HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

Epidemiological Modeling and Policy

Marc Lipsitch

UC Berkeley

August 12, 2020

Center for Communicable Disease Dynamics

MIDAS Models of Infectious Disease Agent Study

Funded by the National Institutes of Health

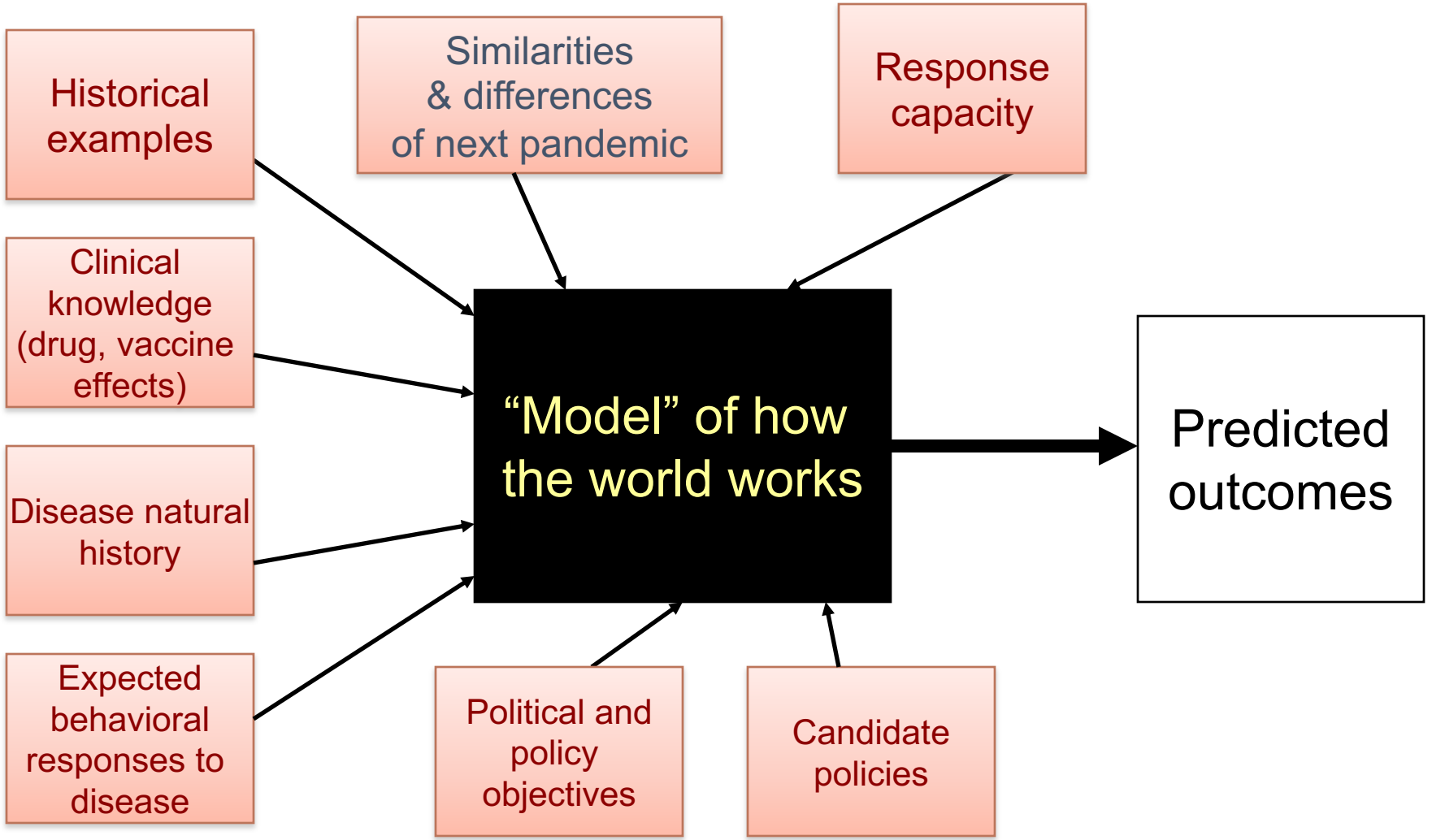
Two roles for models

- *SCENARIOS:* What are the plausible impacts of an event (bioterror attack, accident, flu pandemic)?
  - Scale, time of peak(s), duration
  - For planning: interventions may not be explicitly modeled
- *INTERVENTIONS:* What are the likely consequences of an intervention?
  - Lives saved, change in timing of epidemic, reduction of peak
  - Costs expended and averted
  - Social disruption…..etc.

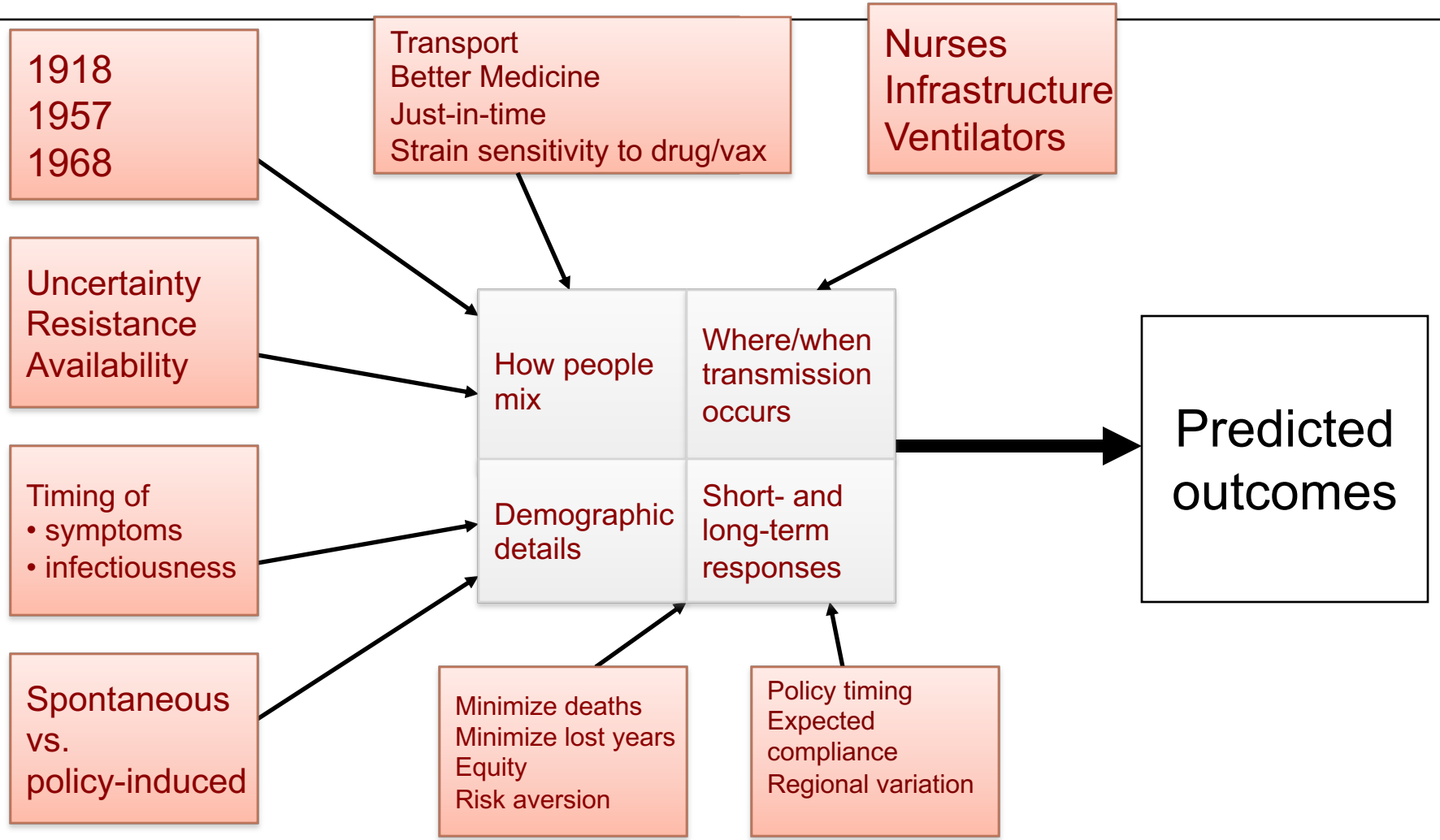
Possible Guides to Decision Making

- Reasoning from historical analogies
  - Previous pandemics
  - Interpandemic influenza
  - Other infectious diseases
- Clinical or public health experience
- Political considerations: do something
- Implicit mental models
- Explicit mathematical models

Decisionmaking requires use of mental models



Mathematical model makes inputs and assumptions explicit



What is special about decision making?

"Pure science"

Consequence of judging models inadequate = more science, agnosticism

Caution dictates: shun Type 1 error; avoid (provisional) acceptance of hypotheses for which evidence is inadequate

Agnosticism = the default

Decision making

Consequence of judging models inadequate = must rely on something else (mental models, extrapolating history) for decision

Caution dictates: protect people (+- save $$)

Agnosticism = paralysis, inability to inform cautious action

Sources of uncertainty/error when models are used for decision making

- *Model structure, parameter values, initial conditions*
- Framing a very *precise question* (what are we trying to optimize?) and choosing a precise and *appropriate metric* (expected outcome, probability of a good outcome, minimax)
- Thinking *outside the model* – considerations that happen before the model starts or after it ends or outside its geographic or other scope

Some themes

- The data suck
  Fixing them is both the hardest and most important activity for quantitative analysis
- These issues (eg delays) can drastically influence conclusions
  This is applied science, and quantitative skill + knowledge of the applications are both key to doing it well
- A paradox
  Sometimes models' greatest contribution is to say something that is mathematically and scientifically trivial, but important for policy yet
  Proving with a model that "interventions reduce cases if we assume they are effective" is not a great use of time
- Evaluation metrics and other "extra-model" considerations often more important for decision than model details

The data suck

Meteorology (physics, economics, etc)

Epidemiology (esp in crisis)

Pandemic Data analysis is all about (unmeasured, changing) delays

Event almost never observed

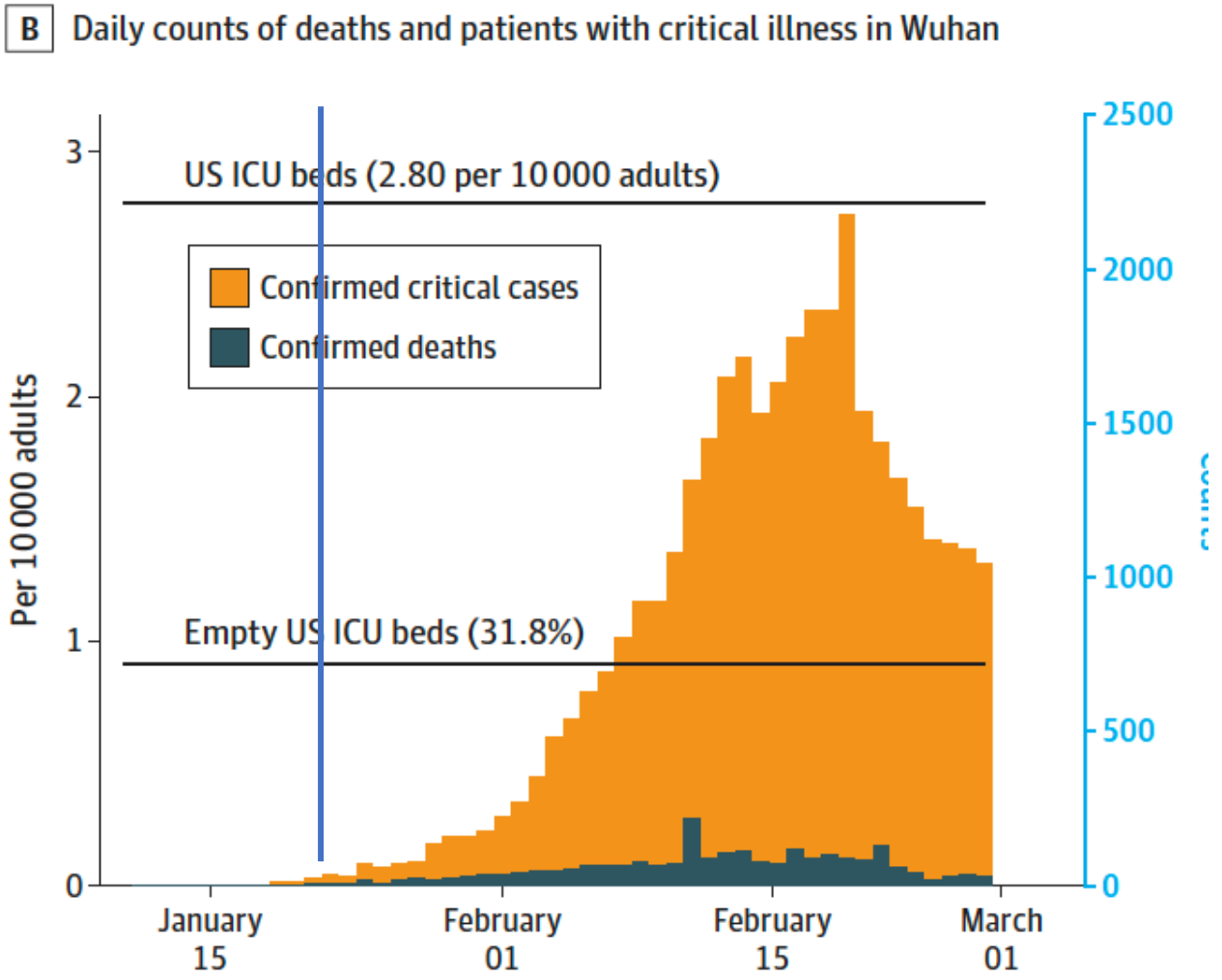
Same symptoms as other conditions; Maybe asymptomatic

Early on, tests limited even for admitted patients; now probably reasonably reliable

Even from best health depts (eg NYC) discharge often not noted

All-cause mortality bump is larger than can account for with confirmed COVID-19 deaths (like flu)

Consequences for control

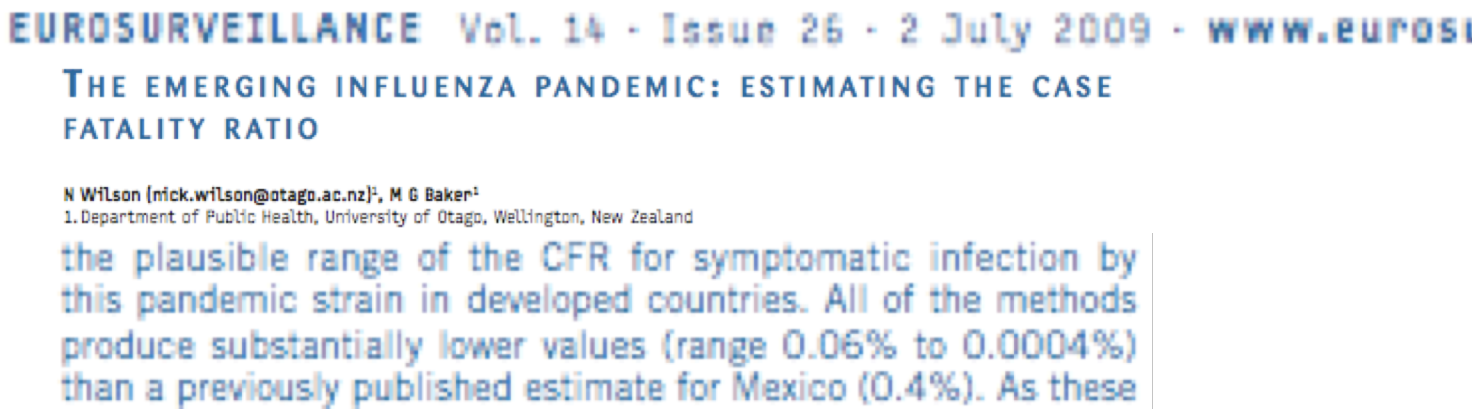


R Li et al. JAMA Network Open 2020

Fixing the data: consequences for analysis

How bad was H1N1 pandemic flu? It was hard to tell!

- Mexico May 4
  - 509 confirmed
  - 19 deaths (4%)
- US May 4
  - 268+786 confirmed + probable
  - 1 death (0.1%)
- Censoring bias (missing deaths; underestimate severity)
- Mild cases not detected (overestimate severity)



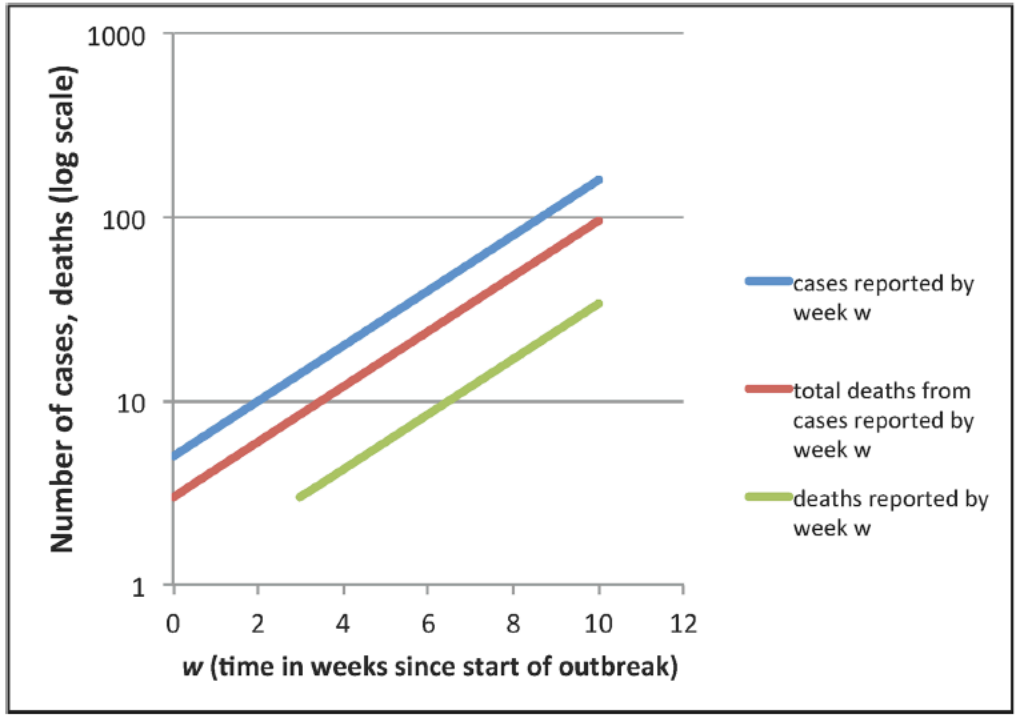
EUROSURVEILLANCE Vol. 14 - Issue 26 - 2 July 2009 - www.eurosu

THE EMERGING INFLUENZA PANDEMIC: ESTIMATING THE CASE FATALITY RATIO

N Wilson (nick.wilson@otago.ac.nz)[1], M G Baker[1]
1. Department of Public Health, University of Otago, Wellington, New Zealand

the plausible range of the CFR for symptomatic infection by this pandemic strain in developed countries. All of the methods produce substantially lower values (range 0.06% to 0.0004%) than a previously published estimate for Mexico (0.4%). As these

- Garske et al. *BMJ* 14 Jul
  - CFR 0.2-1.2%
  - Focus on censoring bias



PLOS | NEGLECTED TROPICAL DISEASES

REVIEW

Potential Biases in Estimating Absolute and Relative Case-Fatality Risks during Outbreaks

Marc Lipsitch[1,2,3]*, Christl A. Donnelly[3], Christophe Fraser[3], Isobel M. Blake[3], Anne Cori[3], Ilaria Dorigatti[3], Neil M. Ferguson[3], Tini Garske[3], Harriet L. Mills[3], Steven Riley[3], Maria D. Van Kerkhove[3,4], Miguel A. Hernán[1,5]

1 Center for Communicable Disease Dynamics, Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, United States of America, 2 Department of Immunology and Infectious Diseases, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, United States of America, 3 MRC Centre for Outbreak Analysis and Modelling, Department of Infectious Disease Epidemiology, Imperial College London, London, United Kingdom, 4 Centre for Global Health, Institut Pasteur, Paris, France, 5 Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, United States of America

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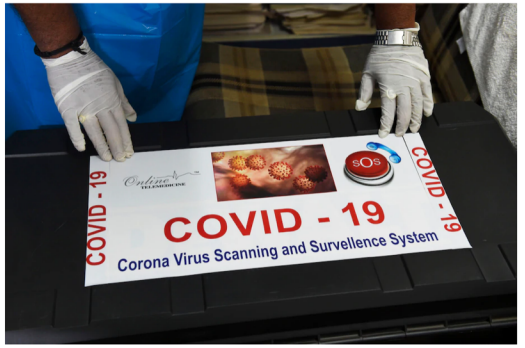
CrossMark click for updates

The Washington Post
Democracy Dies in Darkness

Coronavirus Latest news U.S. map World map Reopening tracker Lives lost Your life at home Extraordinary people

Opinions

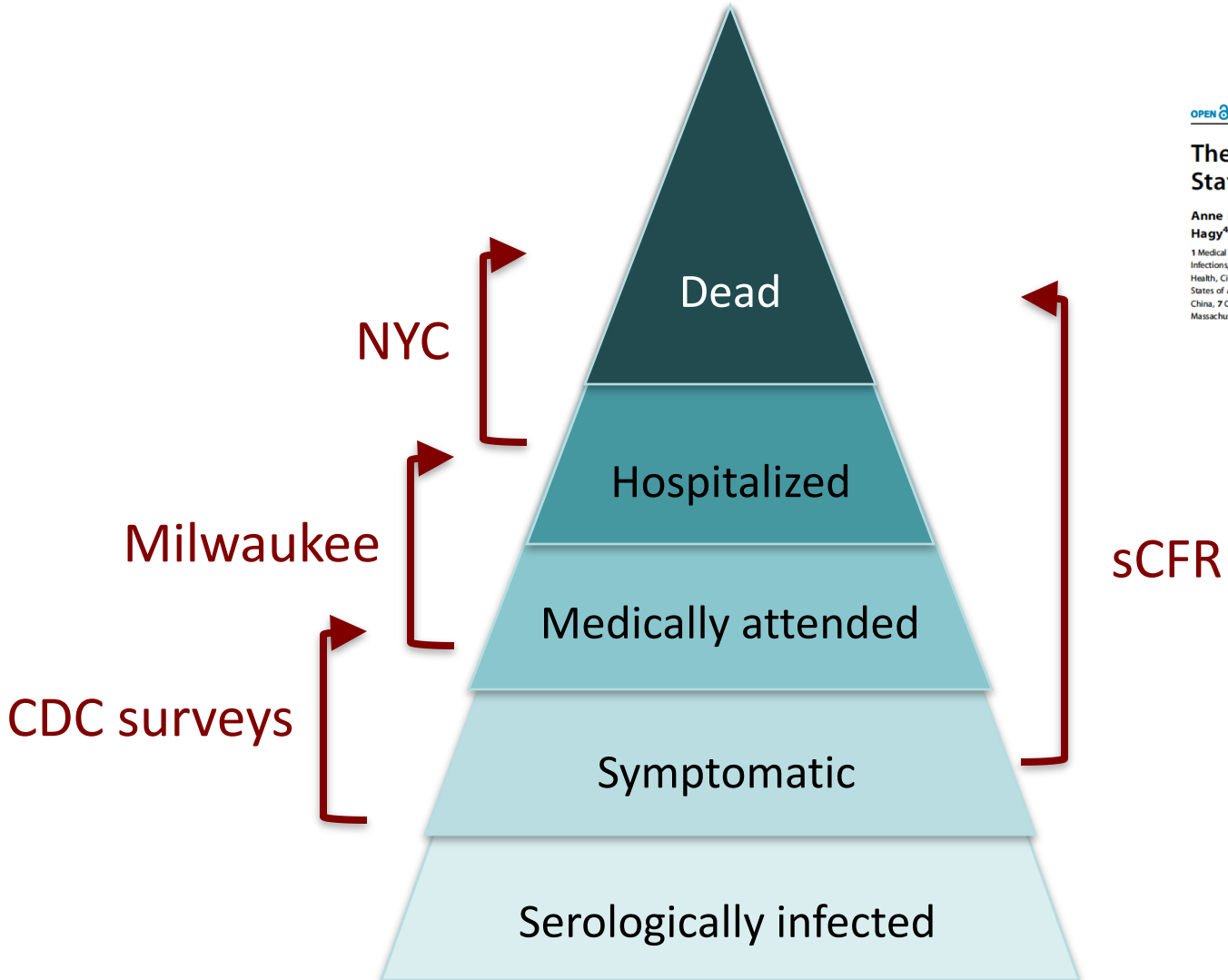
Why it's so hard to pin down the risk of dying from coronavirus



A worker prepares a coronavirus scanning and surveillance system kit in Ahmedabad, India, on March 6. (Sam Panthaky/AFP/Getty Images)

Opinion by **Marc Lipsitch**

Severity pyramid approach: Combining different data sources for a composite estimate of case-severity



OPEN ACCESS Freely available online PLoS MEDICINE

The Severity of Pandemic H1N1 Influenza in the United States, from April to July 2009: A Bayesian Analysis

Anne M. Presanis[1], Daniela De Angelis[1,2], The New York City Swine Flu Investigation Team[3¶], Angela Hagy[4], Carrie Reed[5], Steven Riley[6], Ben S. Cooper[2], Lyn Finelli[5], Paul Biedrzycki[4], Marc Lipsitch[7*]

1 Medical Research Council Biostatistics Unit, Cambridge, United Kingdom, 2 Statistics, Modelling and Bioinformatics Department, Health Protection Agency Centre for Infections, London, United Kingdom, 3 Department of Health and Mental Hygiene, City of New York, New York, New York, United States of America, 4 Department of Health, City of Milwaukee, Milwaukee, Wisconsin, United States of America, 5 Influenza Division, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America, 6 Department of Community Medicine and School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China, 7 Center for Communicable Disease Dynamics, Departments of Epidemiology and Immunology & Infectious Diseases, Harvard School of Public Health, Boston, Massachusetts, United States of America

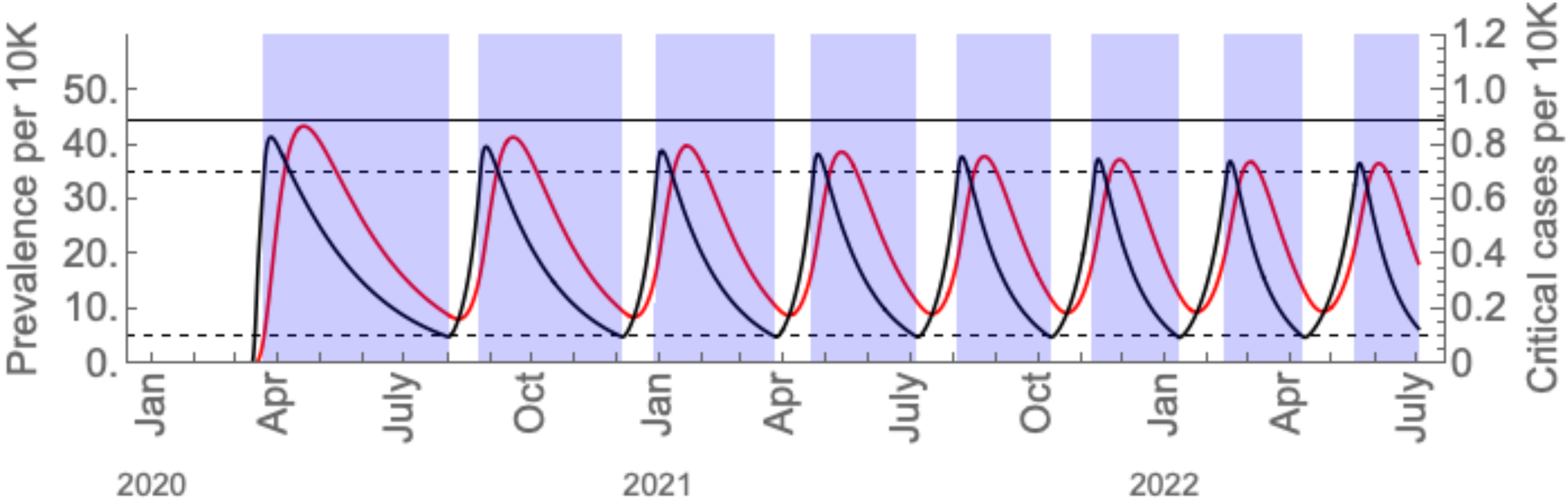
Age-specific severity estimates

	sCHR: ratio of hospitalizations to symptomatic cases	sCIR: ratio of ICU admissions to symptomatic cases	sCFR: ratio of deaths to symptomatic cases
0-4 yr	0.33% (0.21-0.63)	0.044% (0.026-0.078)	0.004% (0.001-0.011)
5-17 yr	0.11% (0.08-0.18)	0.019% (0.013-0.027)	0.002% (0.000-0.004)
18-64 yr	0.15% (0.11-0.25)	0.029% (0.021-0.040)	0.010% (0.007-0.016)
65+ yr	0.16% (0.10-0.30)	0.030% (0.016-0.055)	0.010% (0.003-0.025)
TOTAL	**0.16% (0.12-0.26)**	**0.028% (0.022-0.035)**	**0.007% (0.005-0.009)**
0-4 yr	2.45% (1.10-5.56)	0.321% (0.133-0.776)	0.026% (0.006-0.092)
5-17 yr	0.61% (0.27-1.34)	0.106% (0.043-0.244)	0.010% (0.003-0.031)
18-64 yr	3.00% (1.35-5.92)	0.542% (0.230-1.090)	0.159% (0.066-0.333)
65+ yr	1.84% (0.21-25.38)	0.100% (0.035-4.711)	0.028% (0.008-1.471)
TOTAL	**1.44% (0.83-2.64)**	**0.222% (0.134-0.458)**	**0.048% (0.026-0.096)**

Self-reported ILI denominator (NYC data only)

Self-reported frequency of seeking care (NYC/Milw./ CDC data)

Accouting for delays: decisions



Kissler S*, Tedijanto C* et al. *Science* 2020

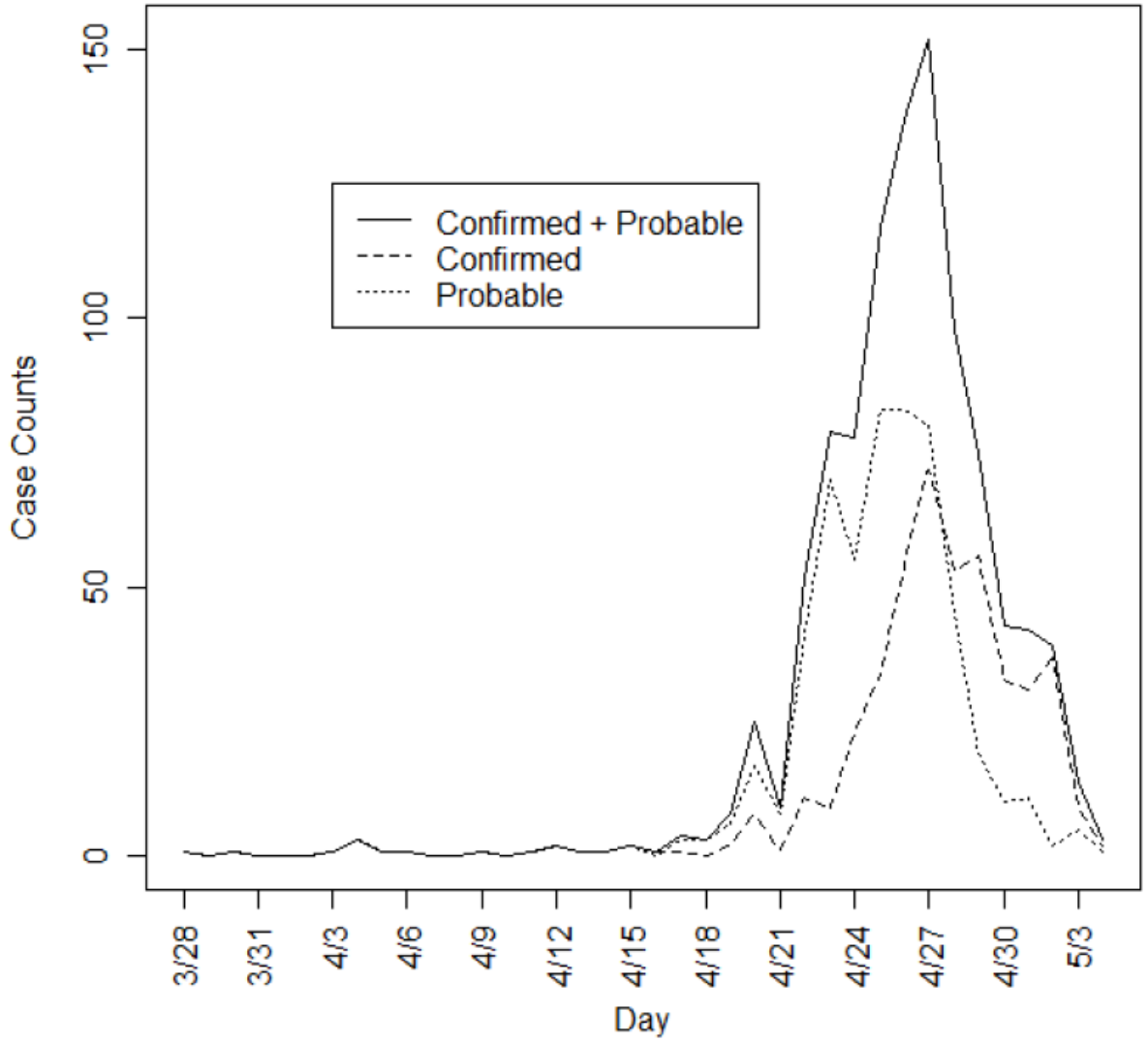
Accounting for delays: analysis

H1N1 Reproduction Number from Early USA data

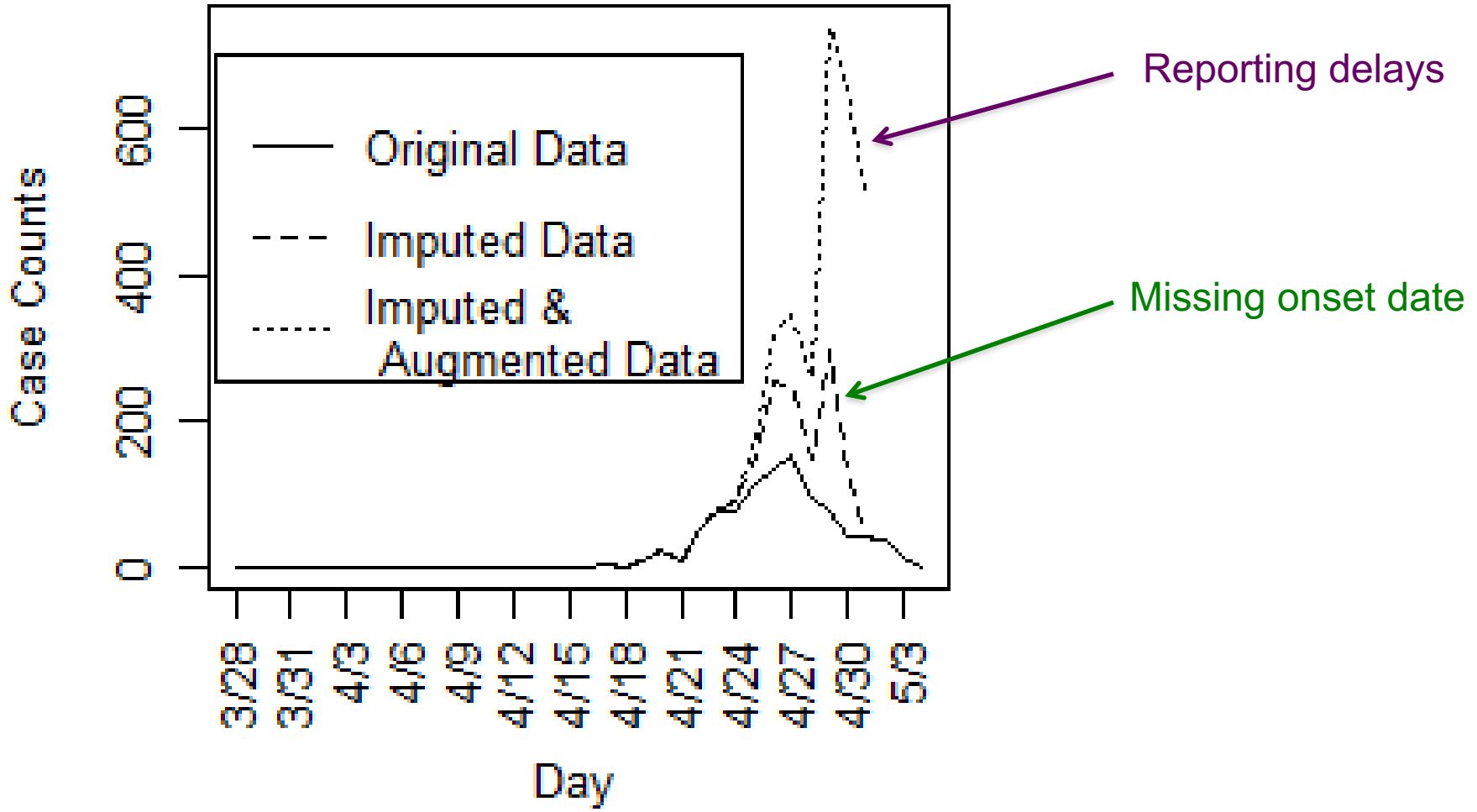
Laura Forsberg White (BU/HSPH)
Jacco Wallinga (RIVM/HSPH)
Lyn Finelli (CDC)
Carrie Reed (CDC)
Steven Riley (Hong Kong U)
Marc Lipsitch
Marcello Pagano (HSPH)

Influenza & Other Respiratory Viruses 2009

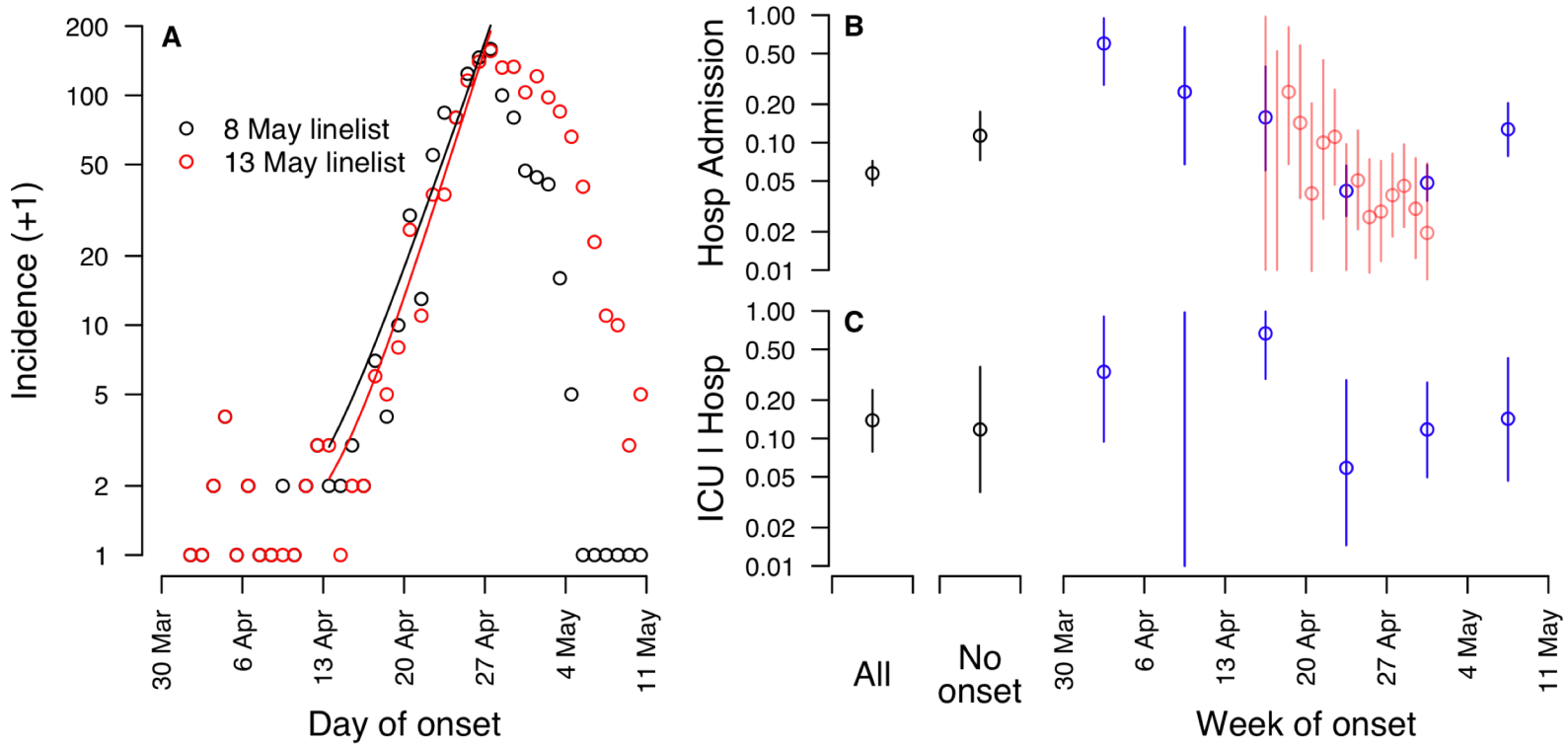
United States reported cases as of May 8



Correcting for missing onset date, reporting delays



Numbers are questionable because ascertainment is imperfect and changing in space and time



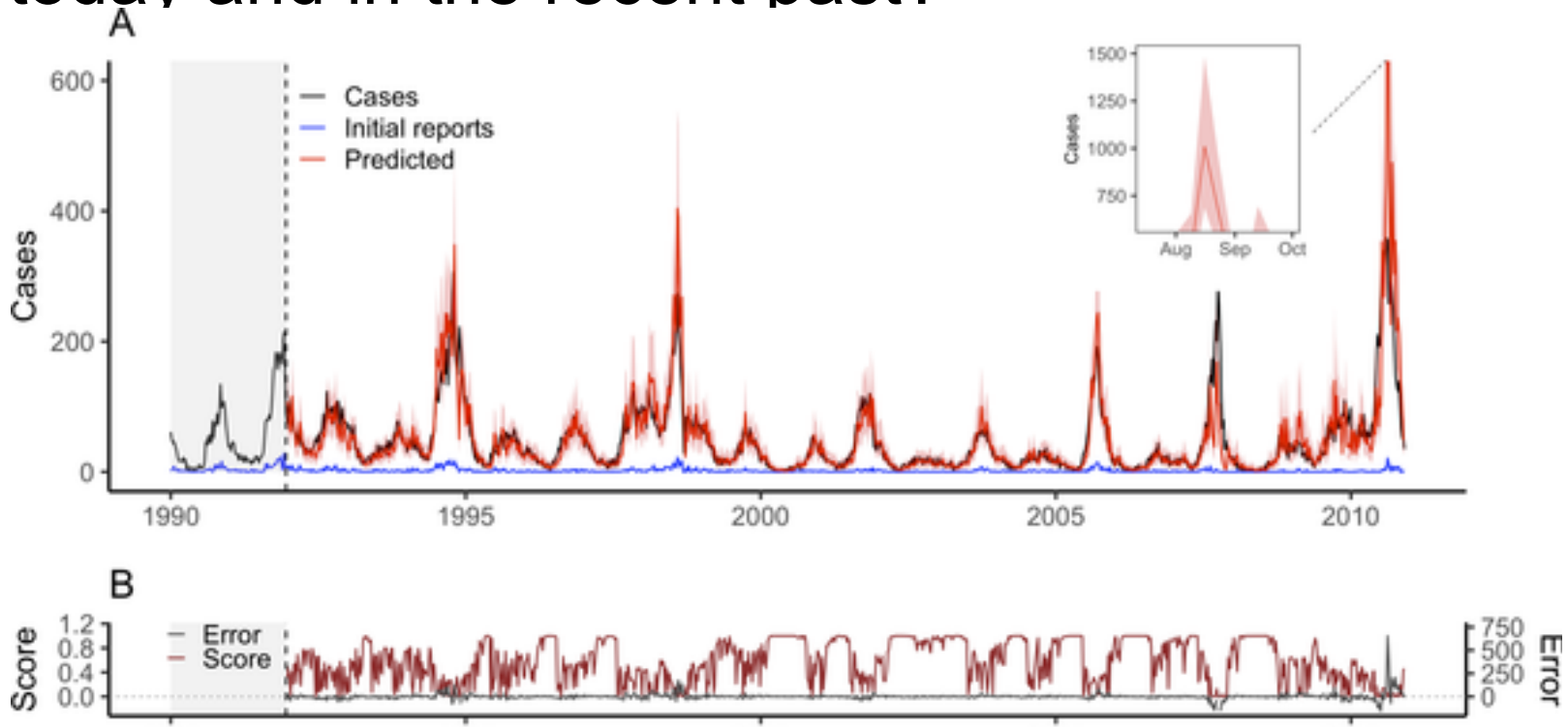
S. Riley et al. unpublished

Estimation of R_0: impact of data inputs

	Data to 4/26	Data to 4/28	Change in estimate from analytic change
Original data	1.95	1.51	
Account for missing onset dates	2.19	2.31	+10-40%
Account for reporting delays	2.27	2.52	+4-10%
Account for increased reporting	1.73	1.81	-20-30%

Nowcasting: part of the solution

- Given how many cases we know about today and in the recent past, how many cases will we eventually know about that occurred today and in the recent past?



S McGough et al. 2020 *PLoS Comp Bio*

I could go on with examples from this and prior epidemics

- Today's data set and tomorrow's may not say the same about today
- Testing detects a changing and unknown proportion of cases
- Different jurisdictions generate data in fundamentally different ways
- There is not always a good incentive to be transparent about these details, and people are busy

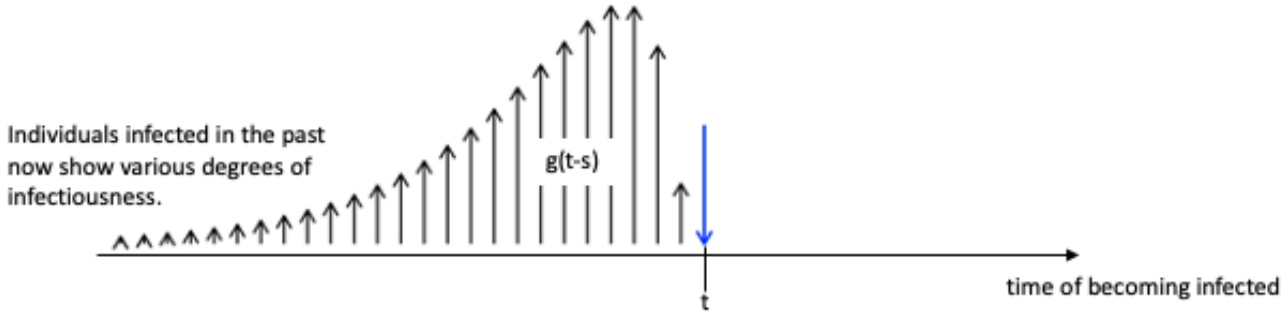
Before drawing strong policy conclusions from noisy data please check with someone who has been working in the field for a long time: a cautionary tale

Methods for reproduction number

Cori Method

R_t is the average number of new infections caused at time *t*, **by a person already infectious at time *t*.**

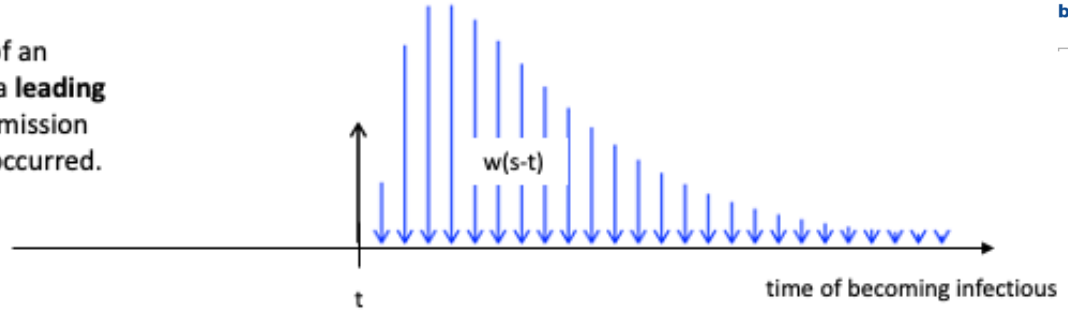
→ R_t reflects transmission happening at time t.



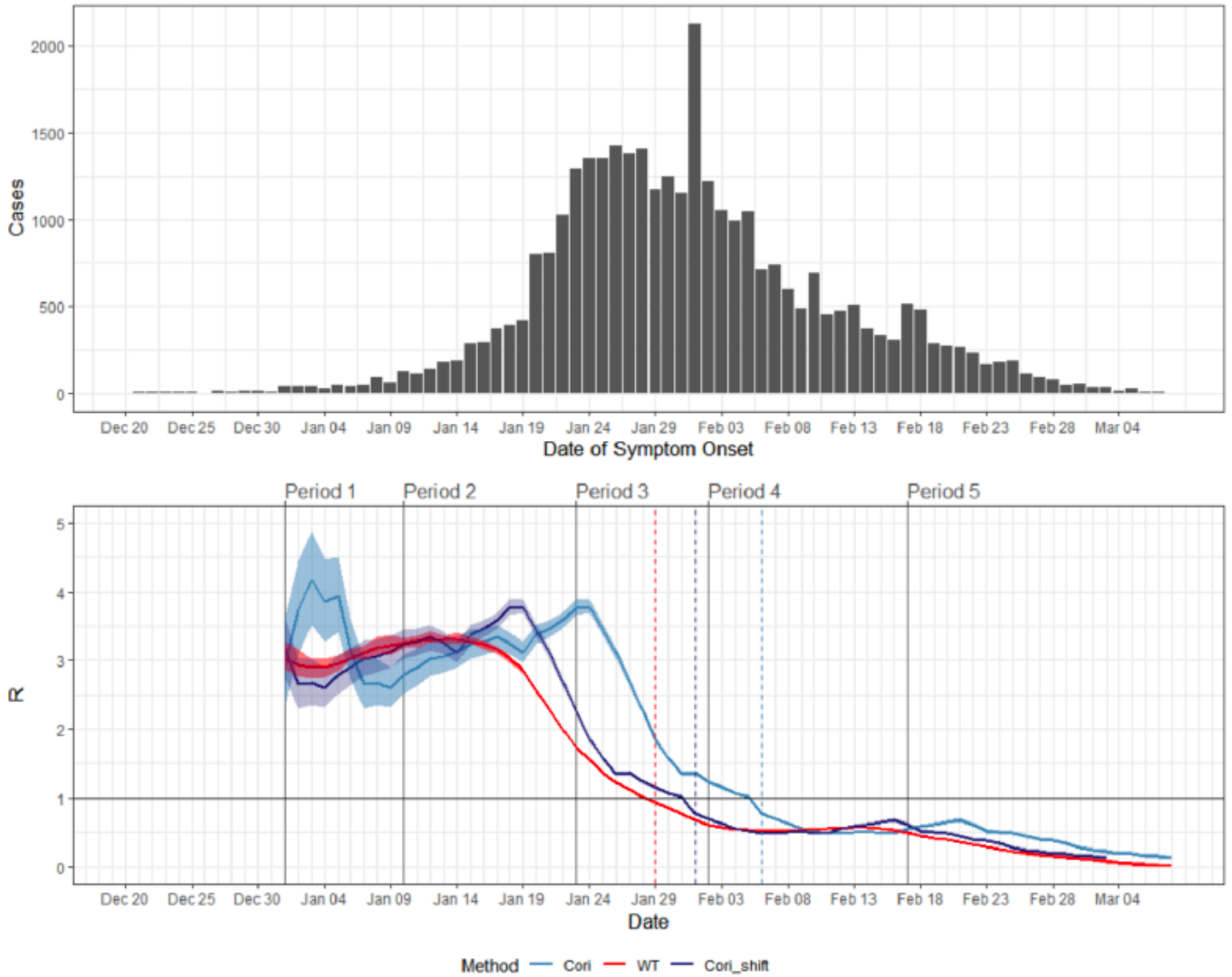
Wallinga and Teunis Method

R_t is the average number of new infections caused (eventually) **by a person who becomes infectious at time *t*.**

→ From the perspective of an observer at time *t*, this is a **leading** estimate. It predicts transmission events that have not yet occurred.



Subtle methodologic choices can lead to major errors in policy evaluation



K Joshi, S Cobey, M Lipsitch

Comment on data from Pan et al. JAMA 2020

The New York Times

Opinion

The United States Needs a 'Smart Quarantine' to Stop the Virus Spread Within Families

Evidence from around the world shows that stay-at-home orders take us only so far.

By Harvey V. Fineberg, Jim Yong Kim and Jordan Shlain

Dr. Fineberg, Dr. Kim and Dr. Shlain specialize in public health.

Sometimes the most important contributions to policy are scientifically dull: expressions of ignorance

CORONAVIRUS

Two Coasts. One Virus. How New York Suffered Nearly 10 Times the Number of Deaths as California.

Marc Lipsitch, a Harvard professor of epidemiology and the director of the Center for Communicable Disease Dynamics, created one of the first modeling tools used in the U.S. for the COVID-19 pandemic. The model was available to both city and state officials in New York in February, a full week before the first confirmed New York case. The state said the Lipsitch model was not one they looked at for guidance. The city did make use of it, and concluded that just a couple of dozen sick people in New York could ultimately produce more than 100,000 cases by the middle of April, which is quite close to what happened.

This work contained nothing scientifically novel

https://rebeccakahn.shinyapps.io/COVID19/

But it did say something important to policy makers (we didn't realize at the time that it was particularly important): Not having a problem you can see should not be reassuring: there may be a problem you don't see

Paradox

Saying the ”obvious” with a model can prompt total rethinking from decision makers but

Saying the obvious with a model is not scientifically rewarding, and is often dependent on model assumptions

(Partial) Resolution?

A model that confirms strongly held priors (often by assuming them) is not useful

A model that causes questioning of strongly held priors (by showing something which is obvious to the modeler, but not necessarily the decision maker, can be useful

Extra-model considerations

How to prepare for/respond to the risk of bioterrorist smallpox (2002)

Terrorists may attack us with smallpox

Choices (simplified)

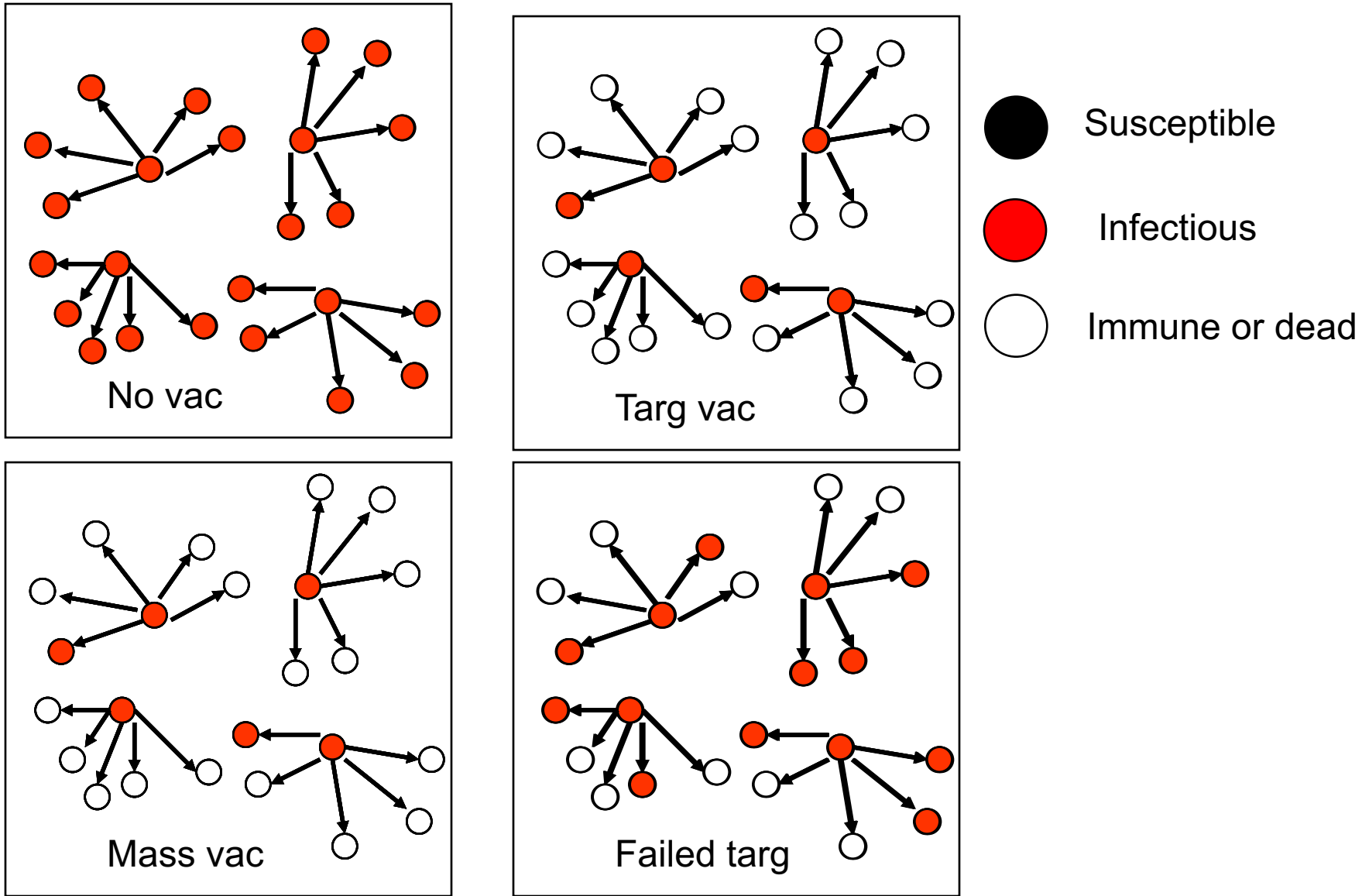
1. Mass vaccinate before anything happens*
2. Mass vaccinate in response to an attack
3. Use targeted vaccination after an attack to vaccinate contacts of infected people (as in the successful eradication campaign)

*Assume for that in 2002 #1 is dangerous and politically unacceptable. So choice is between 2 and 3

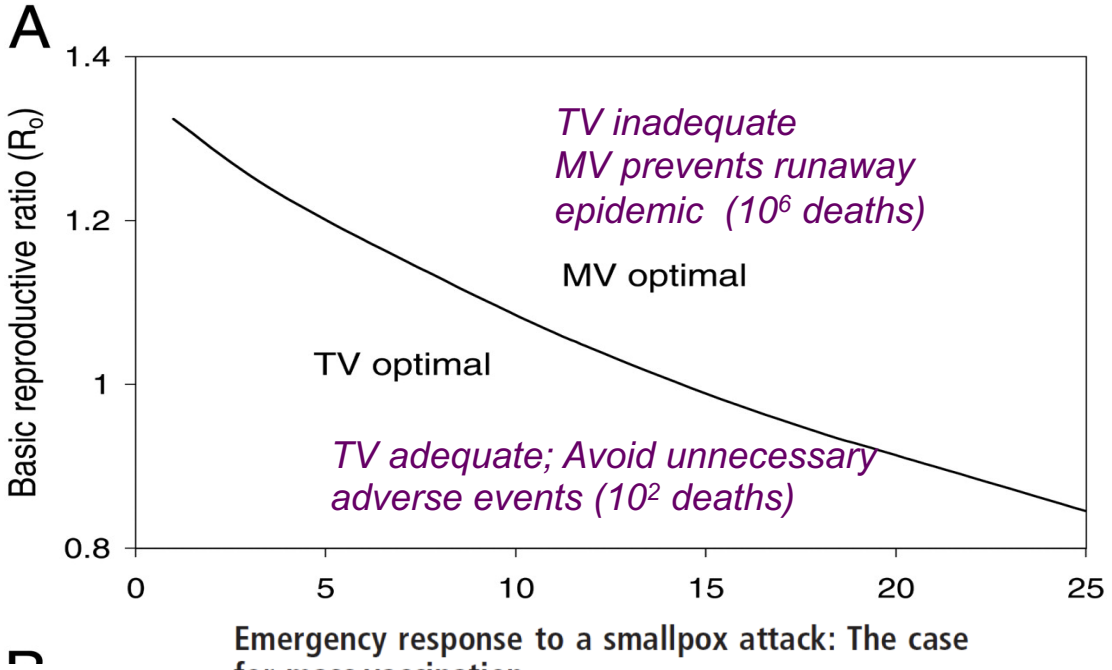
Assumptions about smallpox

- Without a vaccination campaign, millions of cases and deaths occur with high probability given an attack
- Mass vaccination leads to almost certain death of a small fraction of vaccinees due to adverse reactions (order hundreds in US)
- With mass vaccination, only very few secondary cases would occur because disease spread would be stopped by “herd immunity” – each primary case would create only <1 secondary case. But more vaccines used, greater cost.
- With traced vaccination, the same protection might occur, but there is a risk (bigger than with mass vaccination) that it could fail, leading to a large epidemic (millions)
- MV vs TV: tradeoff certainty of more vaccines, more cost and more adverse events vs. reduced risk of large epidemic

Vaccine policies



Formulating different questions with different metrics for success



Emergency response to a smallpox attack: The case for mass vaccination

Edward H. Kaplan*†, David L. Craft‡, and Lawrence M. Wein§

*Yale University School of Management, and Department of Epidemiology and Public Health, Yale School of Medicine, New Haven, CT 06520-8200; and ‡Operations Research Center and §Sloan School of Management, Massachusetts Institute of Technology, Cambridge, MA 02139-3407

Intervention	No residual immunity		
	Deaths per 1000	VE_{III} (%)	Cases prevented per dose
None	97.2	–	–
80% mass vaccination after any cases			
1st case	0.9	99	0.50
15th case	9.4	86	0.77
25th case	13.7	80	0.73
80% targeted vaccination after any cases			
1st case	10.9	88	2.01
15th case	19.6	78	1.57
25th case	28.2	68	1.17

Science AAAS

Containing Bioterrorist Smallpox
M. Elizabeth Halloran, *et al.*
Science **298**, 1428 (2002);
DOI: 10.1126/science.1074674

Implied minimax metric: pick the strategy that minimizes the risk of the worst outcome -> MV better
(also: makes inappropriate assumptions about natural history that favor MV)

MV better to prevent death in most situations (not all)
Abstract emphasizes how TV better in cases prevented per dose
No clear policy conclusion (better natural history)

For this problem, the Kaplan model had lousy assumptions but I argue a better metric: minimax. Minimize the chance of the worst outcome. Halloran et al's cases prevented per dose is unlikely to be relevant for decisions.

Moreover, an extramodel consideration, "reload," arguably trumps the findings of the model: post-attack, MV is the only reasonable policy

- Reload: if there is someone willing and able to do one smallpox attack then the same people and others are probably willing and able to do more. (Richard Danzig, former Sec'y of the Navy)
- Implication: once it's happened, our updated estimate of the risk of more attacks should be much higher than our estimate of the probability of attacks is now.
  - *p(2+ attacks | one attack) [POSTERIOR RISK TO SOMEONE NOT IN THIS OUTBREAK]*

  >> p(at least one attack) [PRIOR RISK TO ANYONE IN THE COUNTRY]
- Thus after an attack anywhere in the US, it would be rational for the public to demand mass vaccination because they want to be protected against future attacks. How little one could get away with in this outbreak is probably irrelevant.

Extra-model considerations (and reload) have implications beyond smallpox

Models of pandemic (H5N1) flu containment had as their outcome stopping spread of *one* highly transmissible strain in humans in ~Thailand

WHO plans for "blanket containment" based on modeled feasibility of such an approach

If we did it (never tried this before), wouldn't there be more introductions? If so, (a) reduces case for blanket containment as one of the efforts will fail, and (b) argues that following a successful containment effort, massive poultry culls would become acceptable even if not before – risk-benefit calculus changes.

Conclusions

- The data suck. The bigger the problem, the more they suck. Your team should include someone with experience working on sucky data (preferably infectious disease data) who need not be a mathematician but shouldn't be scared of you.
- Trying to understand the questions and the assumptions of decision makers is fascinating in itself and also helps make more useful models (≠ most scientifically/mathematically interesting)
- Evaluation metrics can be more important than model results in determining best choices – think carefully about them
- Collaboration!