 states, t: day (from state-onset))

- Regression analysis of panel data

$$\beta_{it} = \beta_0 \exp(c_0 t - m_0 w(I_{it}))$$

m_0 :avoidance response, β_0 : baseline attack rate, w(I): prevalence in past week, c_0 : time factor

The time-variant reproductive rate (RR_t) in Yoo et al (2010), changing every day

(= net reproduction number (Rn) in slides #10-20))

We calculate the time-variant reproductive rate (RR_t) as the product of 3 terms:

the attack rate, the proportion of susceptibles in the total population, and the duration in the infective compartment

$$\beta_t \left(\frac{S_t}{N_t(\gamma + \alpha)} \right)$$

Key assumptions of simulation models

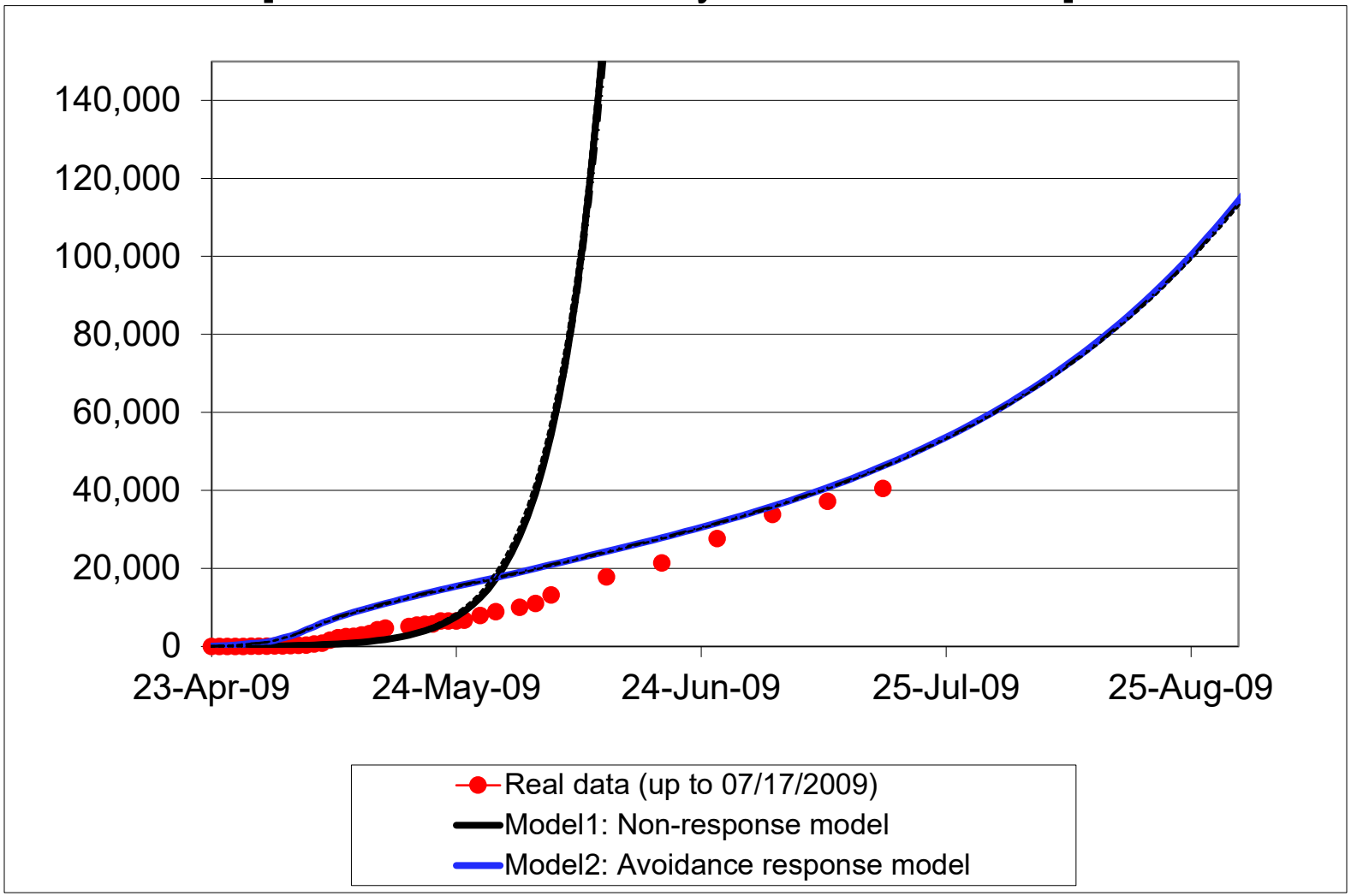
- 3 simulation models in comparison
  - Model 1: Non-response model (without accounting for avoidance response)
  - Model 2: Avoidance response model
  - Model 3: same as Model 2, but assumes a second upsurge started Oct. 1, 2009
- Proportion of labo-confirmed cases among infected
  - 5% (CDC 2009)
- Pandemic influenza vaccine effectiveness
  - 50% (sensitivity analyses in NBER paper)
- Novel H1N1 flu vaccine supply (data as of early Oct. 2009)
  - Oct. 1-7: 1 million; Oct. 8-14: 6 million;
    Oct. 15- Dec. 2: 3 million [doses per day]
  - 196 million doses in total

Test Validity of Avoidance Response Model:

novel H1N1 influenza epidemic path in the U.S.

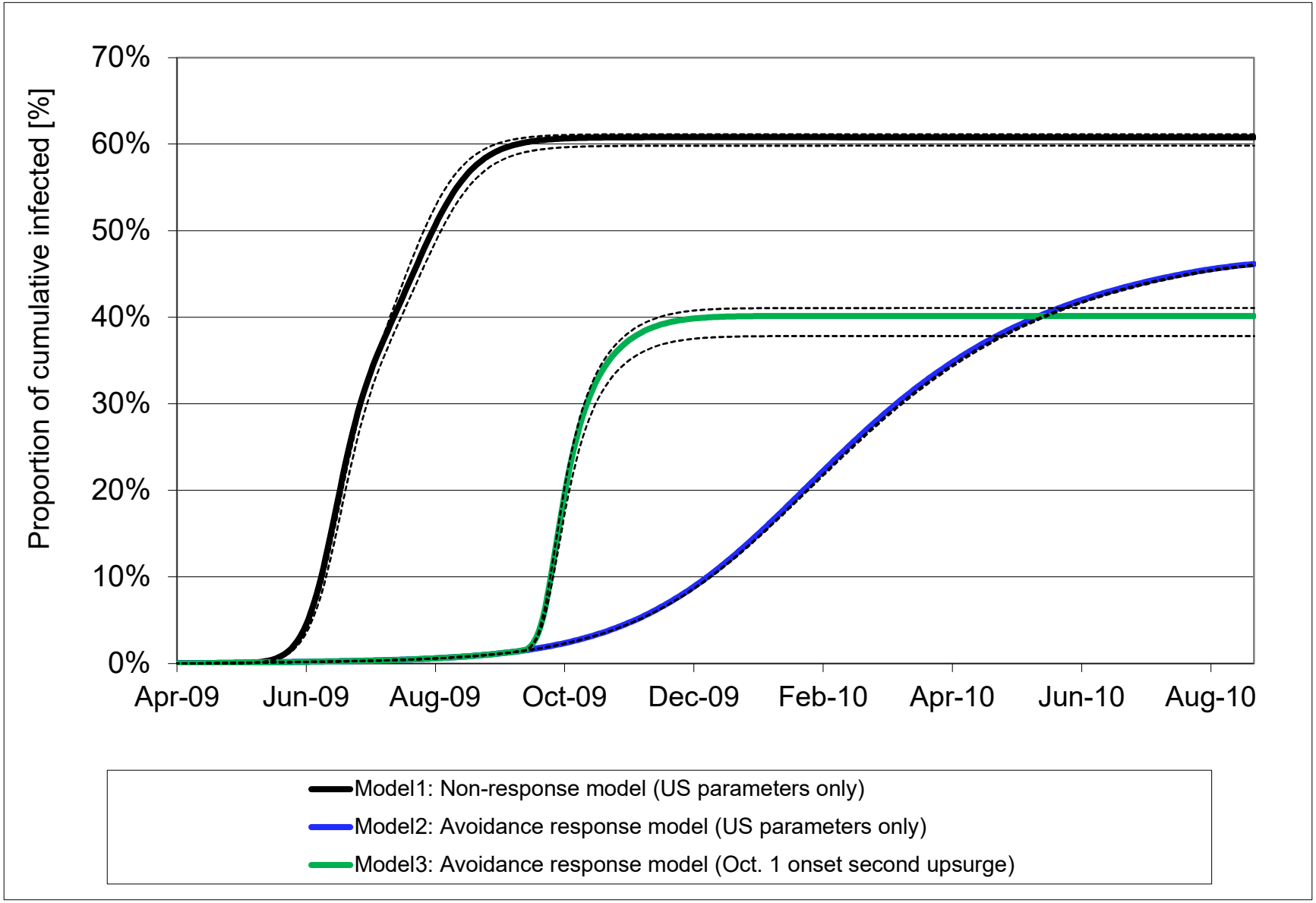
from April 23 to August 31, 2009 (day 86)

[Cumulative laboratory confirmed cases]



Forecast US “baseline” pandemic path: 04/23/09-09/05/10

[Proportion of cumulative infected among total population [%]



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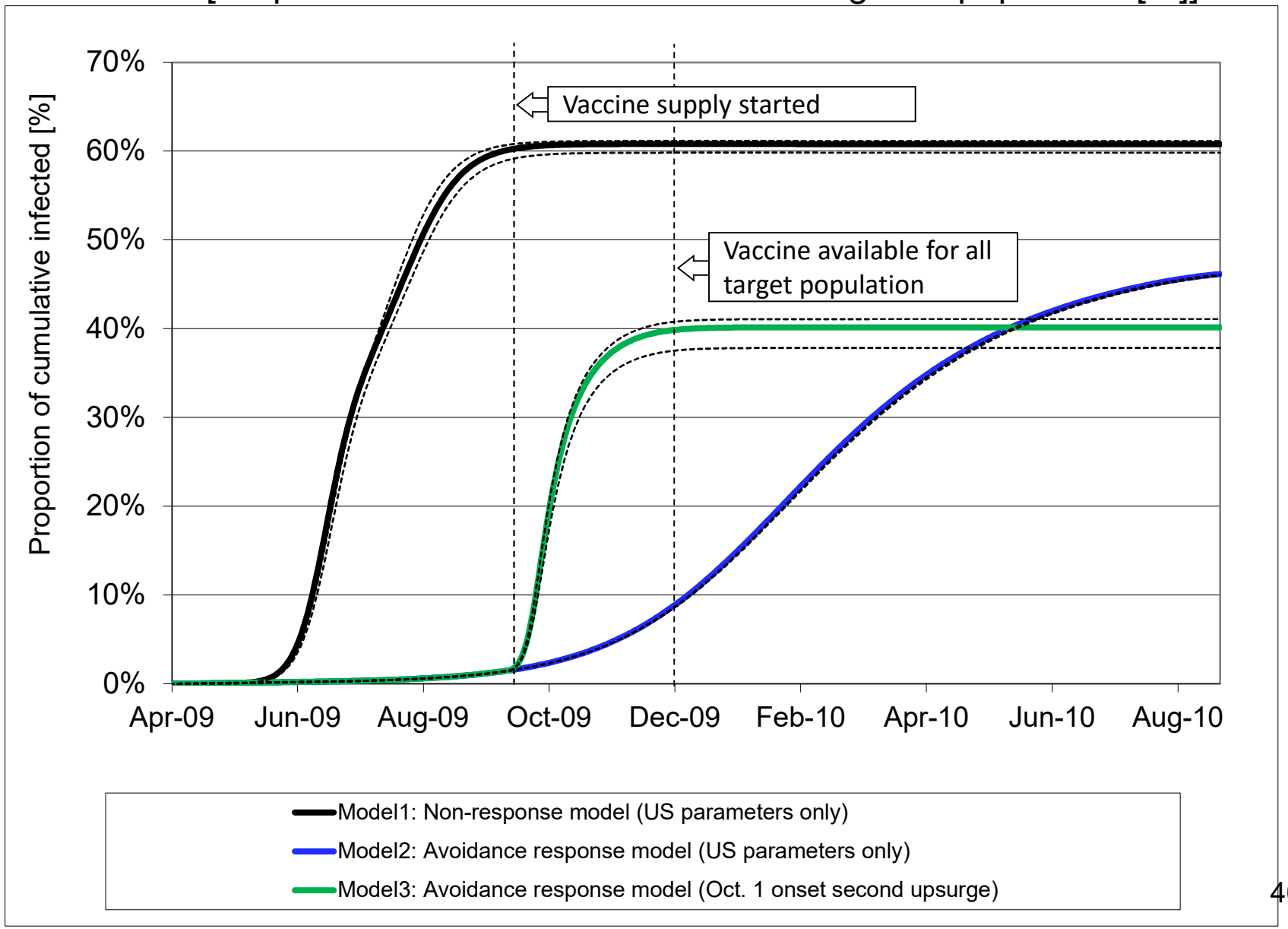

Estimated effectiveness of vaccination programs in 3 Models

Change in the final size [% of cumulative infected among total population]

Model	Model assumptions		Final size	
	Avoidance response	2nd upsurge in Oct. 2009	No vaccination	Change with vaccination
1	No	No	61.1%	0.0%
2	Yes	No	46.2%	-11.6%
3	Yes	No	40.1%	-6.2%

- Pandemic influenza vaccine effectiveness: 50%
  - Vaccine supply (data as of early Oct. 2009): Oct. 1-7: 1 million; Oct. 8-14: 6 million; Oct. 15- Dec. 2: 3 million [doses per day]; 196 million doses in total

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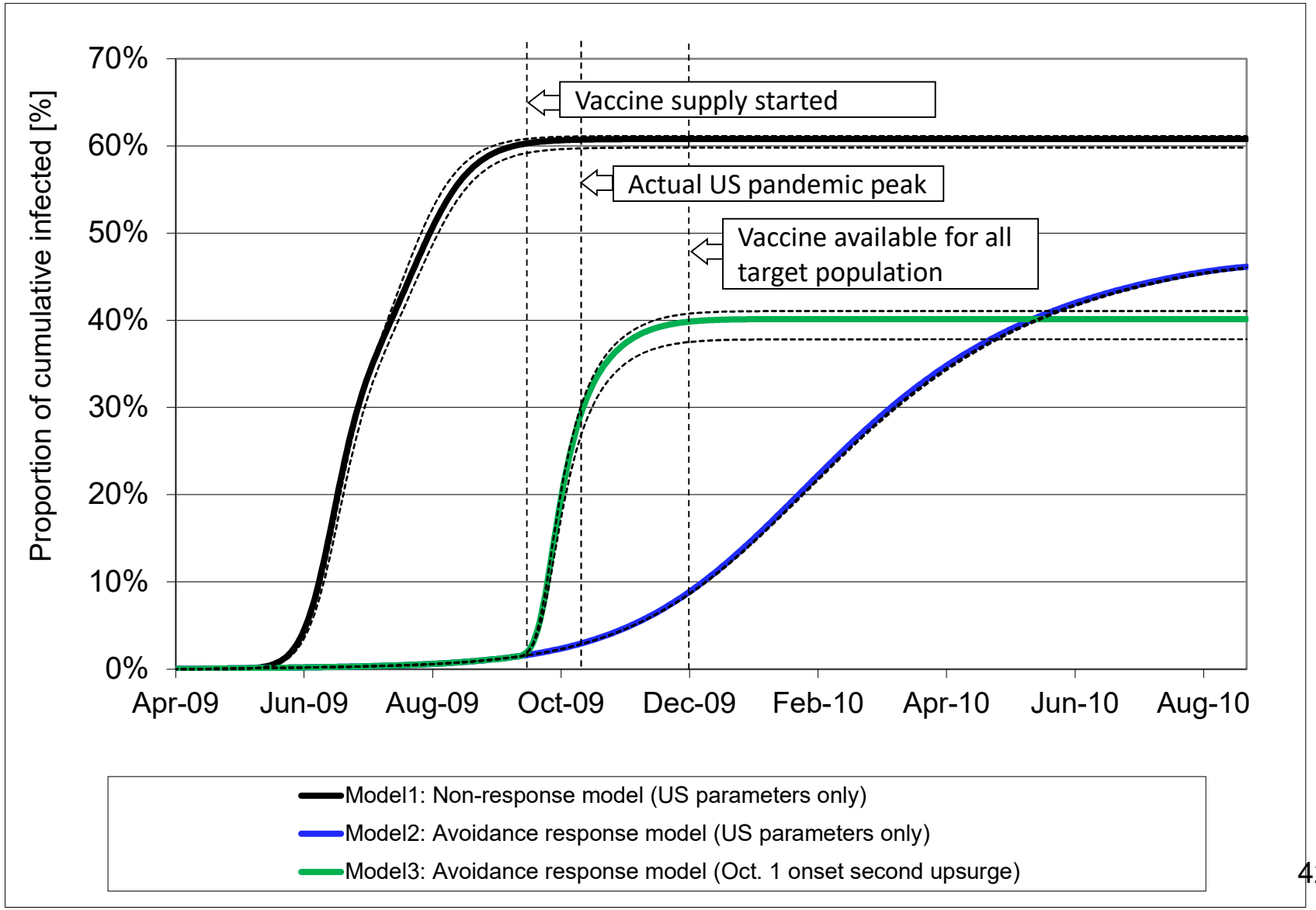

Estimated effectiveness of vaccination programs in 3 Models
Change in Peak Timing (Observed peak = end of Oct. 2009)

model	Final size		Timing of peak	
	No vaccination	Change with vaccination	No vaccination	Change with vaccination
	[1]	[2]	[3]	[4]
1	61.1%	0.0%	7/9/2009	0
2	46.2%	-11.6%	2/13/2010	+30 days
3	40.1%	-6.2%	10/19/2009	-1 day

Model 1: Non-response model (without accounting for avoidance response)
Model 2: Avoidance response model
Model 3: Avoidance response model, with a second upsurge started Oct. 1, 2009

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Most important principle in data analysis

Garbage in, garbage out.

3 Compartment Model of Epidemic
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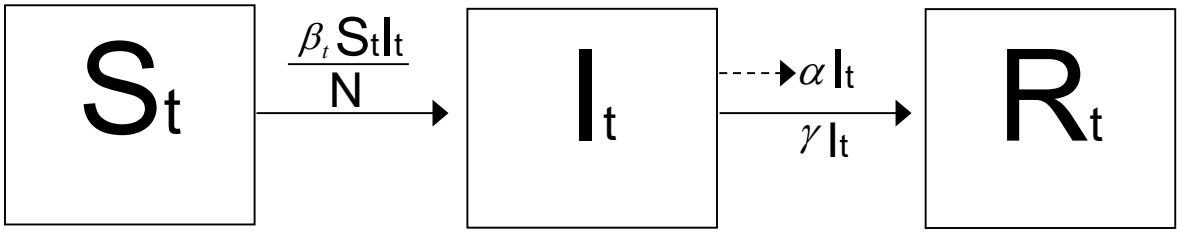

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- Regression analysis of panel data

$$\beta_{it} = \beta_0 \exp(c_0 t - m_0 w(I_{it}))$$

m_0 :avoidance response, β_0 : baseline attack rate, w(I): prevalence in past week, c_0 : time factor

the time-variant reproductive rate (RR_t)

We calculate the time-variant reproductive rate (RR_t) as the product of 3 terms:

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$$\beta_t \left(\frac{S_t}{N_t(\gamma + \alpha)} \right)$$

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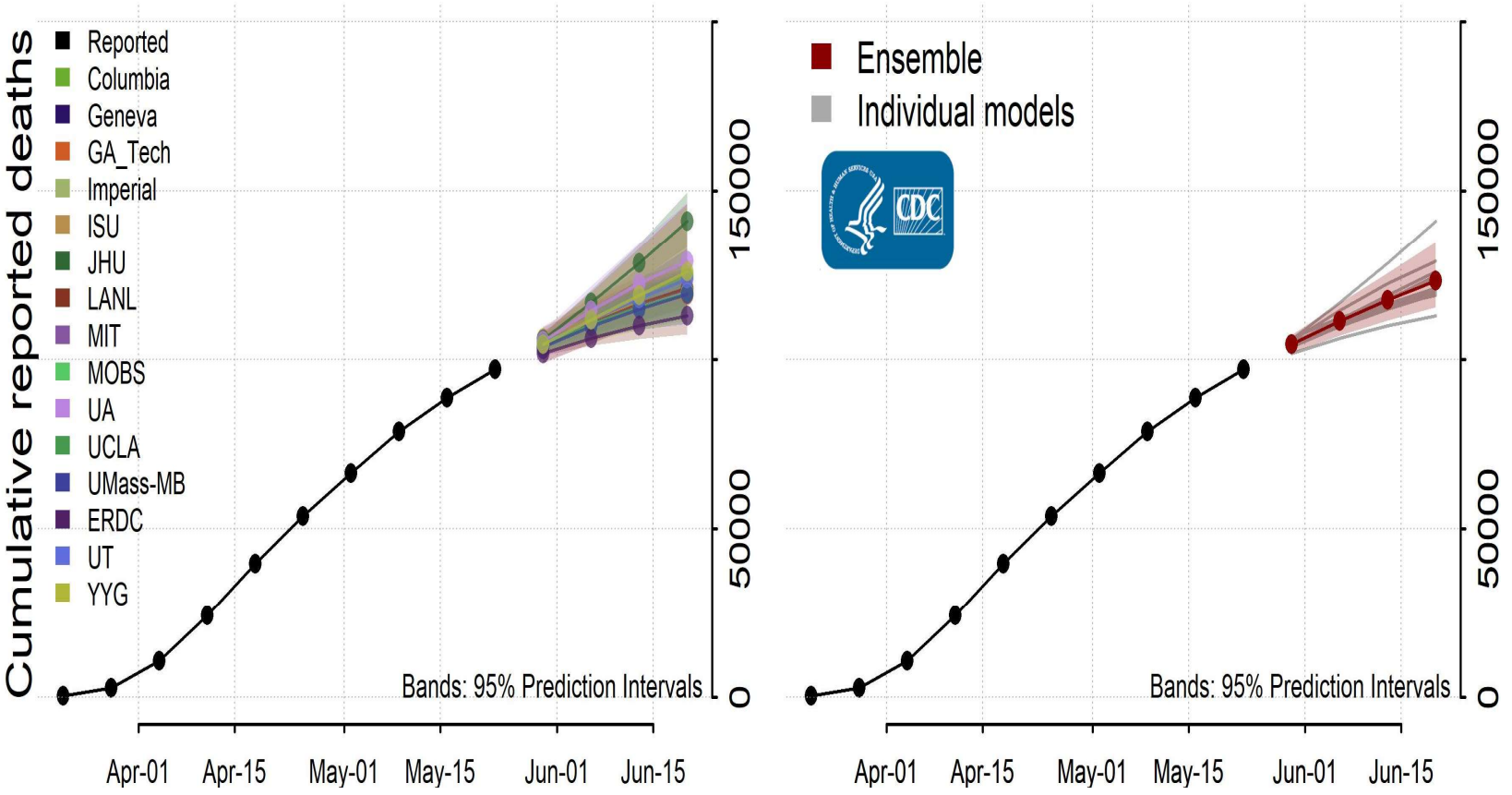
CDC's forecast: Deaths of COVID-19 (as of May 27, 2020)

https://www.cdc.gov/coronavirus/2019-ncov/covid-data/forecasting-us.html

National Forecast



Questions for Students

- What are the big differences b/w the estimates in CDC (previous slide) and those in Japan (that you have seen somewhere before)?

- You might want to simulate (# of infected, # of ICU beds needed) by yourself?

→ CDC provides FREE software "COVID-19 Surge" (https://www.cdc.gov/coronavirus/2019-ncov/hcp/COVIDSurge.html)

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IV) Discussion

- A) How applicable is the basic SIR model for the COVID19?
- B) What are obstacles to use math-models in policy-making in Japan?

V) Next Week

Discussion Points
(Note: (?) indicates limited evidence as of today)

A) How applicable is the basic SIR model for the COVID19?

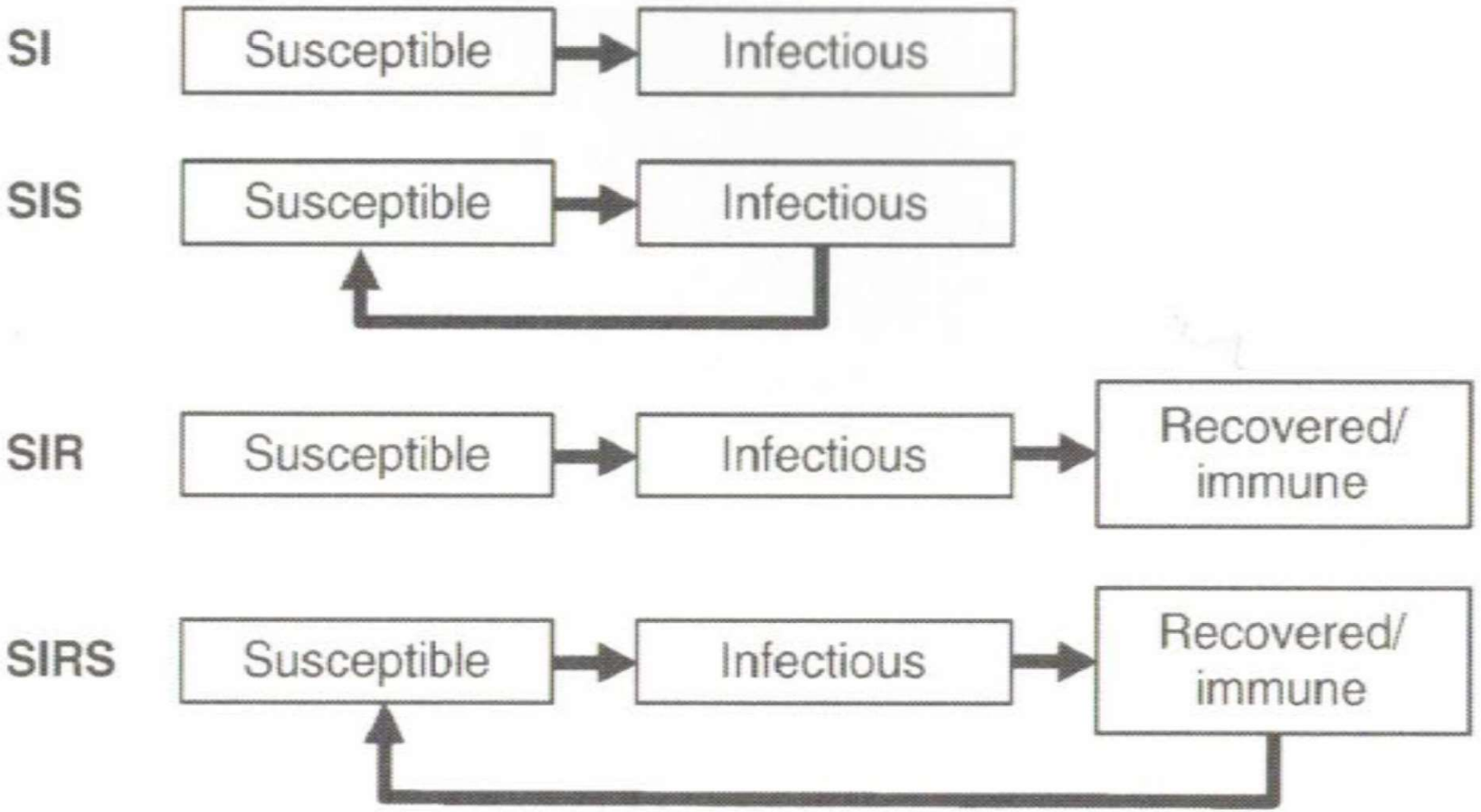
- Infection w/out symptoms → Spread speed↑, Hard to trace infected (under-count "S" in the SIR model?)

- Multiple infections (?, how much % of infected?)
  - → Herd Immunity more difficult, i.e., longer time to reach herd immunity ?
  - → Not SIR model but SIRI or the mix of these models? (See next slide)

- Poor antibody response (?, how much % of infected?)
  - → Vaccine effectiveness↓ or the vaccine development would be difficult ?
  - → Herd Immunity more difficult, i.e., longer time to reach herd immunity ?
  - → Not SIR model but the mix of SIS, SIR and SIRS models?

B) What are obstacles to use math-models in policy-making in Japan?

Common structures for models used to describe the transmission of infections.
(source: Vyunncyky 2020, p.16) (same as slide #27)



Road Map

I) Introduction of Presenter (and Students)
II) Basic Backgrounds of the COVID-19
III) Mathematical Modeling
IV) Discussion

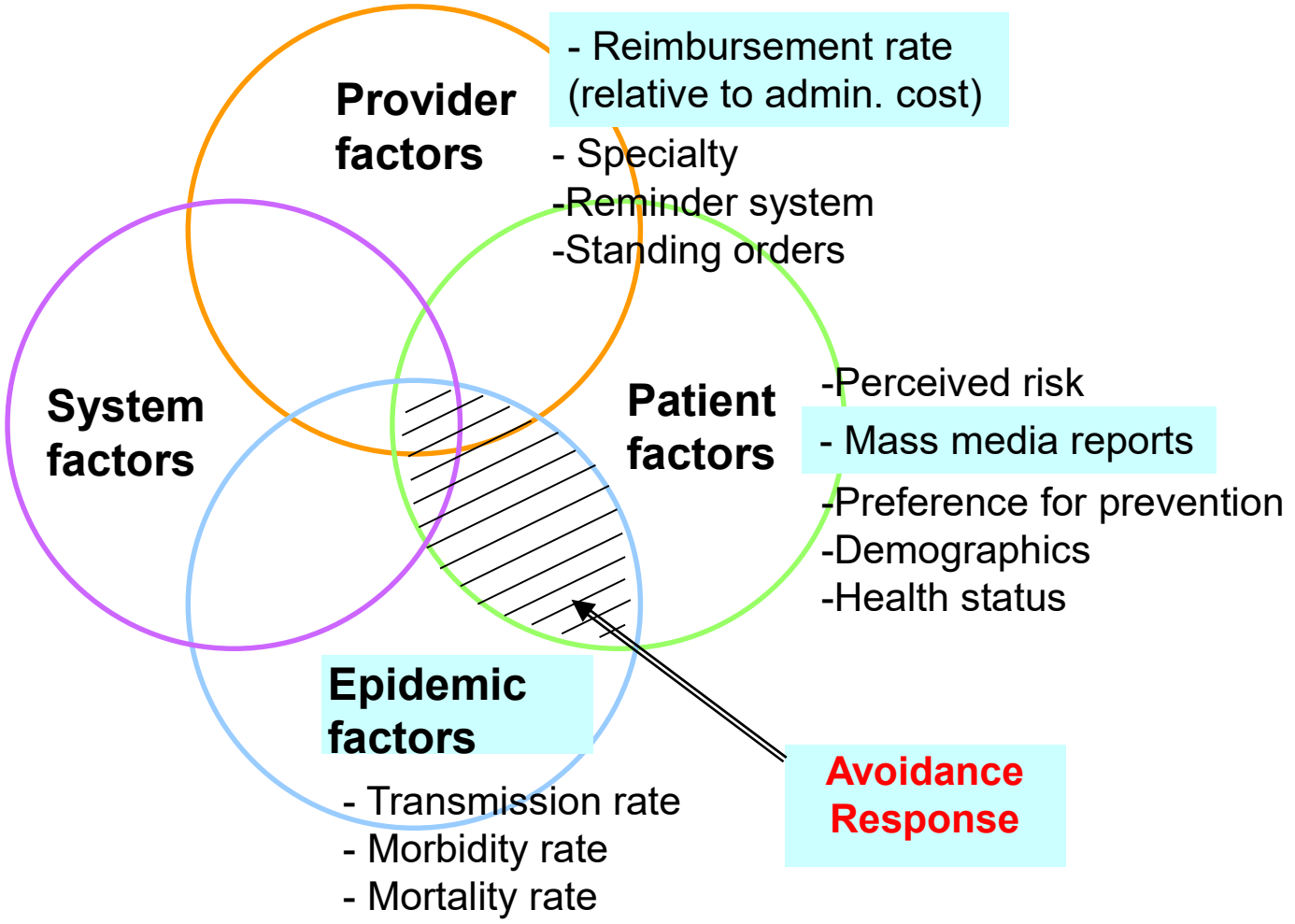
V) Next Week

Topic: “Individual behavior changes that affect epidemic levels”

Goal: To study the individual behavior changes, which affect epidemic levels, in terms of (a) methods to quantify determinants of these changes and (b) theories to explain these changes.

Conceptual Framework of Preventive Behavior: Case of Infectious Disease by Yoo (2011)

Modified (CDC Task Force on Community Preventive Services, MMWR 1999)



Questions?

References

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- Yoo BK, "How to improve influenza vaccination rates in the U.S.," ***Journal of Preventive Medicine & Public Health,*** 2011 Jul;44(4):141-8
- Yoo BK, Kasajima M, Bhattacharya J, "Public Avoidance and the Epidemiology of Novel H1N1 Influenza A," ***National Bureau of Economic Research Working Paper***, w15752, 2010, www.nber.org/papers/w15752