Timely Identification of Control Strategies for Emerging Infectious Diseases

Mathematical Modeling[†] of Infectious Diseases: Dynamics and Control

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[†]"And the mathematical method of treatment is really nothing but the application of careful reasoning to the problems at hand." Sir Ronald Ross

Outline

- My sole purpose this morning is to motivate and describe models with several unusual features:
  - o they are generic, so suitable for any directly-transmitted disease, though inevitably less so than disease-specific models
  - o their stages are clinically-distinguishable, so durations can be guesstimated from initial case-series, and
  - o some of their specific rates vary with time, reflecting social responses

- Armed with analyses Zhilan Feng will present this afternoon, we'll endeavor to assist public health decision makers during epidemics

- As the next new disease likely will emerge in Asia, I hope you'll also attend her presentation

Outline (cont'd)

- With mathematical models, one can evaluate actual interventions retrospectively as well as possible ones prospectively (tomorrow's lecture)
- So we'll explain why a costly, socially-disruptive measure widely employed against SARS was less effective than a relatively economical, society-uniting one
- Both were implemented in Singapore, where SARS was controlled by public health authorities, hospital infection-control staff, and the populace
- Your health ministry held informative daily briefings attended by the press, which further disseminated the best available information

Outline (cont'd)

- I'll illustrate features of your collective response, which we believe contributed more to control than quarantine, the costly, socially-disruptive intervention

- I'll provide a heuristic argument this morning (could also compare simulations with and without) and Zhilan a more rigorous one this afternoon

- But, as responses are by definition dynamic, models with constant specific rates derived from fixed sojourn distributions[†] are inappropriate

- One can simulate any model, but time-varying specific rates complicate analysis, so Zhilan will choose values from interesting regions of parameter space

[†]Donnelly et al. 2003. Lancet 361:1761-66
Lipsitch et al. 2003. Science 300:1966-70

Outline (cont'd)

- I'll also compare your response to that in Taiwan, about which we are learning from Ying-Hen Hsieh, who will speak on Wednesday

- As the accuracy and completeness of data presently available to us from outbreaks in these settings differ, apparent differences could be artifactual, so I'll focus on similarities

- Some probable cases were still hospitalized when our Singapore dataset was created, so my conclusions may be quantitatively incorrect

Limitations

- We do not know which 11 probable cases were quarantined, or anything about cases only suspected of having SARS

- Even the 32 confirmed post-discharge via culture or serology, some of which may have been among cases ruled out on clinical grounds

- Moreover, as 6/45 TTSH staff with antibodies did not become ill[†], evidently clinical cases were the tip of the proverbial iceberg

[†]Wilder-Smith et al. 2005. Emerg Infect Dis 11:1142-45

Outline (cont'd)

- Nevertheless, I'll share our understanding of social responses in Singapore as well as Taiwan
- And why we believe, given Zhilan's analyses and access to observations as soon as available – however inaccurate or incomplete – we could assist in better allocating available resources
- When a mutation increasing transmissibility of avian influenza person-to-person occurs, or …

Duration of Clinical Stages

- Within weeks of a traveler from Guangdong Province infecting others in Hong Kong, several case-series were published and the responsible pathogen was identified
- From case series available at www.nejm.org on 3/31 and 4/7[†], we estimated a roughly 6 day incubation period, 4 day prodrome and 8 day acute illness
- From cases reporting well defined exposures (by 4/14), Stefan Ma concluded that the median and mean incubation periods were 5 and 5.2 days in Singapore
- Among cases discharged (by 6/2), the mean interval from onset to discharge was 13.5 days, and one would expect clinicians to err on the side of caution

[†]Tsang et al. 2003. N Engl J Med 348:1975-83
  Lee et al. 2003. N Engl J Med 348:1986-94

Latent period

- While we can guesstimate clinical stage durations from the earliest case-series,

- We cannot guesstimate – except via experience with diseases caused by related pathogens – when infected people become infectious

- So, our models allow people to be infectious at any time, and we deduce this information by estimating stage-specific infection rates

- As we estimate the prodromal infection rate to be nil, our latent period is about 6+4=10 days

How early could we know?

- The WHO consensus is that infected people were not particularly infectious until acutely ill, but we believe we could have reached this conclusion sooner
- Because the distribution of infectiousness affects the effectiveness of possible interventions[†], policymakers need to know this as soon as possible
- On Friday, I'll show this information for smallpox, which essentially explains why the strategy known as surveillance and containment eradicated it
- Dashun Xu, one of Zhilan's students, is working on how early we could have reached this conclusion

[†]Fraser et al. 2003. Proc Natl Acad Sci 101:6146-51

Other Contributors

Singapore:

- Mark Chen
- Annelies Wilder-Smith
- Heng Bee Hoon
- Leo Yee-Sin

Taichung:

- Ying-Hen Hsieh

Tuebingen:

- Klaus Dietz

West Lafayette:

- Zhilan Feng
- Dashun Xu

Others (cont'd)

- We're grateful to all and welcome others, but you should know that
  - o we believe modelers contributed little to local or global responses to SARS, and that
  - o our focus is helping officials to make wiser decisions in future public health crises
- This requires epidemiologists, economists, mathematicians, physicians, programmers, statisticians, …working together

Outbreak in Singapore†
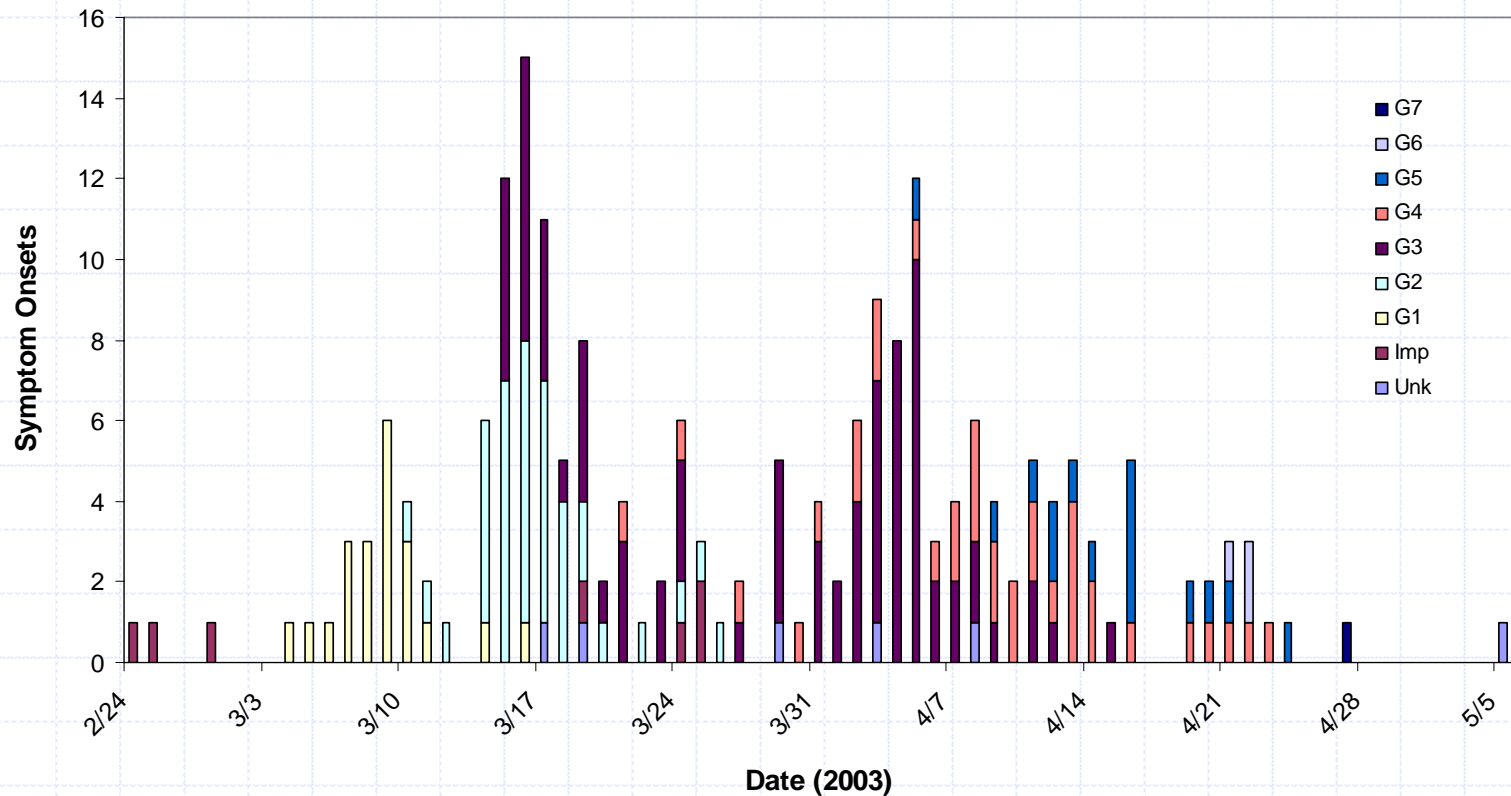
†Does not include 32 suspect SARS cases admitted to TTSH during March or April who tested positive for SARS antibodies or had positive cultures for coronavirus, but were only confirmed post-discharge.
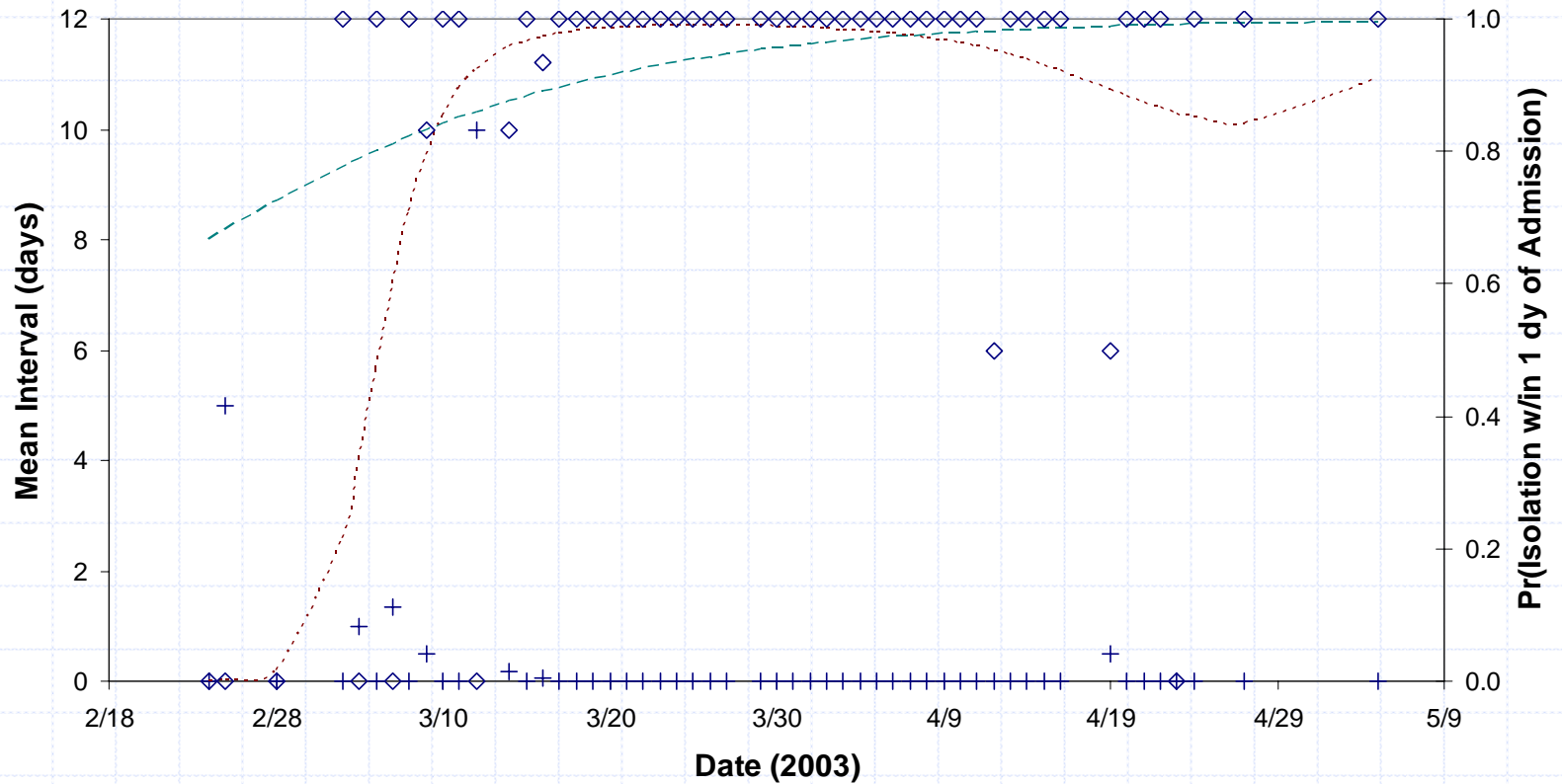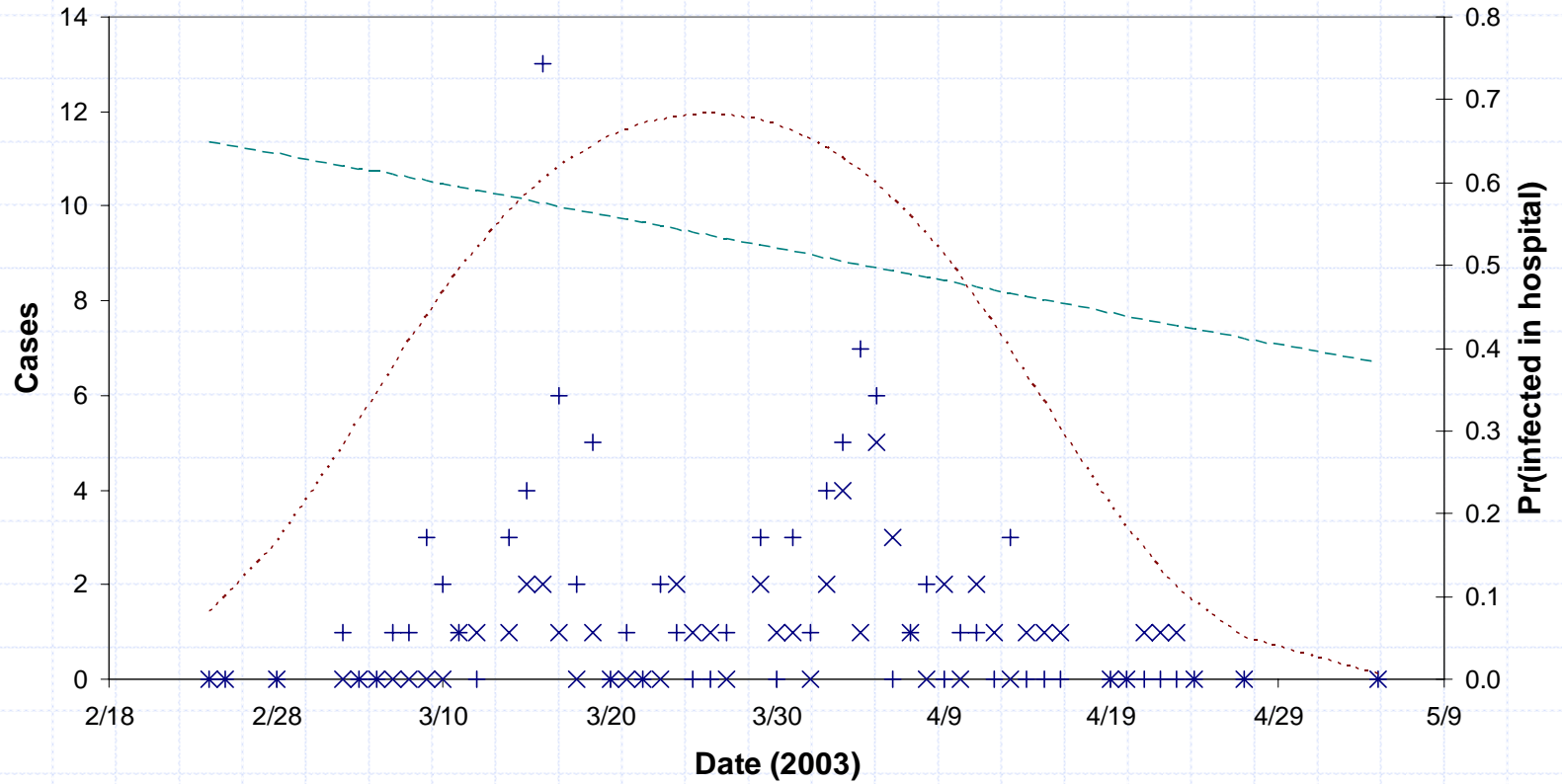
Onset to Hospital Admission
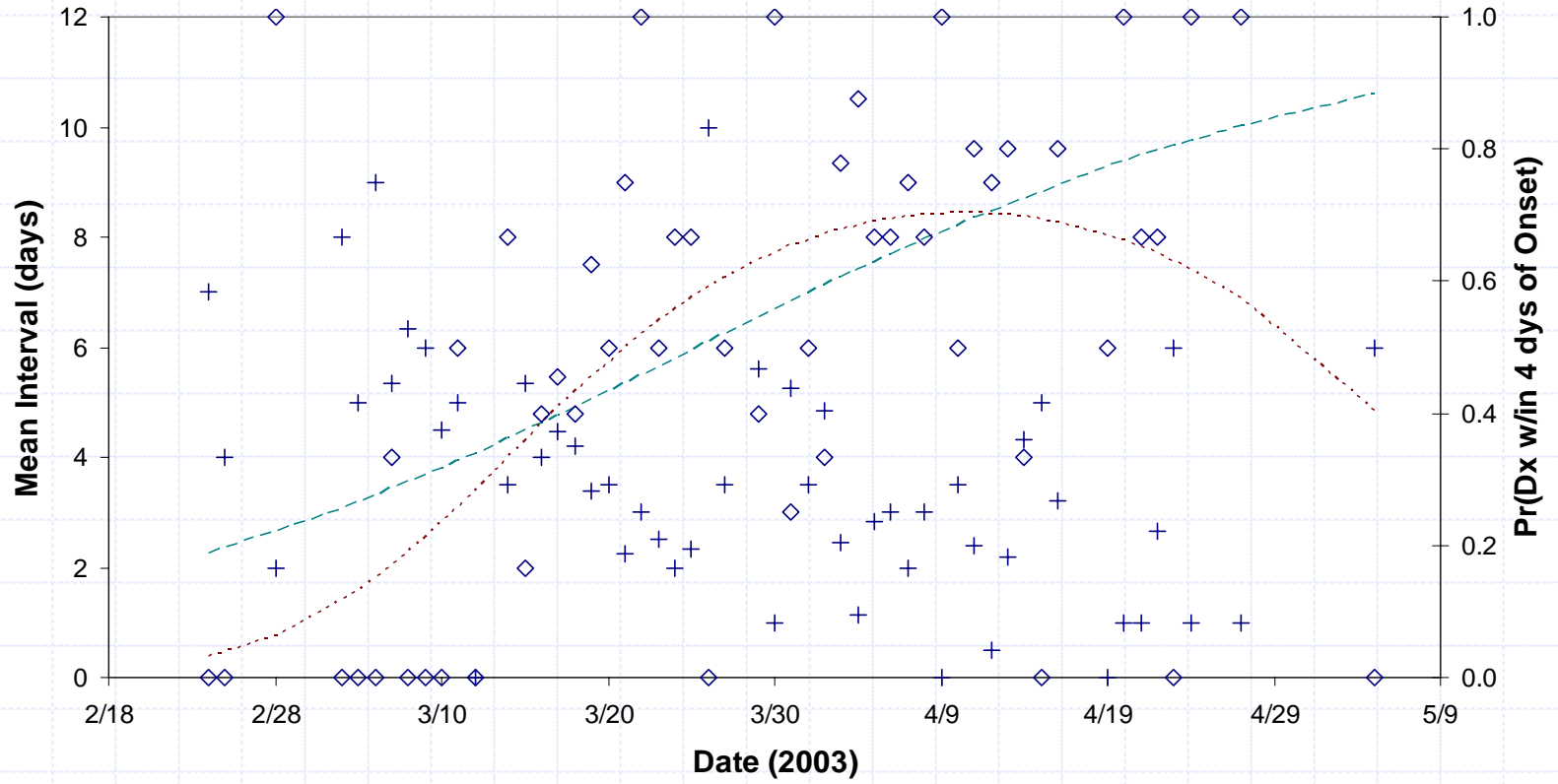
Onset of Infectiousness
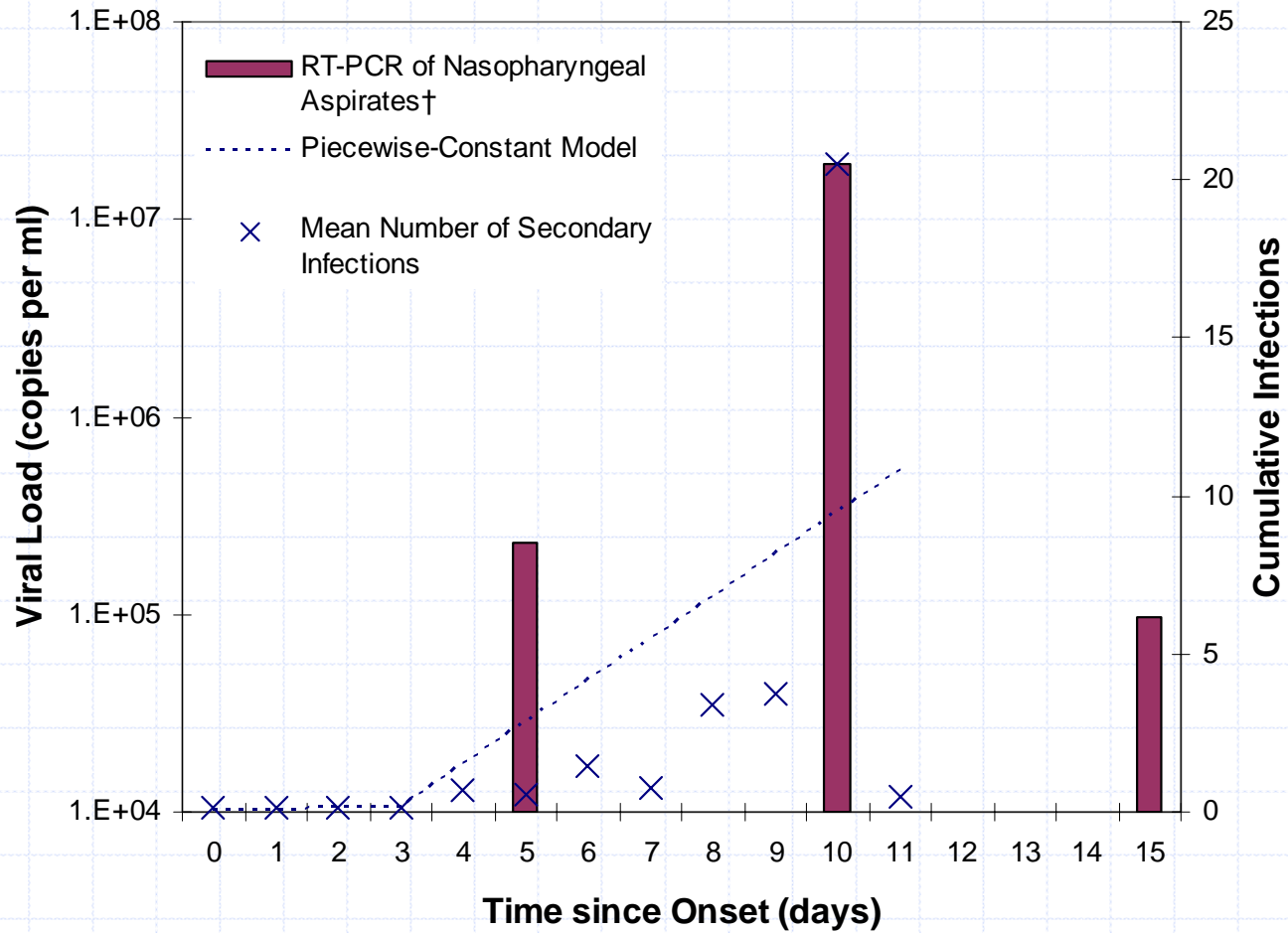
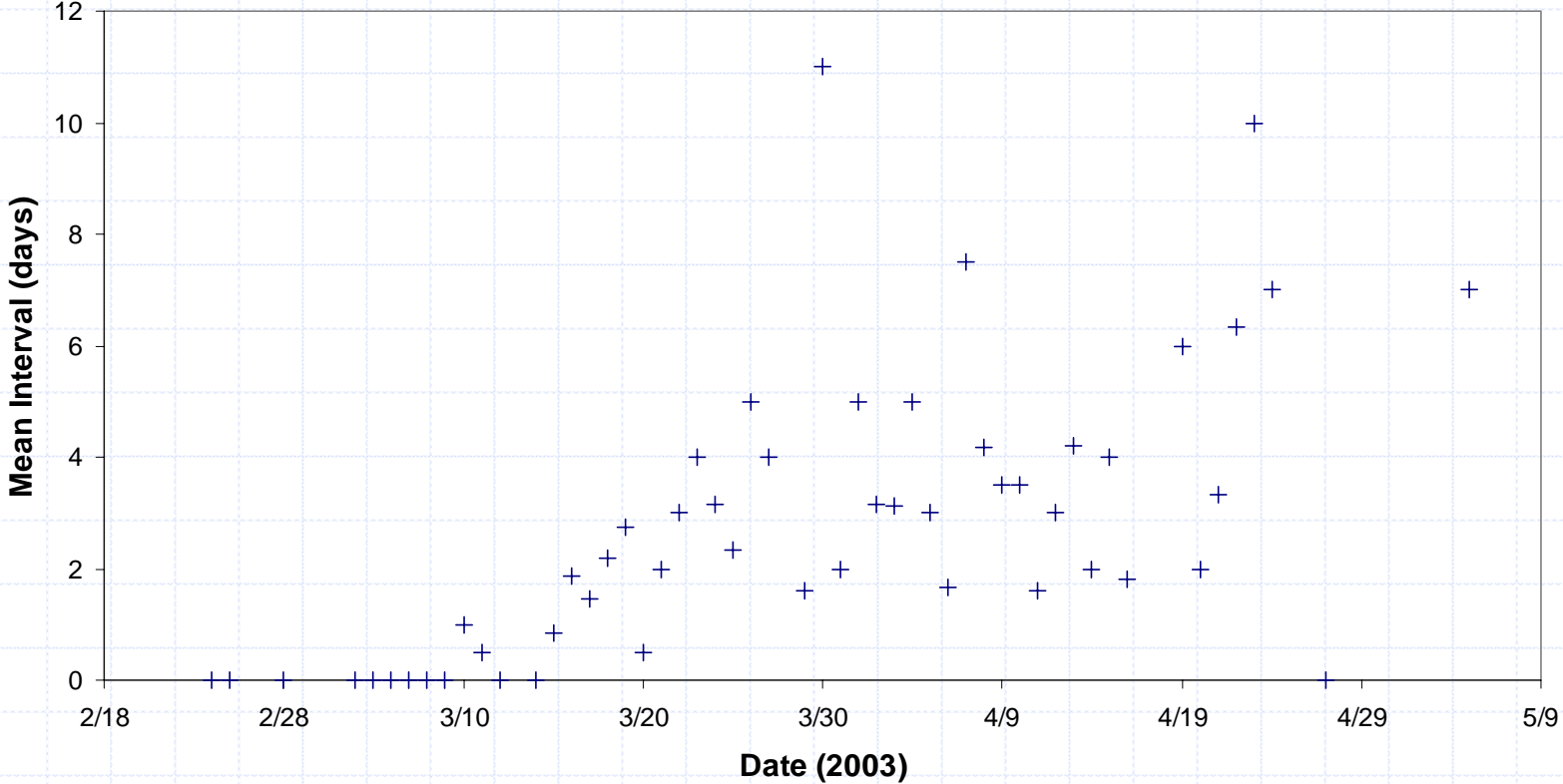†Peiris et al. 2003. Lancet 361:1767-72

# Admission to Isolation

Nosocomial Infections

Admission to Reclassification

When were patients *effectively* isolated?

- Insofar as probable cases may have been isolated more effectively than suspected ones, or rule-out SARS, …
- One might look for temporal variation in intervals from onset to diagnosis as probable SARS
- One would be disappointed
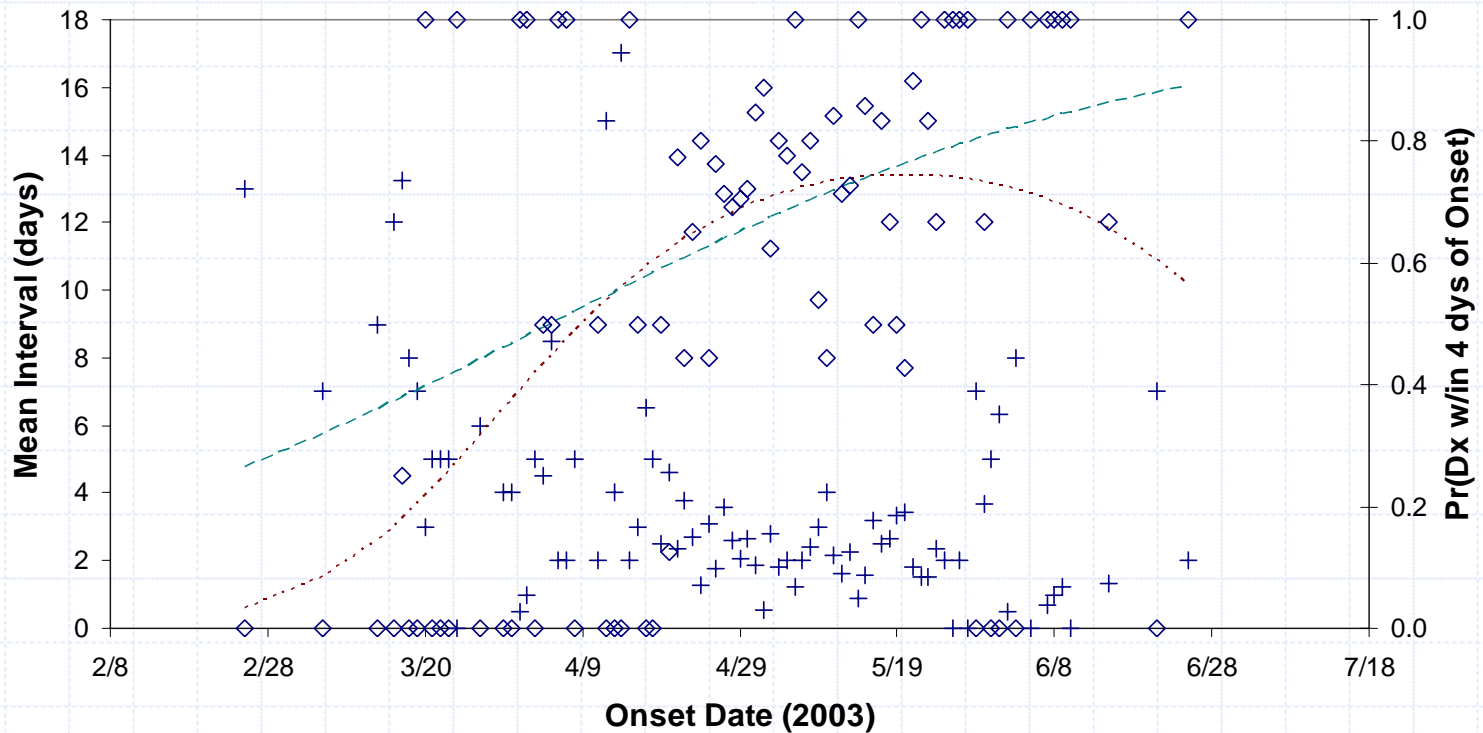
Onset to Classification as Probable
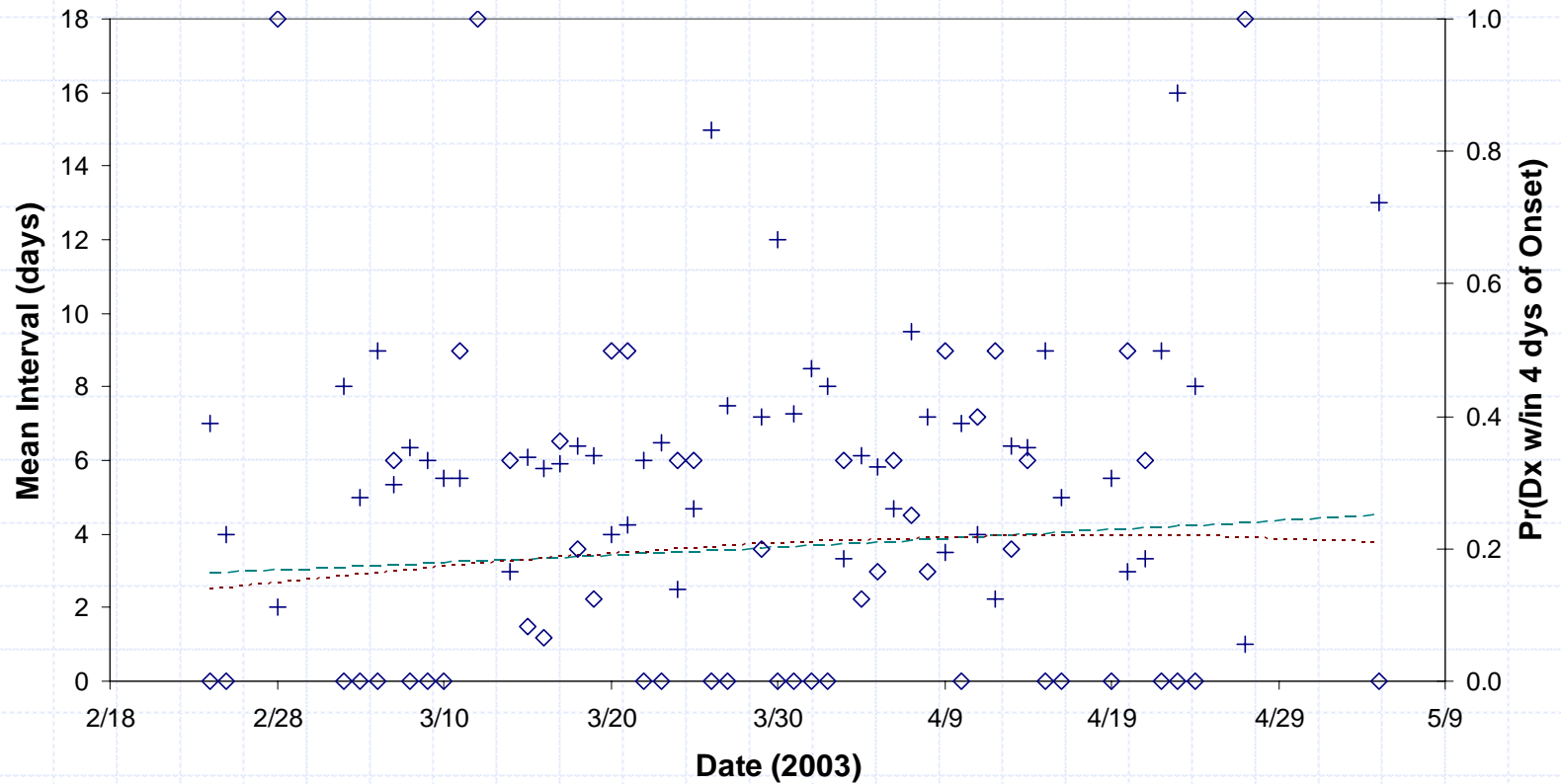
When (cont'd)?

- While we cannot tell – from these data – when patients were effectively isolated, …
- It suffices to note that ill people either sought care sooner or clinicians' diagnostic proficiency increased, or both, as the outbreak progressed
- I'm willing to bet they were isolated more effectively sooner too

Why?

- Because authorities were urging people to seek care on experiencing prodromal symptoms, especially if they might have been infected by someone since diagnosed

- Simultaneously, clinicians were learning the signs and symptoms of SARS

- And hospital infection-control staff were learning that, if they didn't protect themselves and other patients, nosocomial infections would occur

Onset to Admission (in Taiwan)

# Comparison of Responses in these Societies would be Interesting†
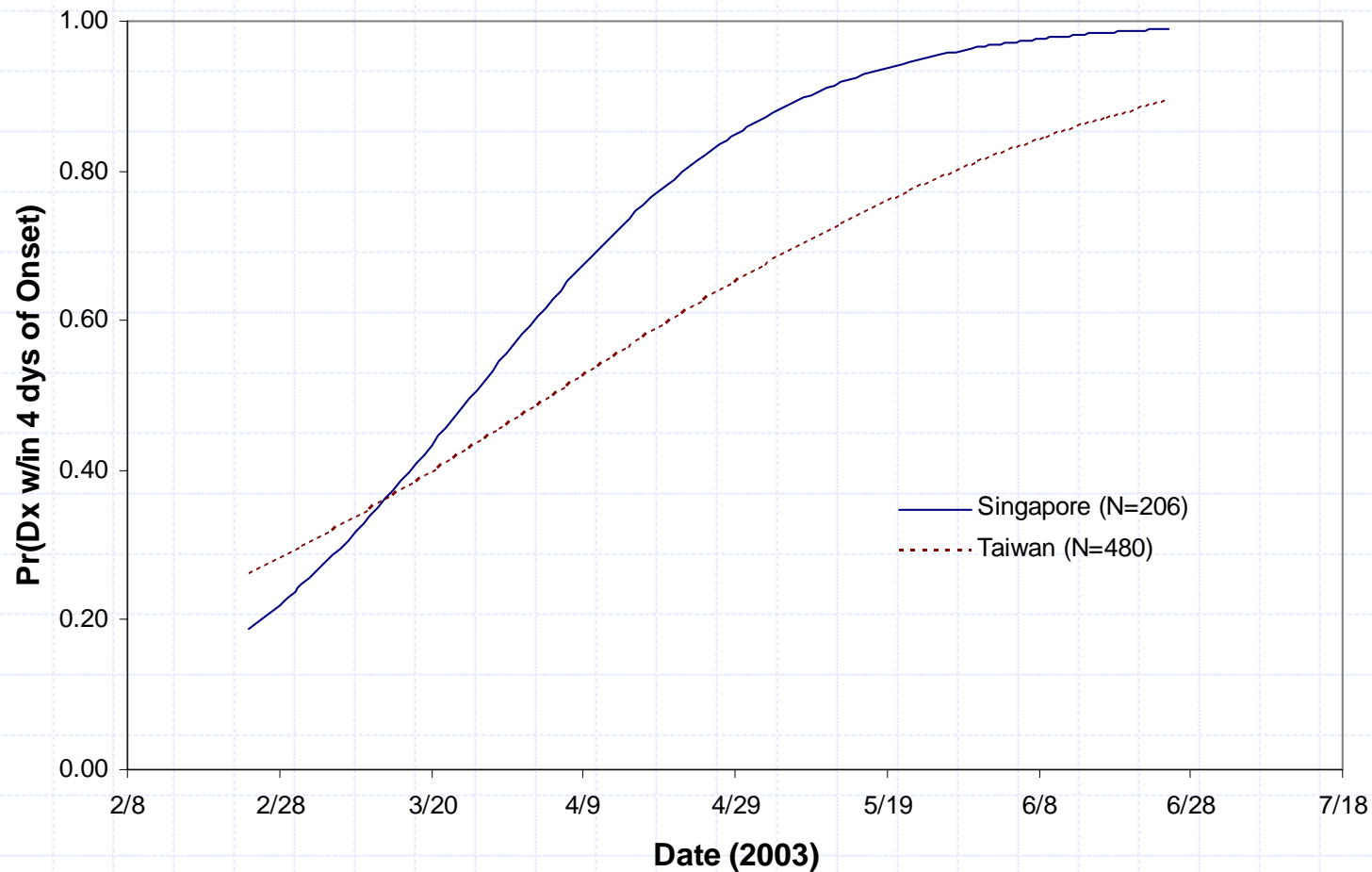
†Taiwan data include 134 laboratory confirmed plus 346 probable cases

Isolation in Taiwan

- We don't have dates of isolation in Taiwan, but do have reclassification dates

- Probability of reclassification within a few days resembles the complement of probability of infection in hospital in Singapore, suggesting that infection control may have improved toward the end of both outbreaks

- Insofar as neither would have been controlled otherwise, this is just common sense

Admission to Review
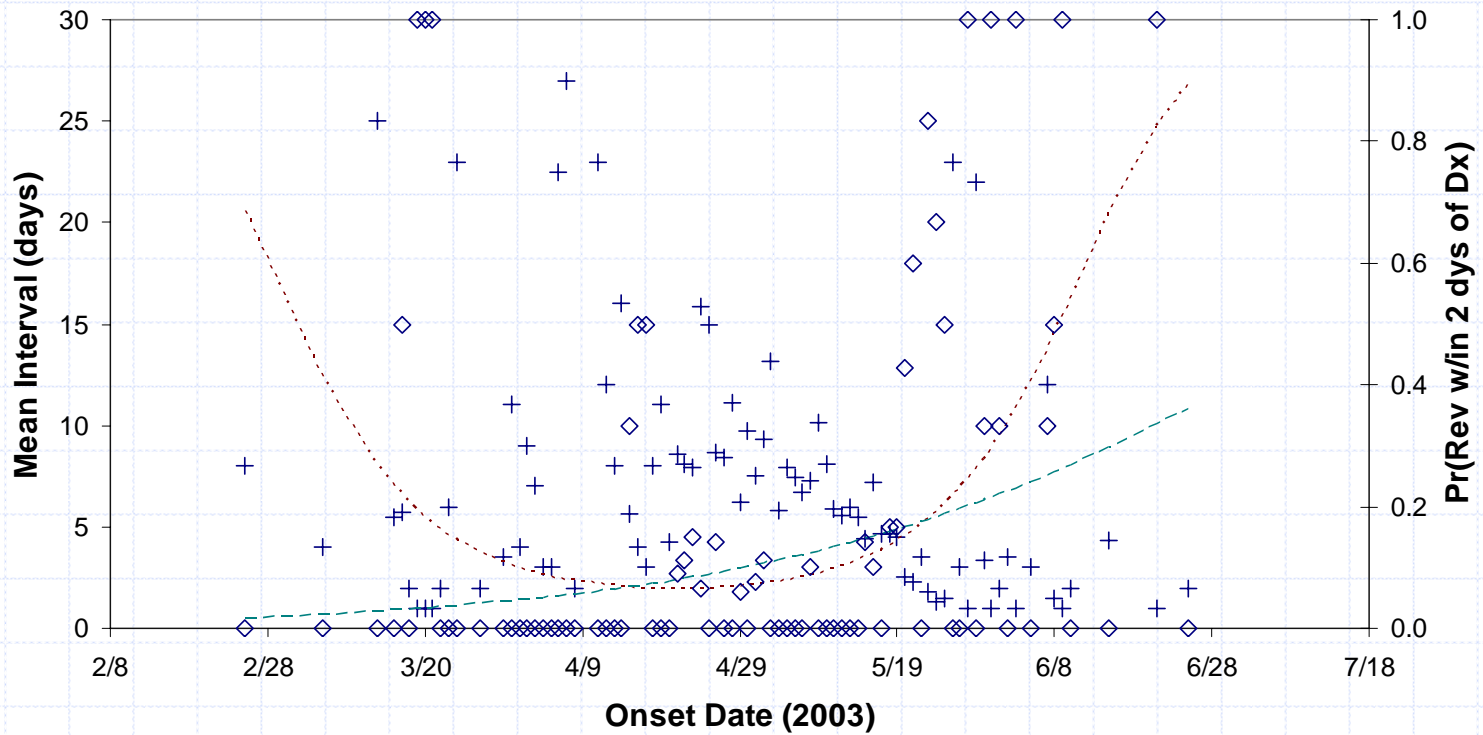
Quarantine

- We know which 23 cases were quarantined in Taiwan, but not which 11 in Singapore
- Can show that contacts were notified earlier (next slide) as the outbreak progressed
- We have not yet figured out when cases were diagnosed as probable in Taiwan. Hospitalization on same day as onset has PVP = 18/207
- Twenty-eight cases were hospitalized on the same day as onset in Singapore, but only nine were diagnosed as probable and isolated that day
- Were those quarantined?

	Quarantined	Not Quarantined	Total
Dx w/in 1 dy	18	189	207
Not Dx w/in 1 dy	5	268	273
Total	23	457	480

Notification to Onset
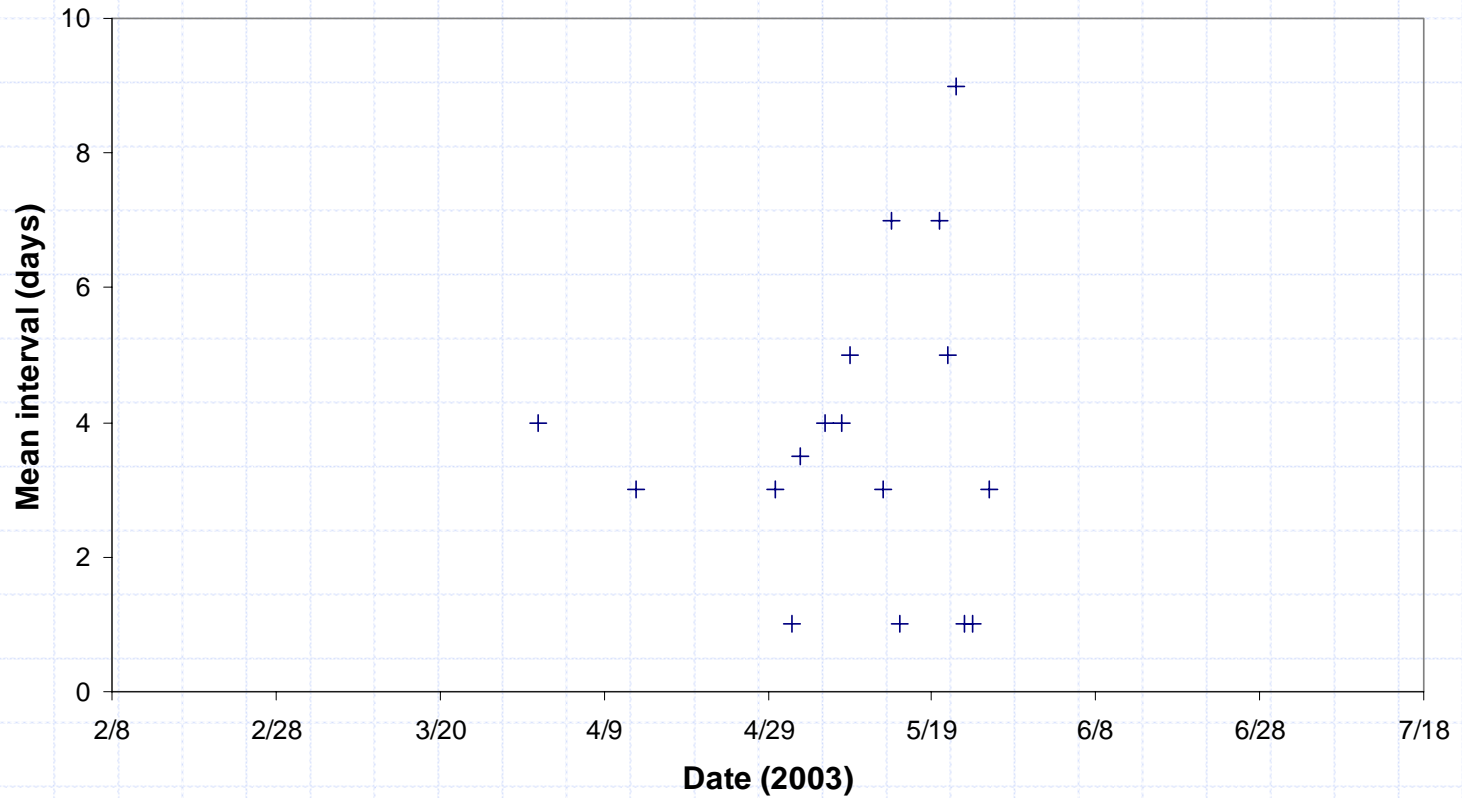
Impact of Quarantine

- To evaluate the impact of quarantine, one requires a mathematical model
- One fits predicted to observed time-series, and compares simulations w/ and w/o quarantine
- Or, calculates the reproductive number and takes its partial derivatives with respect to quarantine
- But we know the answer cannot be great

Reasoning

- On average, cases infected $0.92 = (159/206)*0 + (25/206)*1 + (13/206)*2 + (3/206)*3 + (1/206)*(6+15+21+22+26+40)$ others, and only 11 were quarantined
- If cases quarantined while incubating were isolated perfectly, quarantine could have averted 10 secondary infections
- Yet 159 cases infected no one; what prevented the 148 who were not quarantined from infecting anyone?
- Common sense suggests that timely seeking of medical care, diagnosis, and effective isolation had much more impact
- Could we have reached this conclusion early enough to recommend that authorities focus on effective health communications?

Cost of Quarantine

- 7,863 possible contacts quarantined in Singapore, of whom only 11 were diagnosed[†]

- 55,632 (contacts) and 95,828 (travelers) quarantined in Taiwan, of whom only 23 and 1, respectively, were diagnosed[‡]

[†]Tan, CC 2005. Public health response: a view from Singapore, pp. ?-? in *SARS: The First New Plague of the 21st Century*. Blackwell Publishing, Oxford
[‡]Hsieh, YH et al. manuscript. Impact of intervention measures and public response for severe acute respiratory syndrome outbreak: a retrospective analysis

Simulations

- Simulations with an earlier model (whose current version I am about to unveil) with and without quarantine (but all else equal) …

- Indicated that, conditional on these time-varying social responses (present in both simulations), quarantine averted only 5 cases

- We haven't repeated these experiments because we hope to learn which cases were quarantined and remedy other limitations listed earlier

Proposal

- First I'll describe our generic models, whose states are clinically distinguishable

- And, because mean sojourns in stages change during outbreaks, some specific-rates of transition among them are time-varying

- And then I'll describe how we propose to use them to assist in decision-making during future emergences of new human diseases

Model I

Features:
1. Infection, onsets of prodrome and acute illness, and recovery define stages
2. Stage-specific infection rates
3. Time-varying proportion of contacts quarantined at rate (incubation pd * pr dx during acute illnesss)$^{-1}$, where this pr also is time-varying
4. Other time-varying rates: presentation, diagnosis, and effectiveness of isolation during both stages
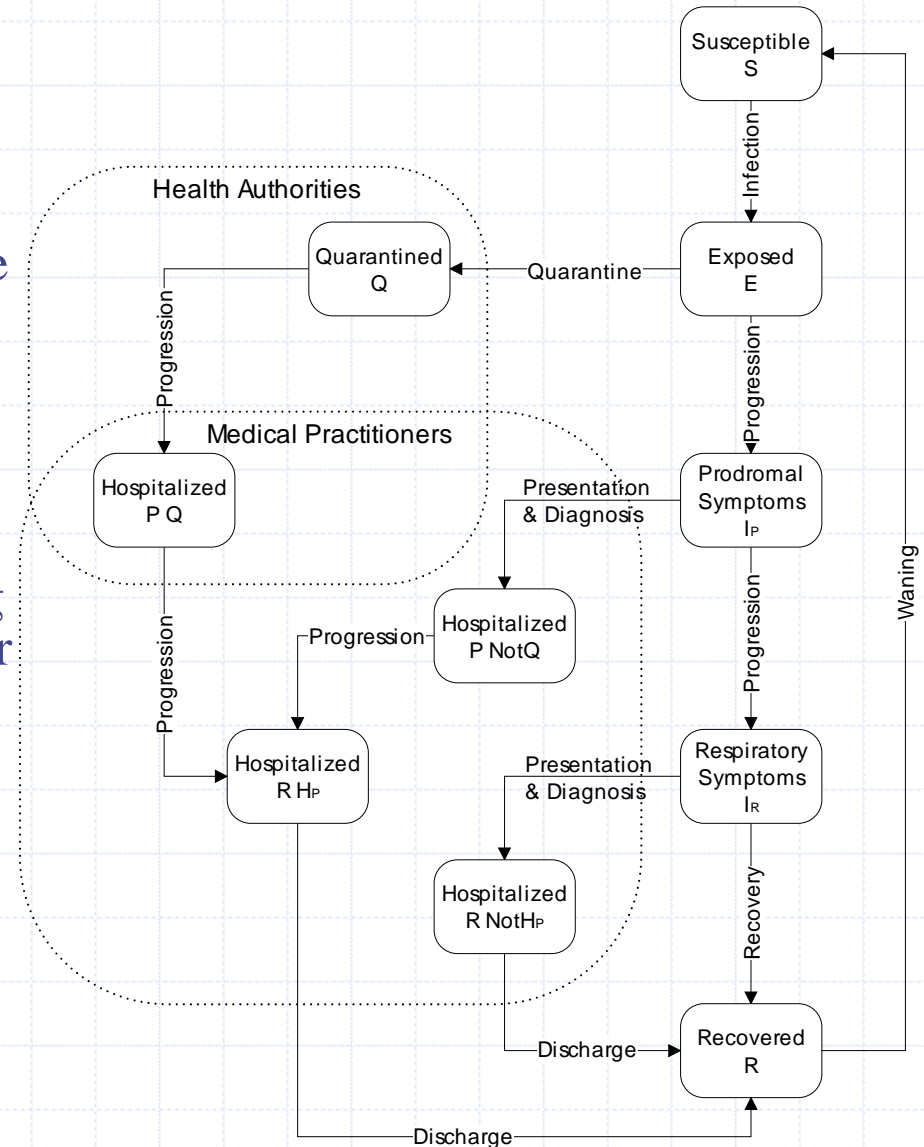
Model II

Additional features:

1. Ill people seek care in clinics and emergency rooms, but are not isolated until hospitalized (or classified as probable)
2. Presentation and diagnosis separated, permitting evaluation until suspects are reclassified or ruled out
3. Medications shorten course if begun during prodrome, but reduce infectiousness whenever begun
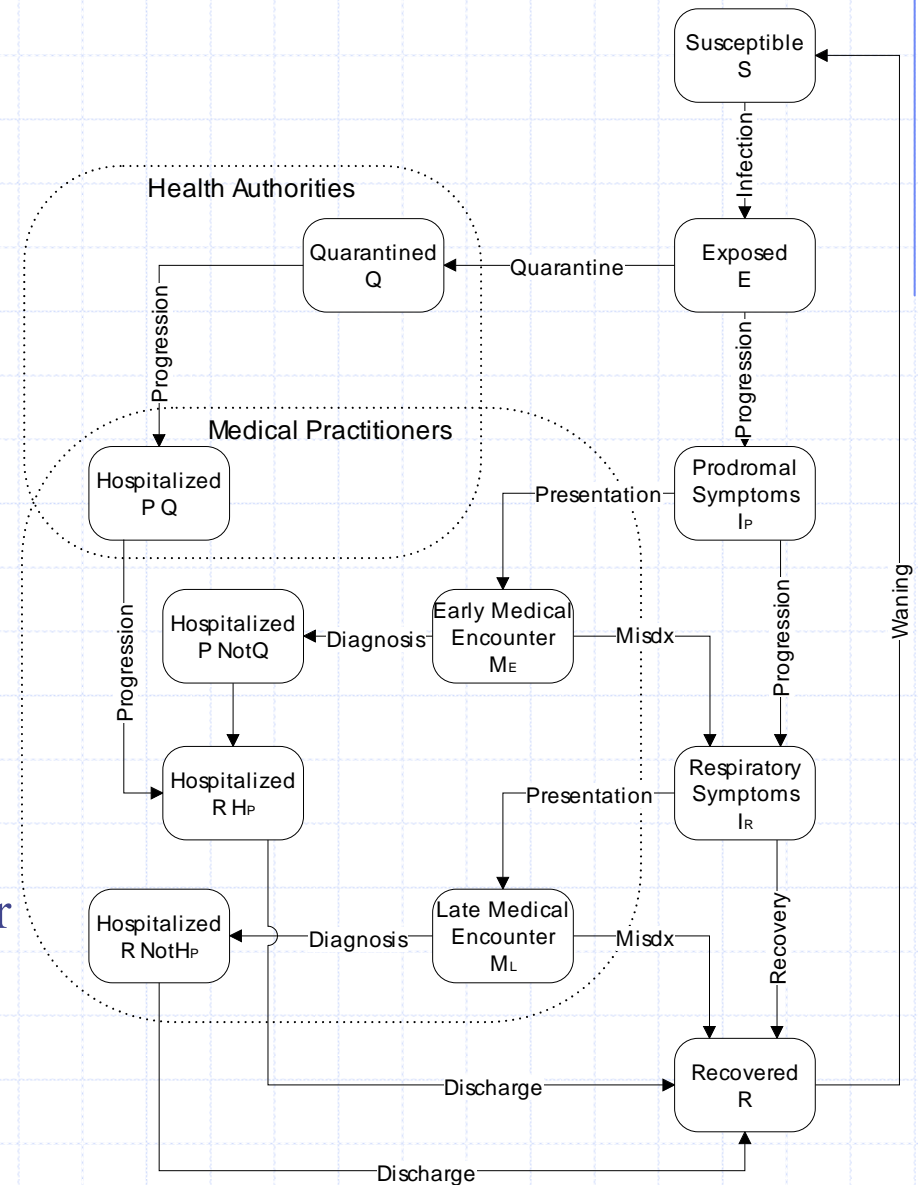
Proposal (cont'd)

Before any outbreak:

- Write equations, calculate R, and take its partial derivatives with respect to possible interventions
- Zhilan will share her analyses with us this afternoon

During an outbreak:

- Guesstimate stage durations
- Estimate infection rates, and as few other parameters as possible, from best available information
- Evaluate partial derivatives and advise officials which available intervention appears most effective
- Update estimates, … as data become more accurate and complete, and revise recommendations as indicated