HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

Epidemiology of COVID-19: Studies Needed, Challenges and Opportunities

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May 22, 2020

Center for Communicable Disease Dynamics

MIDAS Models of Infectious Disease Agent Study

Funded by the National Institutes of Health

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Defining the Epidemiology of Covid-19 — Studies Needed

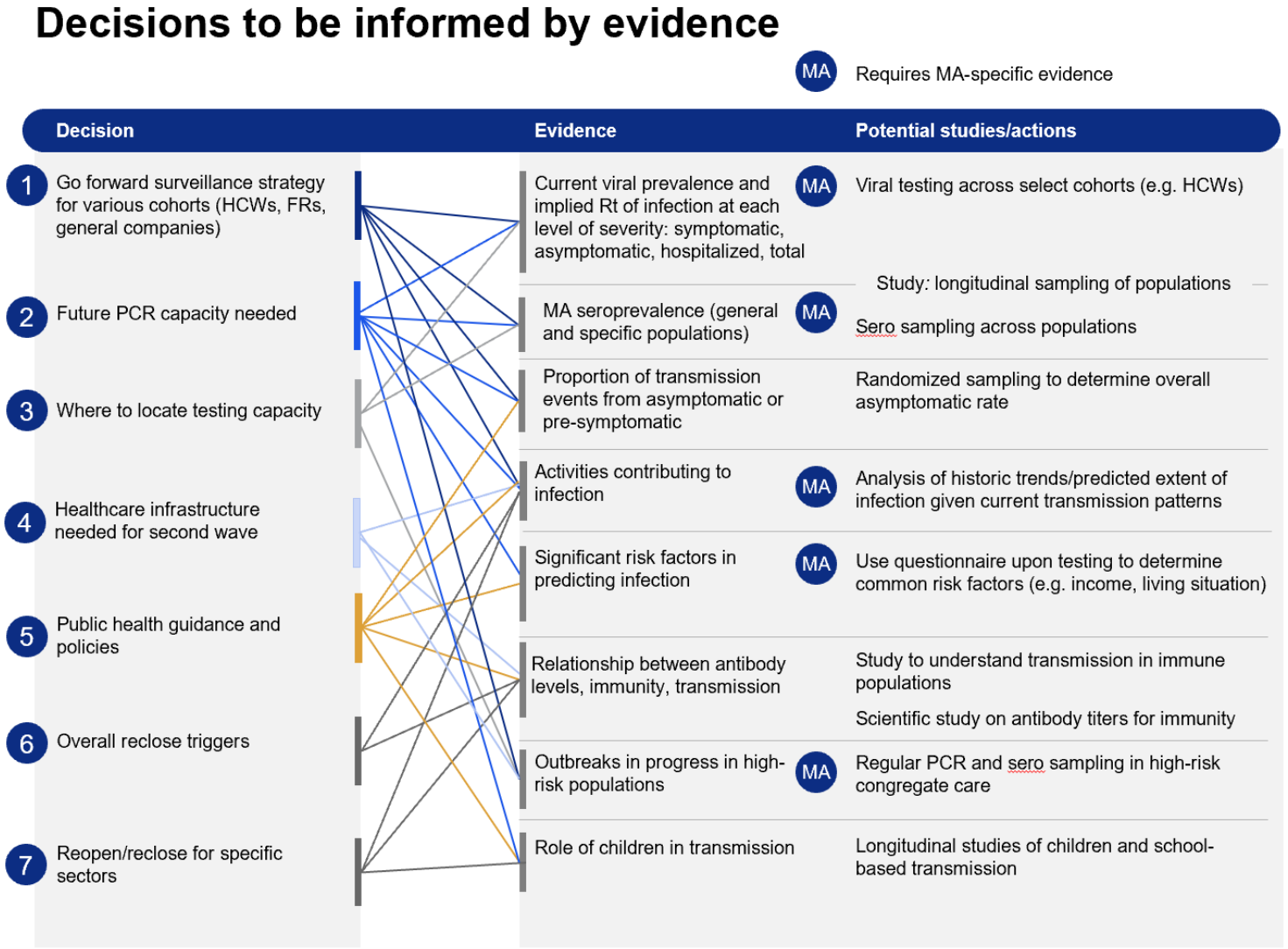
Marc Lipsitch, D.Phil., David L. Swerdlow, M.D., and Lyn Finelli, Dr.P.H.

Types of Evidence Needed for Controlling an Epidemic.

Evidence Needed	Study Type	
No. of cases, including milder ones	Syndromic surveillance plus targeted viral testing	C
Risk factors and timing of transmission	Household studies	B-C
Severity and attack rate	Community studies	B
Severity "pyramid"	Integration of multiple sources and data types	B
Risk factors for infection and severe outcomes, including death	Case–control studies	A-
Infectiousness timing and intensity	Viral shedding studies	B-C

Epublished Feb 19

Epidemiology to inform/ enhance decisions



Massachusetts COVID Command Center

A theme: Each pandemic is different, with its own data-quality challenges

- This paper extrapolated lessons from 2009 H1N1
- Many were relevant, but few were directly applicable due to
  - Different virus and testing challenges
  - Different spectrum of illness
  - Different political and institutional context, eg role of CDC in US response

Number of cases: challenges

- Broad and age-varying spectrum of severity precludes surveillance of one type of case as an indicator

How to maintain surveillance for novel influenza A H1N1 when there are too many cases to count

Marc Lipsitch, Frederick G Hayden, Benjamin J Cowling, Gabriel M Leung

Lancet 2009

- Exacerbated by severe disruptions to the health system that change patterns of care seeking, reduce reliability of traditional indicators (syndromic surveillance, % of visits)
- Hyperpoliticized

Syndromic surveillance and targeted viral sampling

Guidance for 2019-nCov surveillance in high burden settings

Due to high burden of infections in some areas, efforts to track most 2019-nCoV cases have become impractical, leading to increasing burden for the public health system and unreliable data. This surveillance guideline was adapted from an article in *Lancet*, 2009 by Prof. Marc Lipsitch, an infectious disease epidemiologist from Harvard, and colleagues.

Step 1: Syndromic surveillance

Measure the ***incidence of syndromes*** that are common presentations of nCoV: acute respiratory infection, influenza-like illness or severe acute respiratory infection.

Collect, count, and report:

1. ILI or ARI outpatient numbers

and

1. SARI and/or pneumonia inpatient numbers

Methods:

1. Utilize/improve existing ILI surveillance system

or

2. Repeated population-based surveys by tel/internet/SMS

or

3. Enroll a large, geographically dispersed cohort, who report every day/week on symptoms of household members via electronic surveys

Step 2: Targeted viral sampling

For a subset of cases of step 1 syndromes, test for nCoV for the purposes of estimating ***the attributable fraction of each syndrome that is due to nCoV.***

Collect, count, and report (in sustainable time interval)

1. 2019-nCov testing for some or all ARI and/or pneumonia inpatients

and

2. 2019-nCov testing, and viral sample collection, from all SARI or pneumonia patients in ICU

Methods:

1. Ensure specific personnel tasked with collecting, labeling and transporting samples and data

and

2. If random sample testing cannot be ensured, pre-specify standards for testing, e.g. only test deaths/most severe cases, or test one specific ICU every day. Leave little discretion to providers.

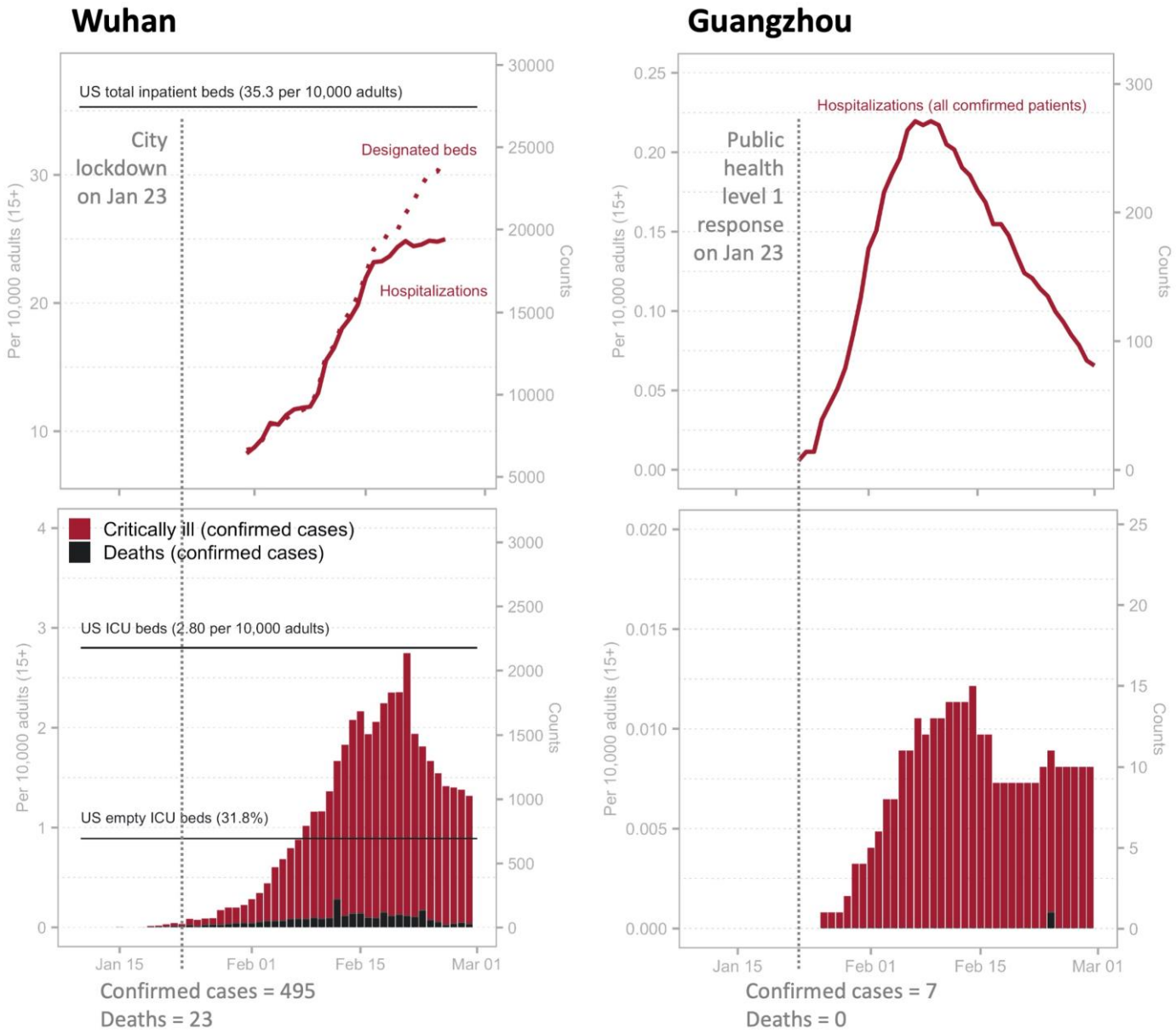
- NOTE: Clinical care should not depend on whether a patient is selected for testing

Step 3: Estimate of incidence of symptomatic nCoV infection = Syndrome incidence X Attributable fraction of syndrome for nCoV

(Can disaggregate by time, space, population subgroups, and different symptoms)

Feb 2, 2020, Ruoran Li (Harvard T.H. Chan School of Public Health), Qi Tan (Harvard Medical School), Marc Lipsitch (Harvard T.H. Chan School of Public Health)

Hospitalized and ICU cases are a lagging indicator due to delays

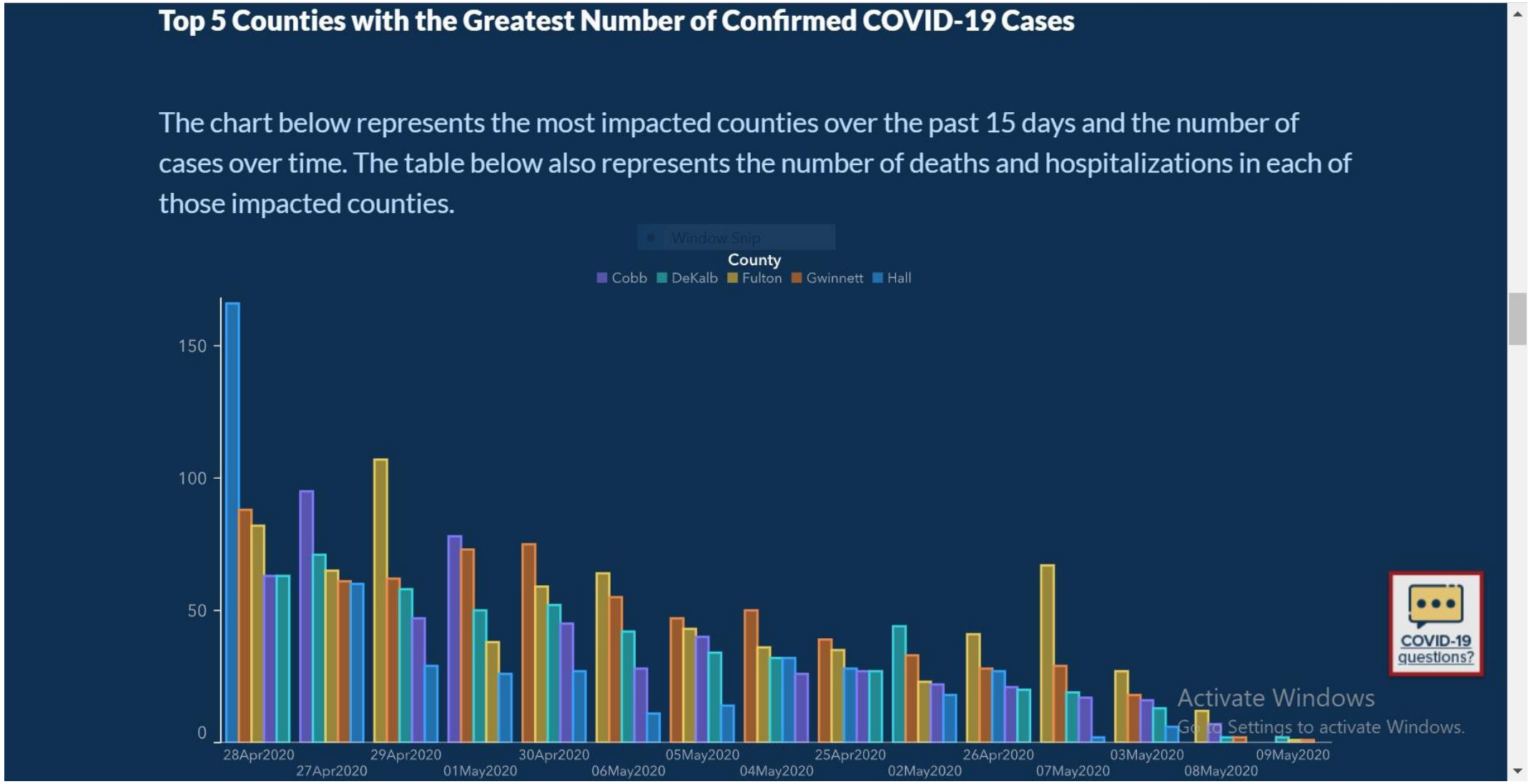


From R Li et al. JAMA Network Open 2020

Representativeness: a constant challenge

- Testing is unpleasant enough (serologic or virologic) that many will decline
- Willingness to be tested likely higher among those who suspect they are (or were) sick
- Vocal criticism of individual studies

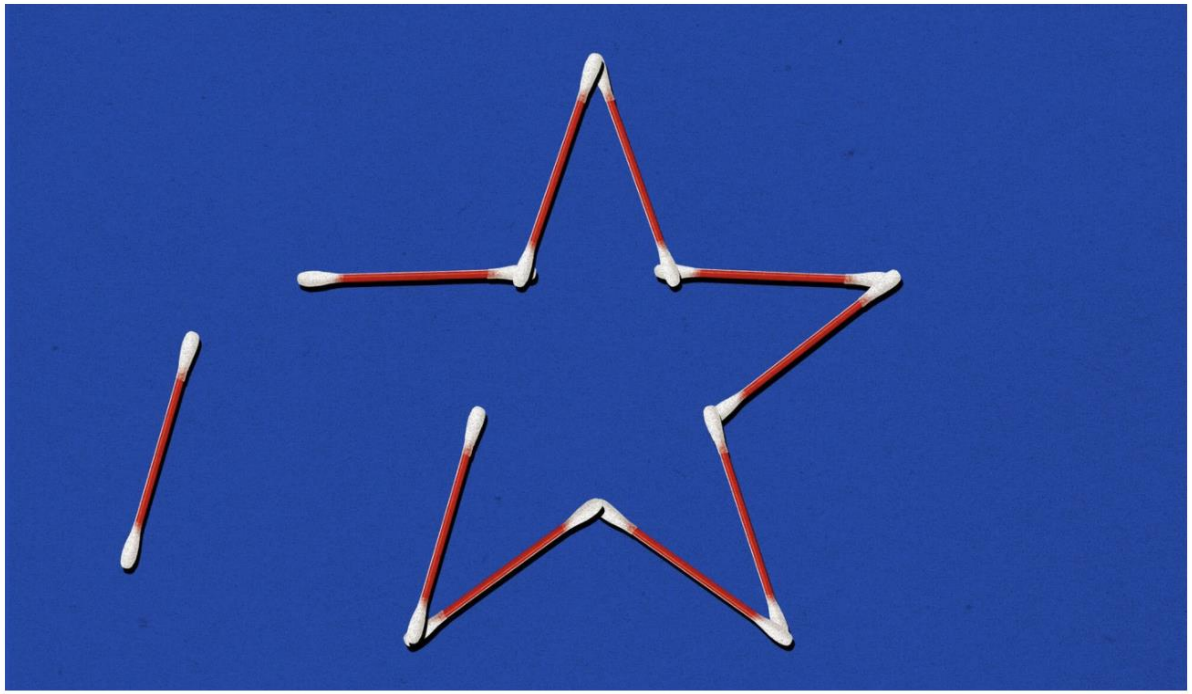
Politicization



How Virginia Juked Its COVID-19 Statistics

The state is combining results from viral and antibody tests in the same statistic. This threatens to confound America's understanding of the pandemic.

ALEXIS C. MADRIGAL AND ROBINSON MEYER MAY 13, 2020



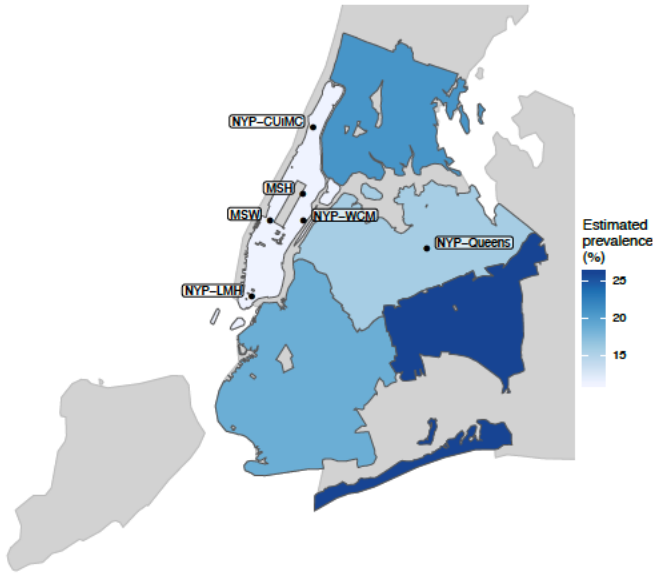
GETTY / THE ATLANTIC

Opportunities to improve case counting

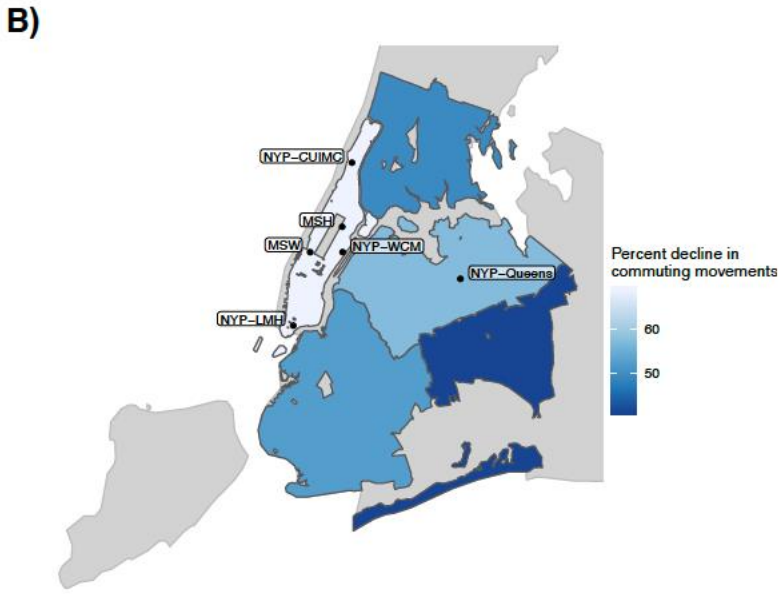
- Prevalence and seroprevalence testing in representative populations
  - Probability sample: national statistical agency (Spain, UK)
  - Virus testing of delivering mothers and infant dried blood spots for maternal serology
  - For health care delivery that is still functioning, testing of those coming in for non-COVID complaints (eg all admissions to hospital, all emergency visits, etc)
  - No good solution to how to get absolute case numbers, but at least relative to determine trend of the epidemic.

Maternal testing at NYC hospitals

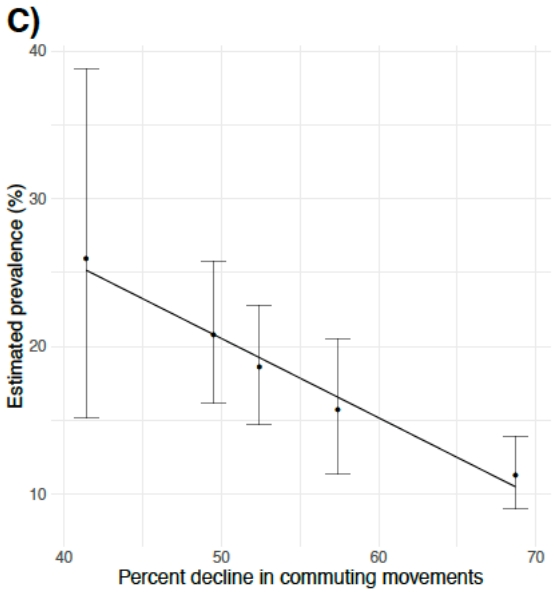
Maternal virus prevalence



Reduction in movement



Correlation

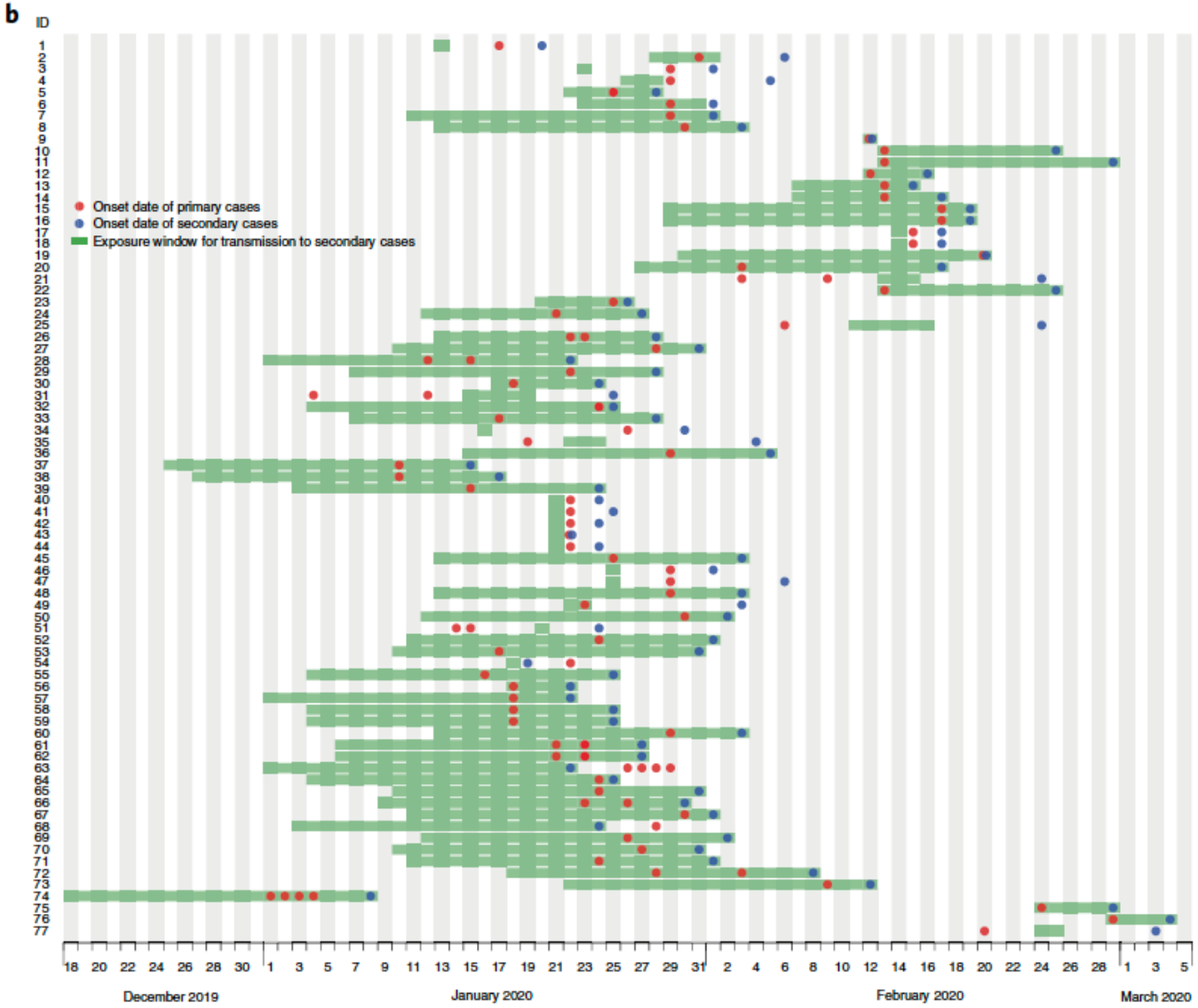


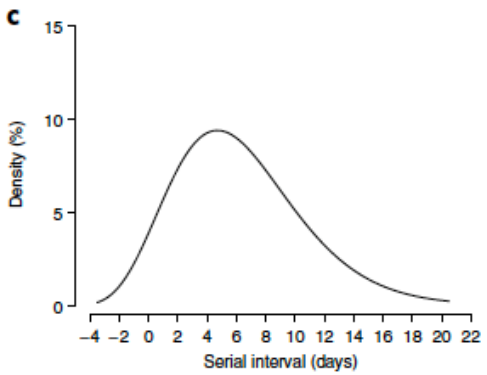
Kissler et al. 2020 https://dash.harvard.edu/handle/1/42665370 preprint

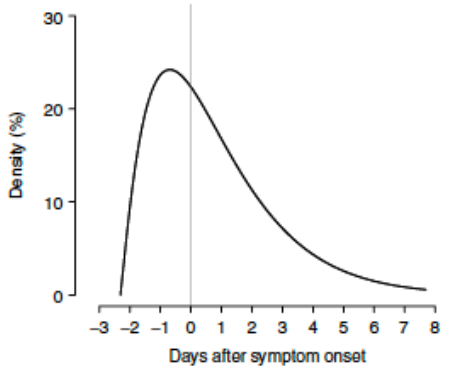
Risk factors and timing of transmission: Challenges

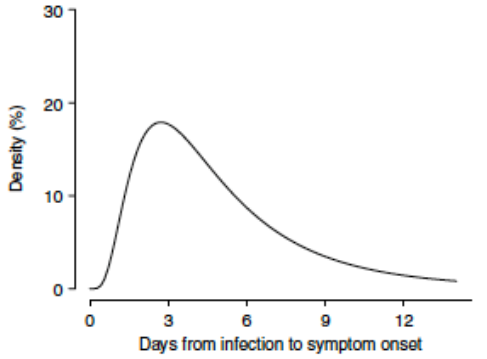
- Variable symptom profile and natural history makes contact tracing hard
- Common symptoms:
  - Fever
  - Dry cough
  - Fatigue
- Severe symptoms:
  - Difficulty breathing, shortness of breath
  - Chest pain or pressure
  - Loss of movement or speech
- Less common symptoms:
  - Aches and pains
  - Sore throat
  - Diarrhoea
  - Conjunctivitis
  - Headache
  - Loss of taste or smell
  - Rash or discoloration

Presymptomatic transmission common



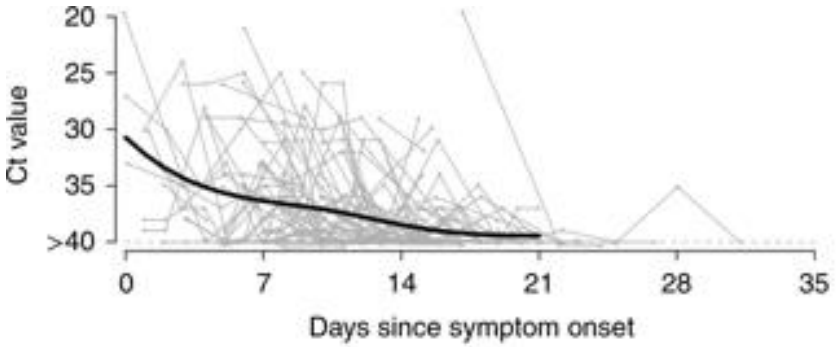


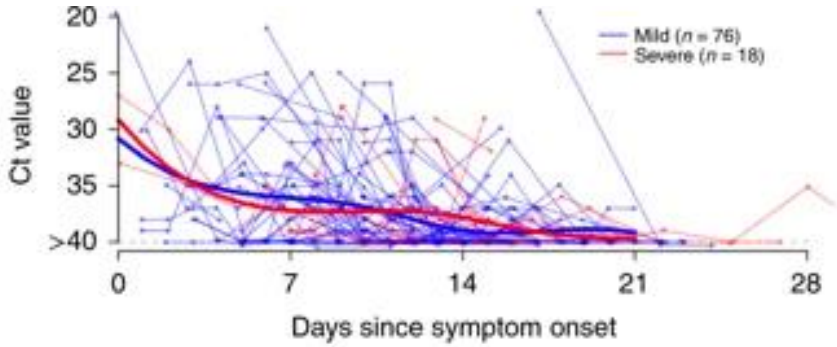


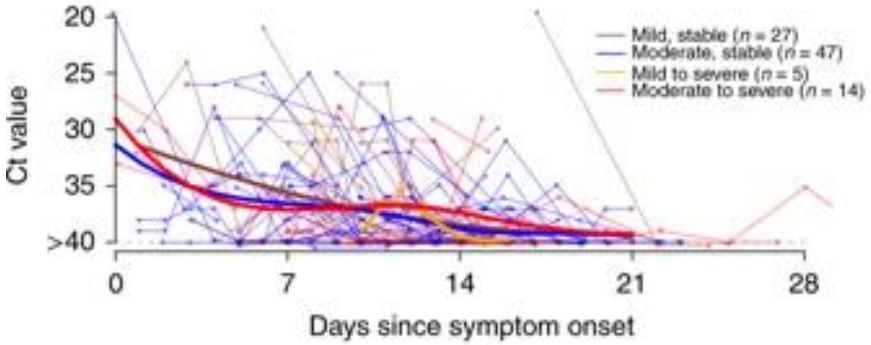


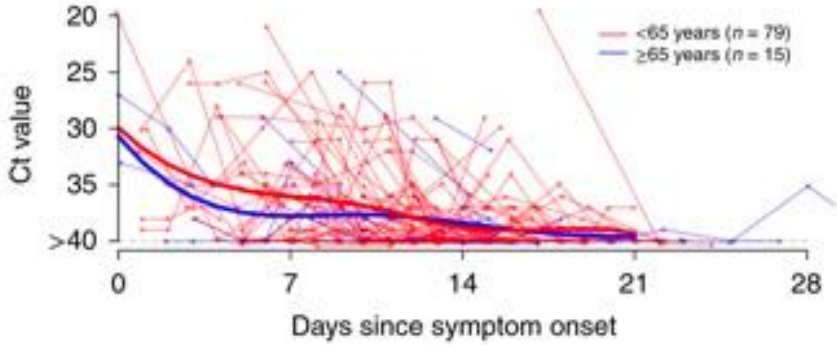
He et al.
Nature Med 2020

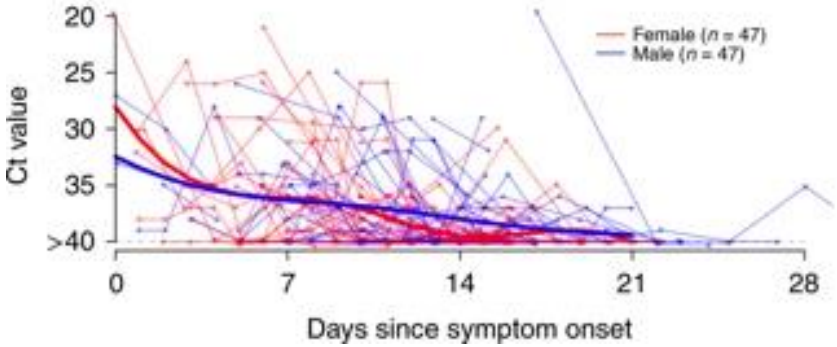
Timing of shedding

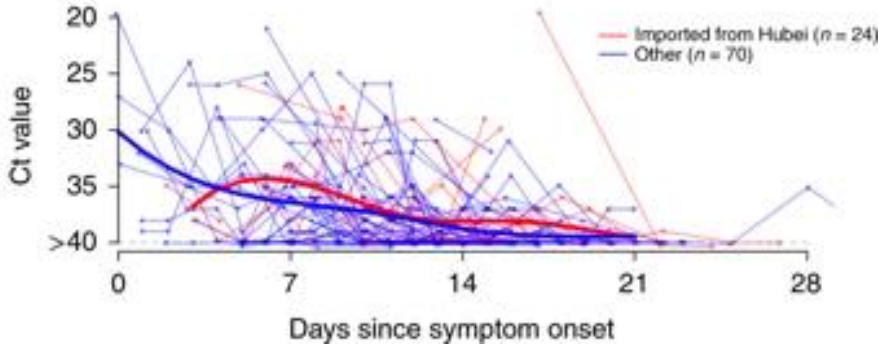








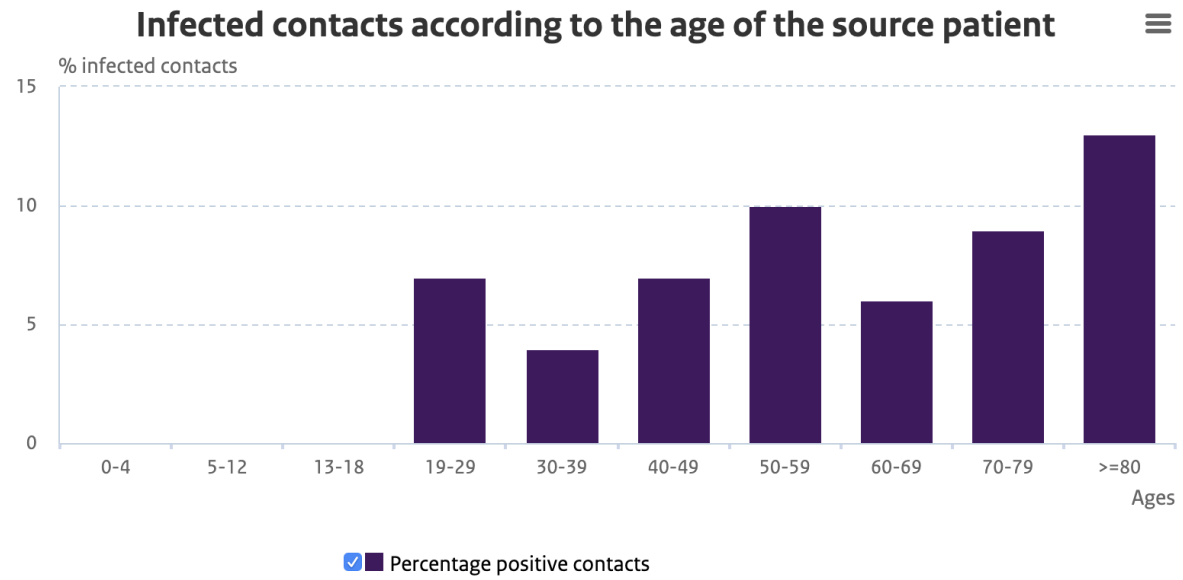




He et al.
Nature Med 2020

Risk factors for transmission still poorly defined, specifically age

- Likely highly contextual
- Role of children as transmitters is key for school opening, but poorly known.



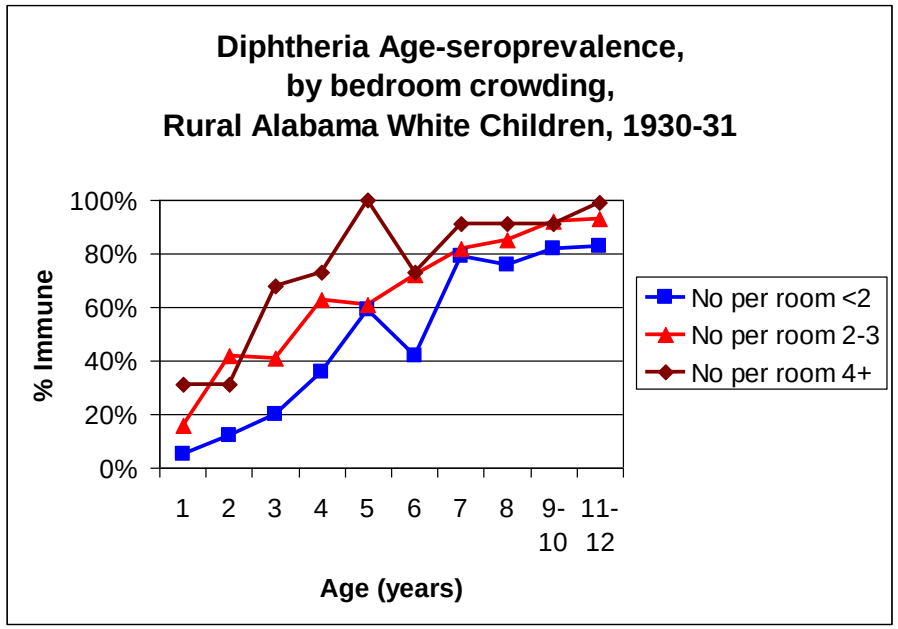
NL RIVM https://www.rivm.nl/en/novel-coronavirus-covid-19/children-and-covid-19

Opportunities: Social seroepidemiology

RESEARCH ARTICLE

Human *Trypanosoma cruzi* infection is driven by eco-social interactions in rural communities of the Argentine Chaco

Maria del Pilar Fernández[1,2,3]*, Maria Sol Gaspe[1,2], Paula Sartor[1,4,5], Ricardo E. Gürtler[1,2]



From: OL Chason, DPH Thesis, HSPH, 1933. Diphtheria Immunity in Rural Alabama: A survey of social conditions, environment, and Schick Test Results

- Poverty, race associated with bad outcomes and with infection risk
- We don't know why
  - Just outcomes, or also infection?
  - Preexisting medical conditions?
  - "social distancing is a luxury":
    - Household crowding/challenge in distancing?
    - Having to work outside the home
  - Public transport?
- Good social epidemiology on causal risk factors for seropositivity much needed!
- Informs interventions!

Opportunities: Local patterns may vary with demography, co-residence patterns

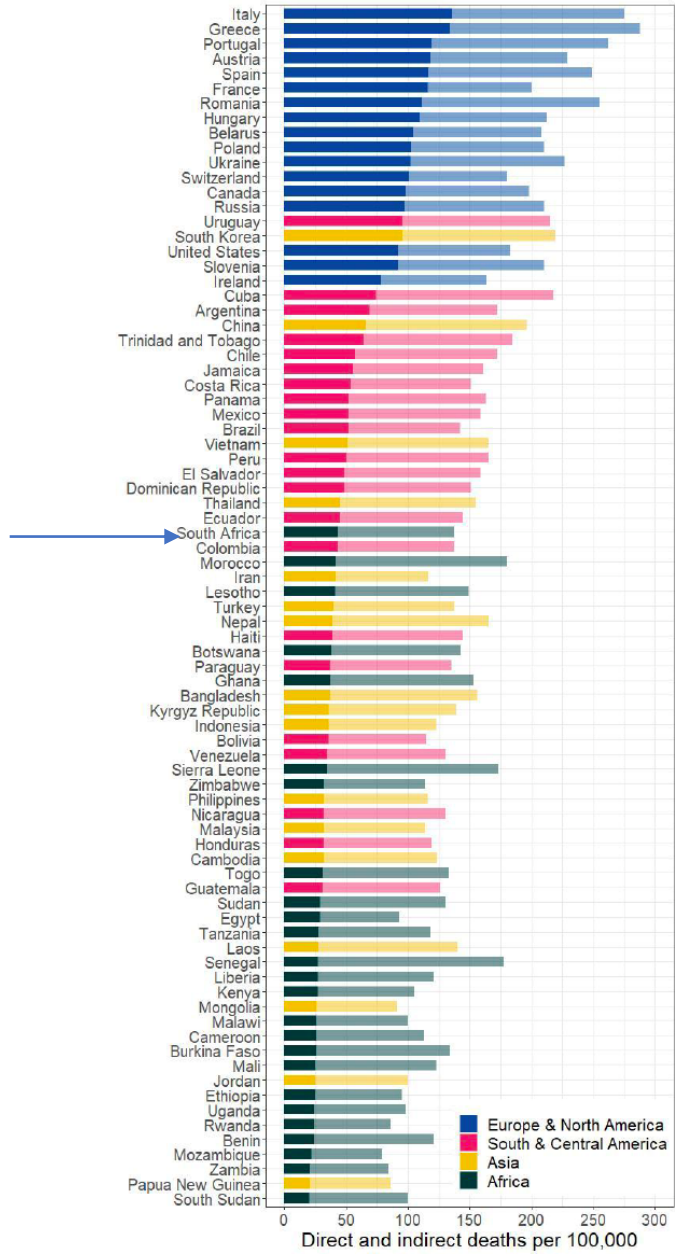


Figure 1. Covid-19 vulnerability to national age and co-residence patterns.

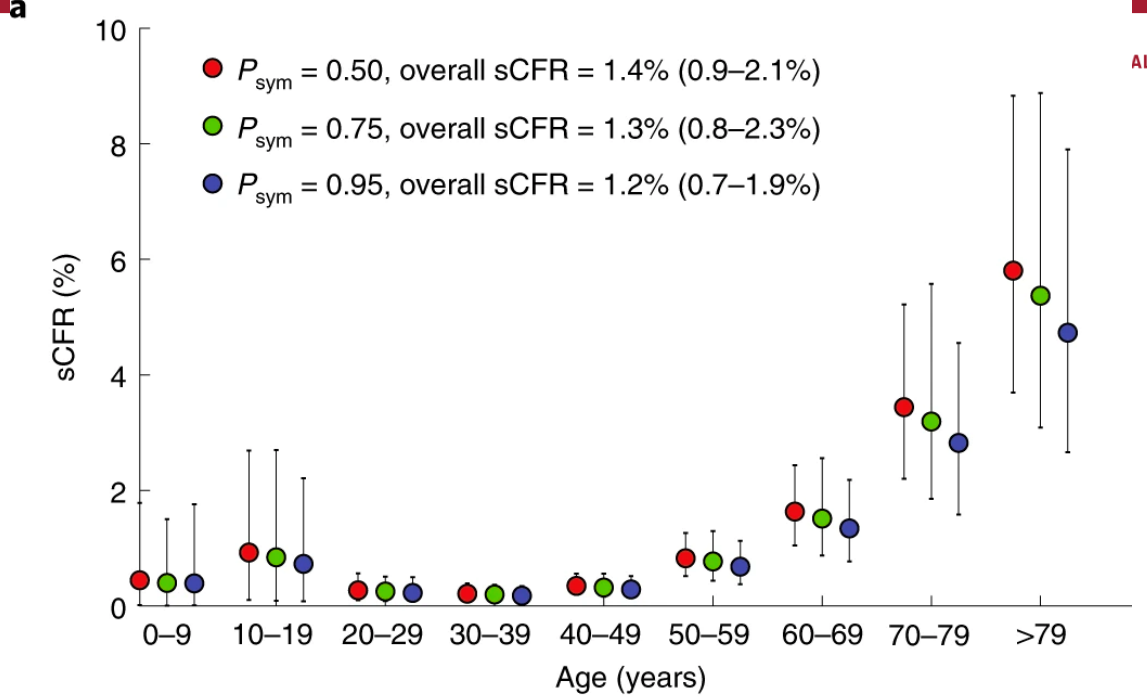
Estimated number of direct (dark) and indirect (light) deaths per 100,000 individuals if 10% of the population living in private households were to be infected by covid-19 at random.

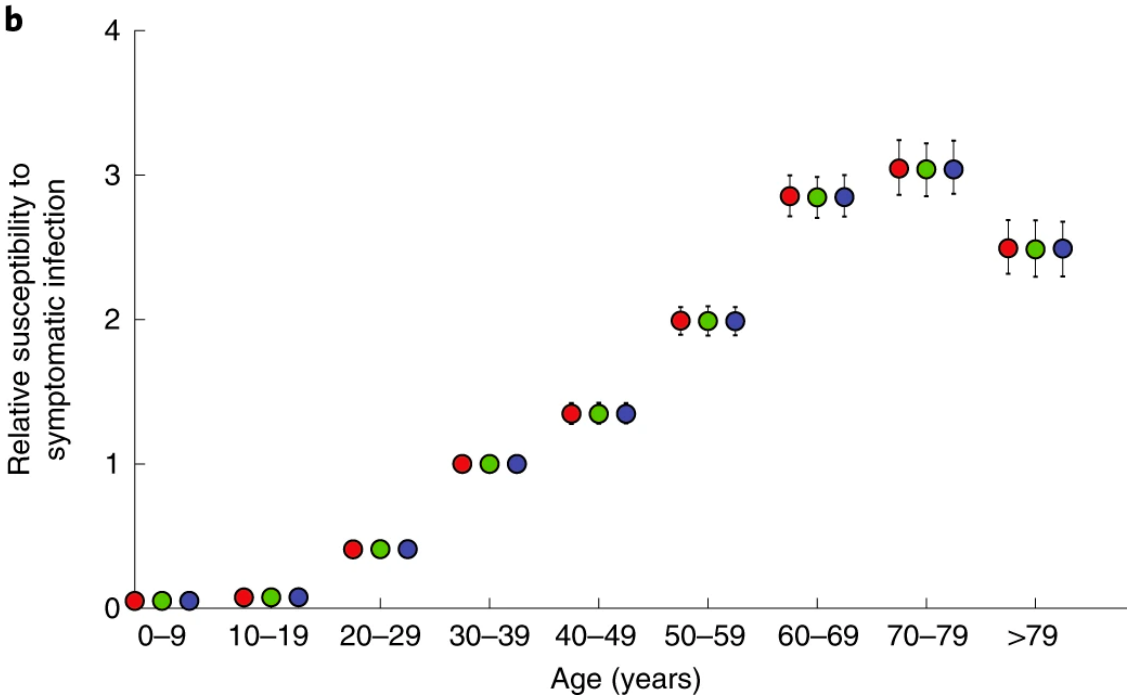
Esteve et al Medrxiv
https://www.medrxiv.org/content/10.1101/2020.05.13.20100289v1

Severity

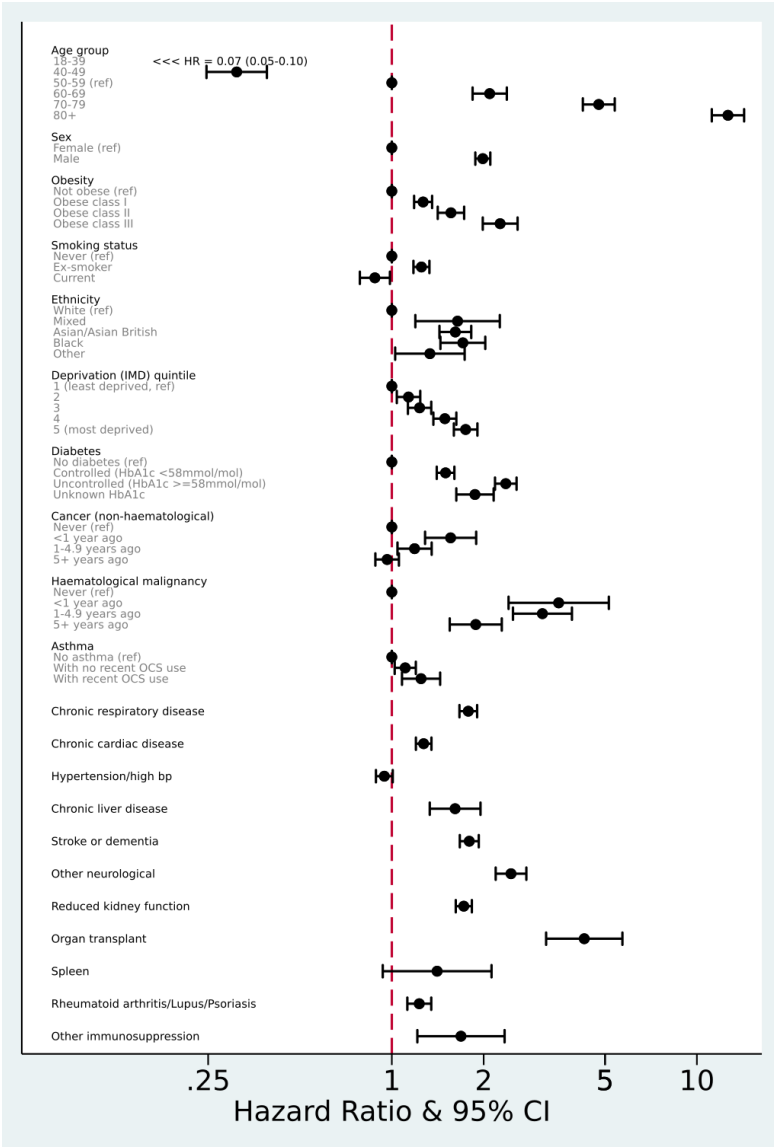
Case-Fatality Ratio among Symptomatics (sCFR) increases dramatically with age

JT Wu et al. Nature Med 2020





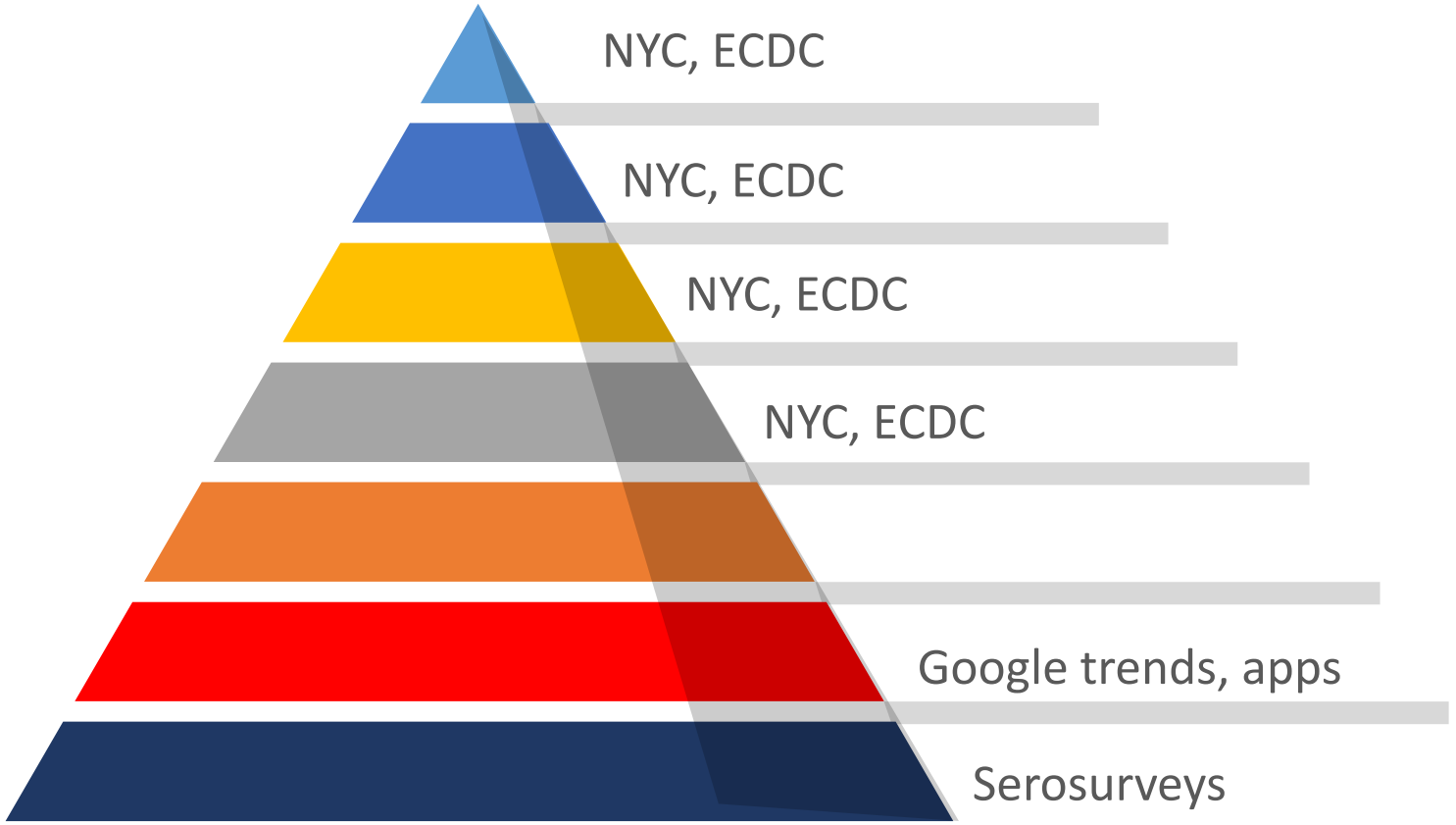
Mortality risk depends on many factors



The OpenSAFELY Collaborative
https://www.medrxiv.org/content/10.1101/2020.05.06.20092999v1

COVID 19 Severity Pyramid

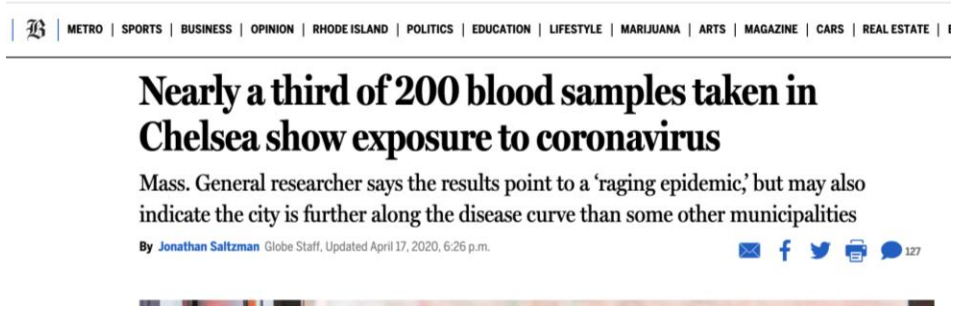
LEVELS		DATA
01	DEATHS	NYC, ECDC
02	MECHANICAL VENTILATION	NYC, ECDC
03	INTENSIVE CARE	NYC, ECDC
04	HOSPITALIZED	NYC, ECDC
05	MEDICALLY ATTENDED ?	
06	SYMPTOMATIC ?	Google trends, apps
07	SEROLOGICALLY INFECTED	Serosurveys



K Joshi and R Niehus

Serological base

Seroepidemiology for estimating herd immunity


B | METRO | SPORTS | BUSINESS | OPINION | RHODE ISLAND | POLITICS | EDUCATION | LIFESTYLE | MARIJUANA | ARTS | MAGAZINE | CARS | REAL ESTATE

Nearly a third of 200 blood samples taken in Chelsea show exposure to coronavirus

Mass. General researcher says the results point to a 'raging epidemic,' but may also indicate the city is further along the disease curve than some other municipalities

By Jonathan Saltzman Globe Staff, Updated April 17, 2020, 6:26 p.m.


The New York Times

1 in 5 New Yorkers May Have Had Covid-19, Antibody Tests Suggest

Accurate antibody testing is a critical tool to determine if the pandemic has slowed enough to begin restarting the economy.

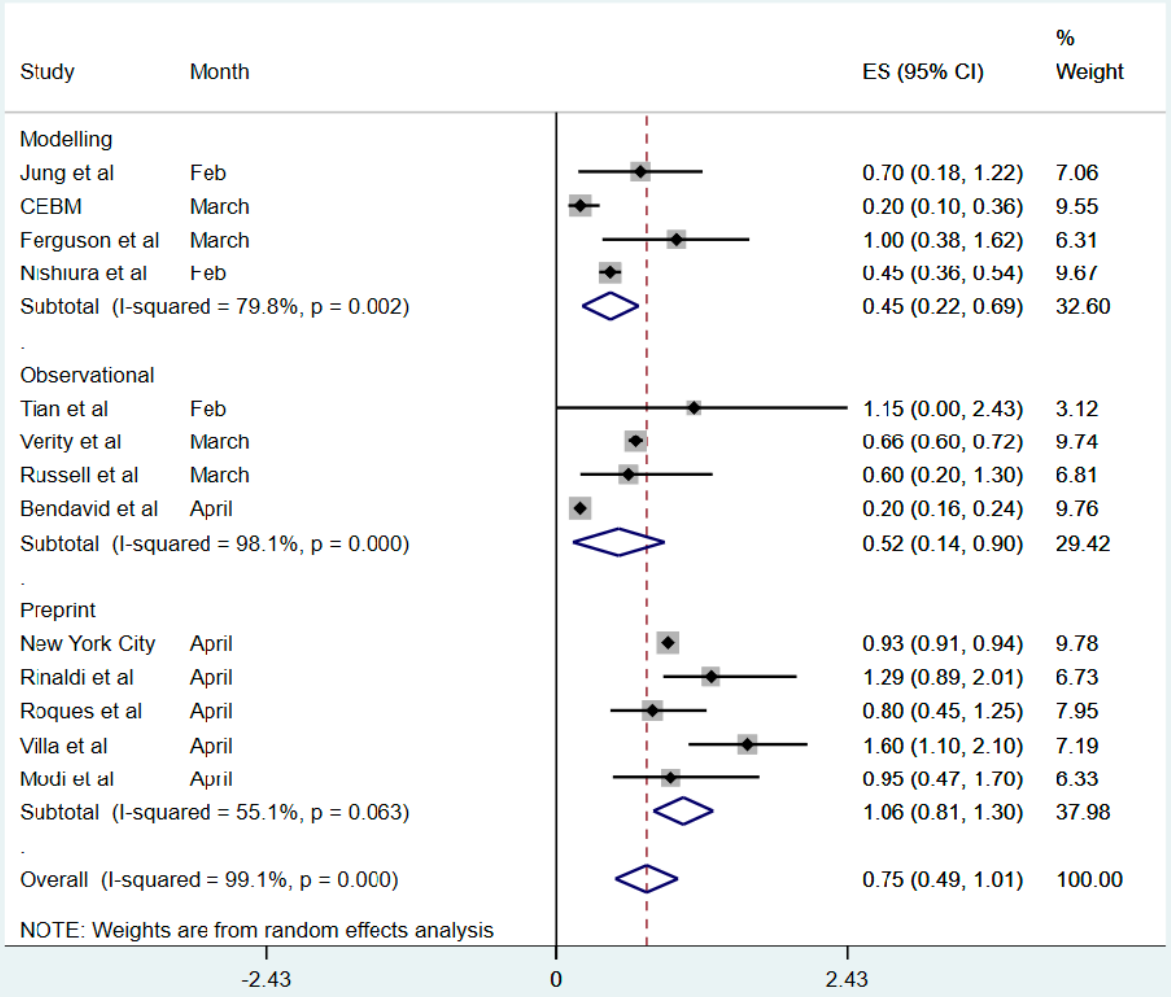
- ✓ Great geographic variation
- ✓ High disease reflects high infection burden
- ✓ Much undetected infection
- ✓ A little nonspecificity can ruin a study
- ✓ Need expert statistical input
- ✓ Hazards of overinterpretation


salon NEWS & POLITICS | ECONOMY & INNOVATION | CULTURE | SCIENCE & HEALTH | FOOD | LIFE STORIES | VIDEO

Medical students, faculty and volunteers take blood samples during a coronavirus antibody study at Mountain View's First Presbyterian Church in Mountain View, Calif. (Ray Chavez/MediaNews Group/The Mercury News/Getty Images)

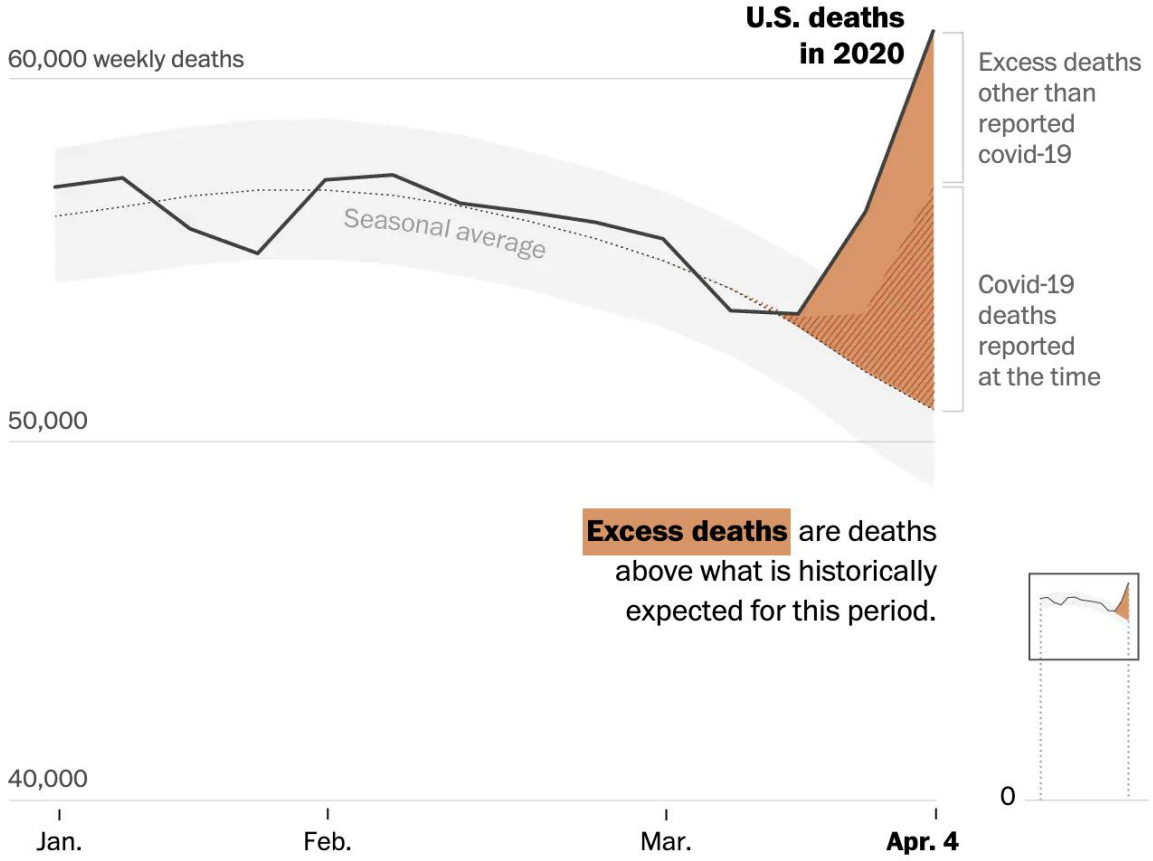
Scientists feud over hyped Stanford coronavirus antibody study: "The authors owe us all an apology"

Infection-fatality rate



G Meyerowitz-Katz et al.
https://www.medrxiv.org/content/10.1101/2020.05.03.20089854v1.full.pdf

Undetected deaths/collateral damage



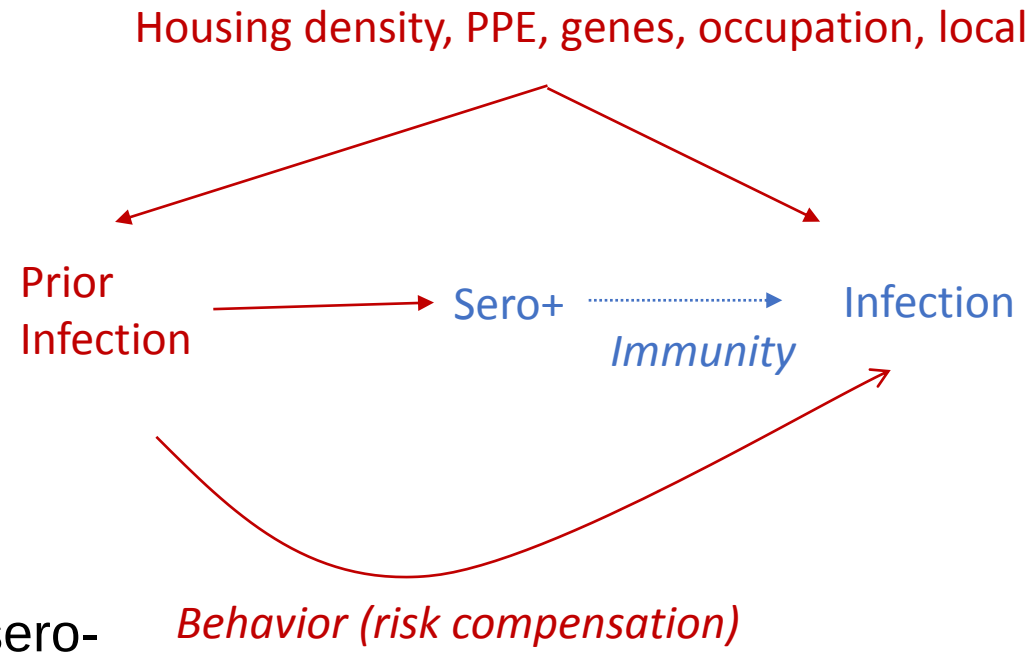
D Weinberger
Yale SPH
Washington Post

Opportunities: severity

- Role of biological age vs exposures esp. those rare in US, China, Europe – explore risk factors in younger populations
- Use of DSS to capture outcomes

Seroprotection: Does antibody indicate immunity to infection? Which? How much?

- Hard study to do
- Confounding is rampant



- Want biological effect only
- Must ensure comparability of sero+ and sero-
  - HCW studies may be optimal
  - Choice of comparators in cohort studies with similar geographic, SES, and occ exposures

Kahn, Kennedy-Shaffer, Robins, Lipsitch
https://www.medrxiv.org/content/10.1101/2020.05.02.20088765v1

Halloran *et al. BMC Medicine* (2017) 15:223
DOI 10.1186/s12916-017-0985-3

BMC Medicine

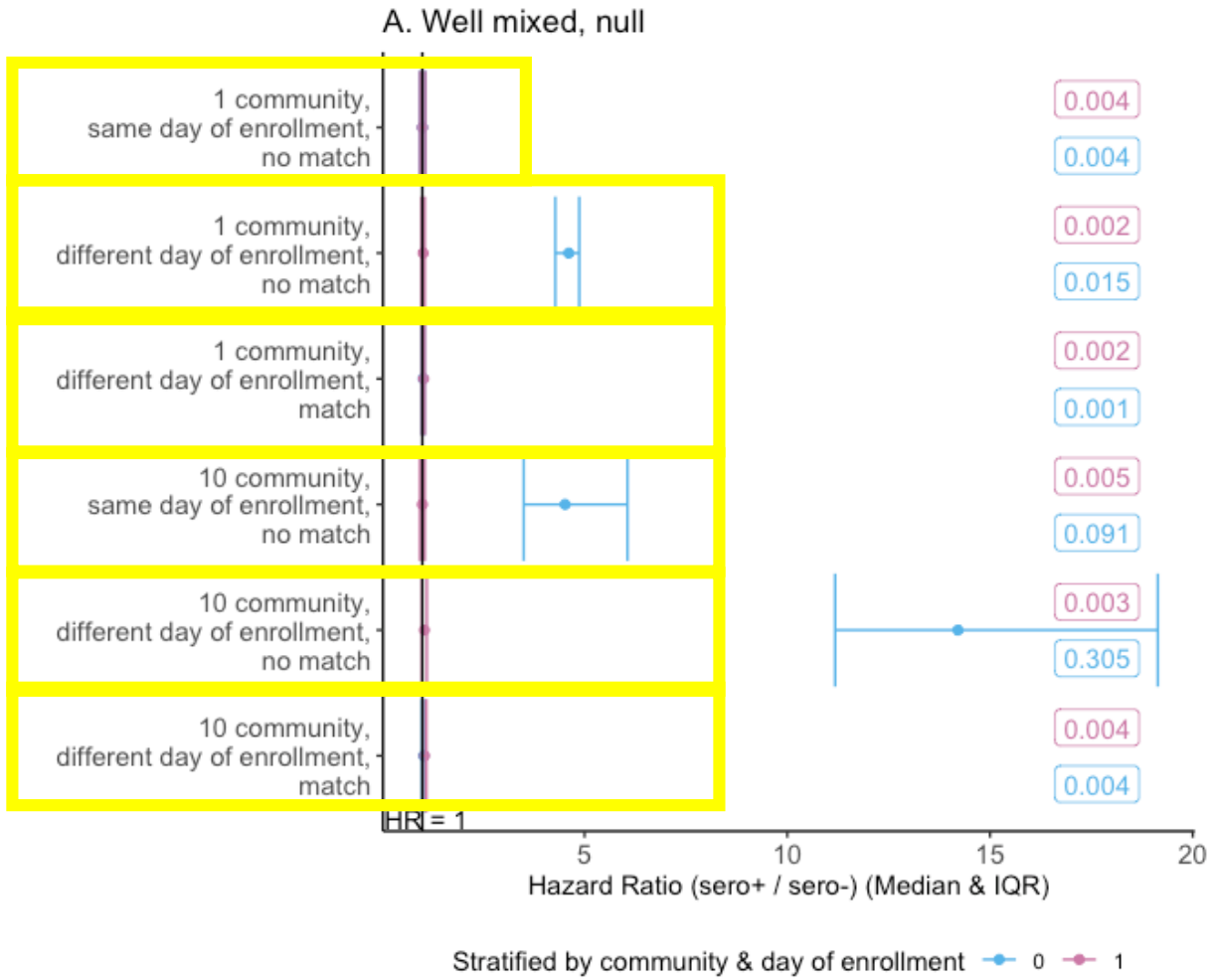
OPINION Open Access

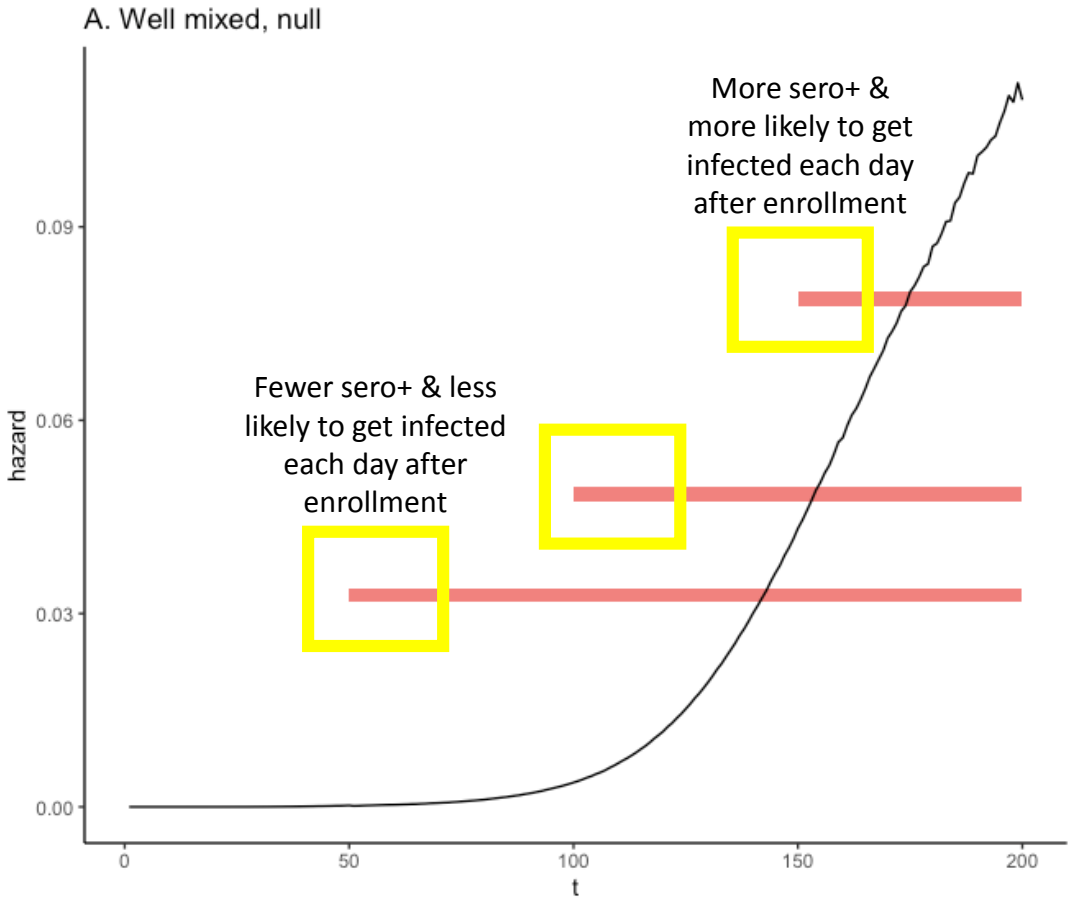
Simulations for designing and interpreting intervention trials in infectious diseases

M. Elizabeth Halloran[1,2*], Kari Auranen[3], Sarah Baird[4], Nicole E. Basta[5], Steven E. Bellan[6], Ron Brookmeyer[7], Ben S. Cooper[8], Victor DeGruttola[9], James P. Hughes[2], Justin Lessler[10], Eric T. Lofgren[11], Ira M. Longini[12], Jukka-Pekka Onnela[9], Berk Özler[13], George R. Seage[14], Thomas A. Smith[15,16], Alessandro Vespignani[17], Emilia Vynnycky[18,19] and Marc Lipsitch[14]

And observartional studies!

Well mixed, no control, null (HR =1)



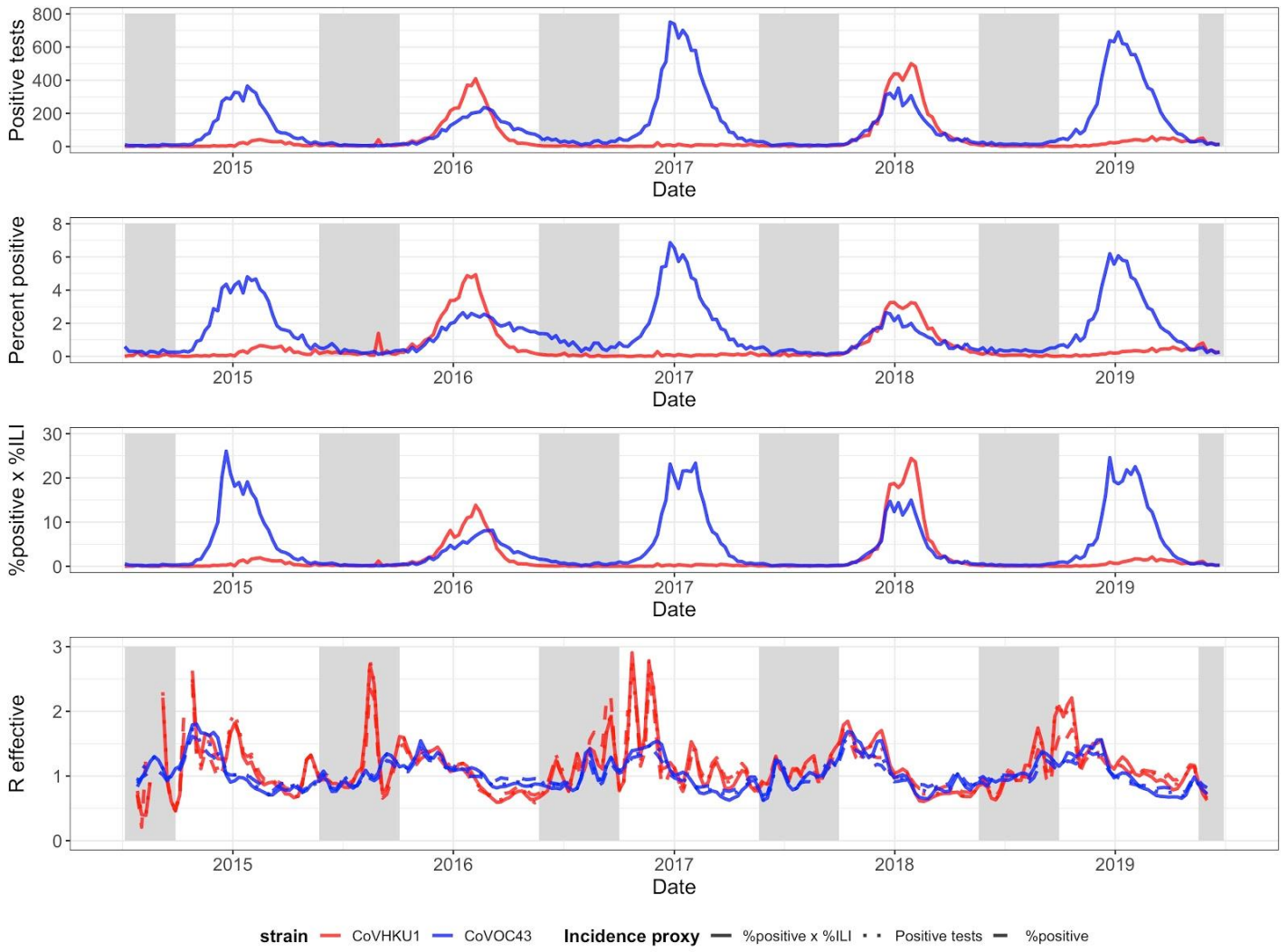


Other potential biases

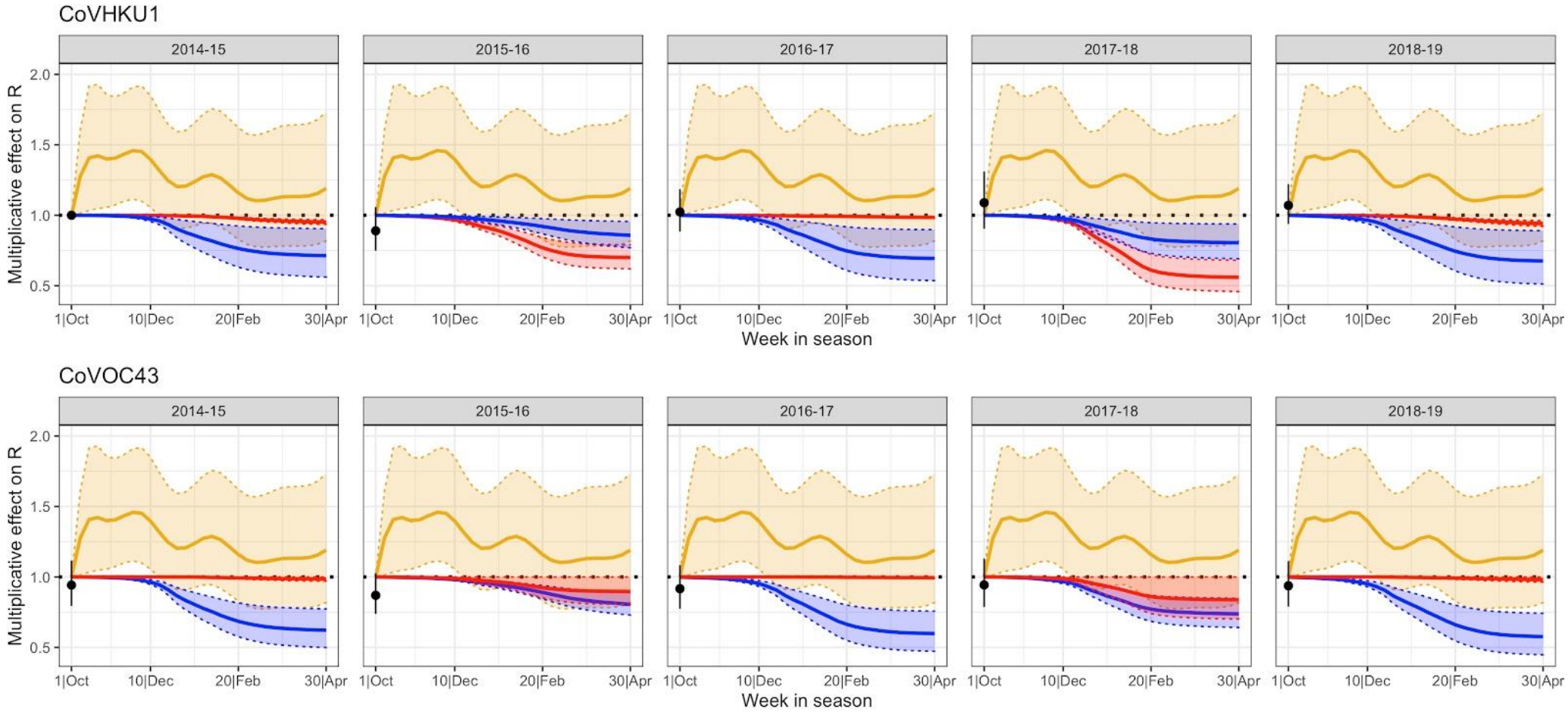
- From epidemic dynamics
  - Clustering within communities: network effects induce confounding between past and future risk of infection
- From other effects
  - Simple differential exposure (occupation, household density, PPE for HCW, etc)
  - Risk compensation

Seasonality

Beta coronavirus incidence in the US

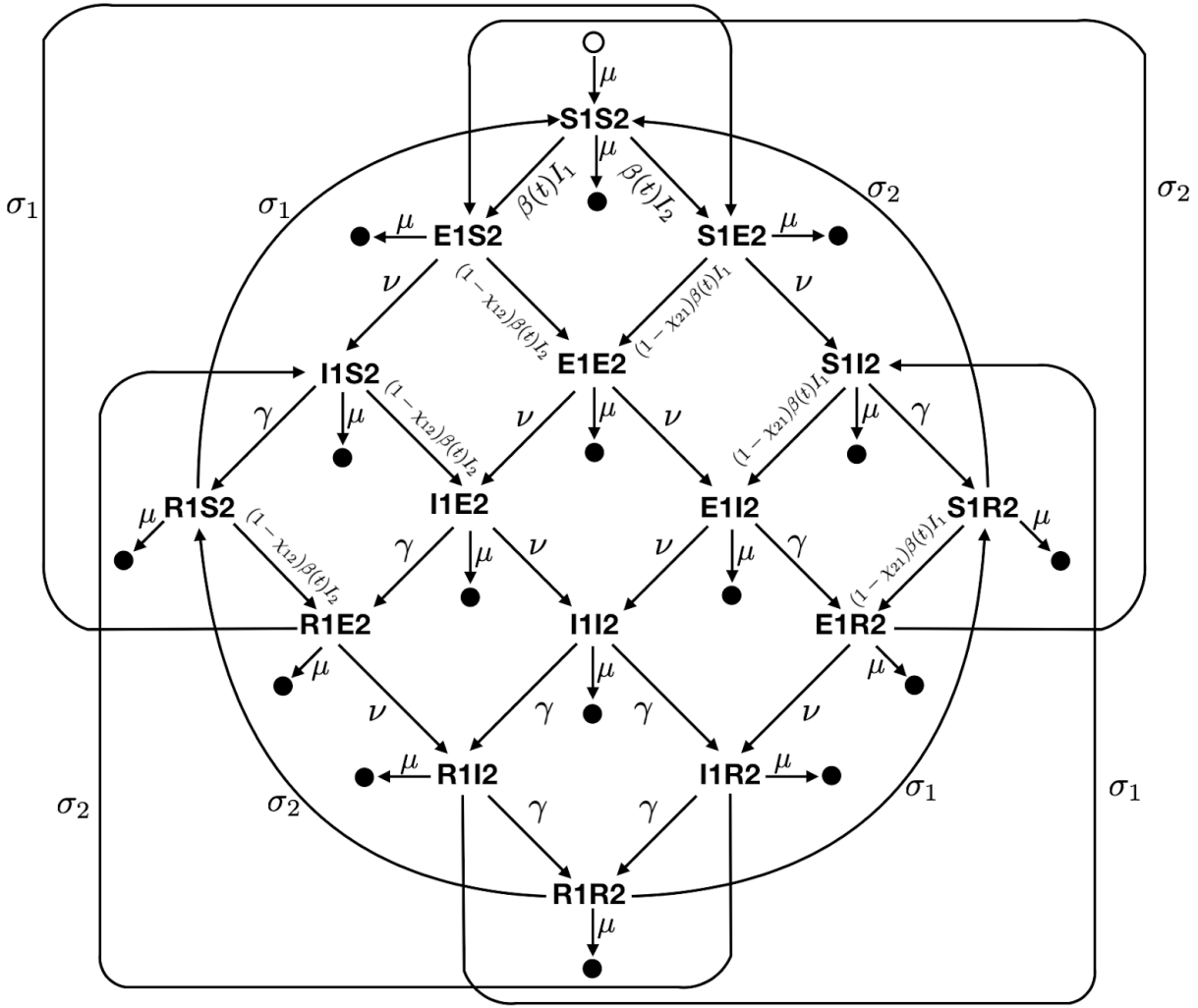


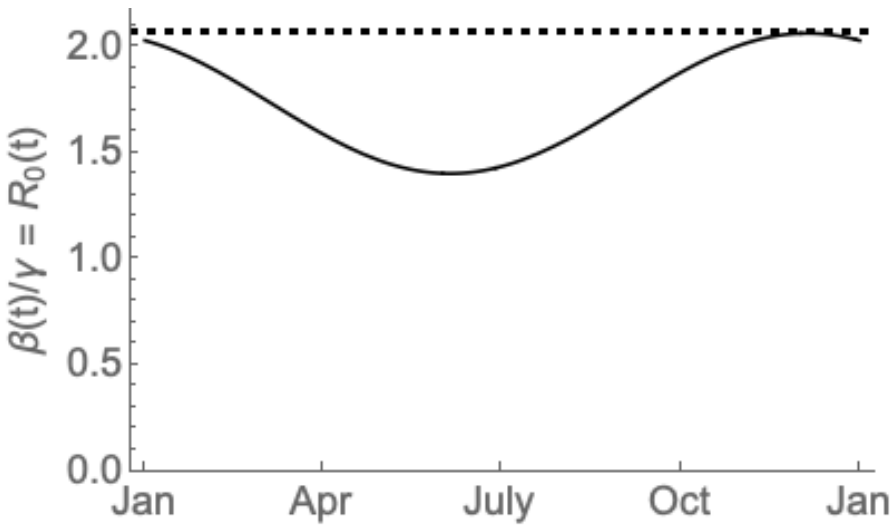
Decomposing R_e



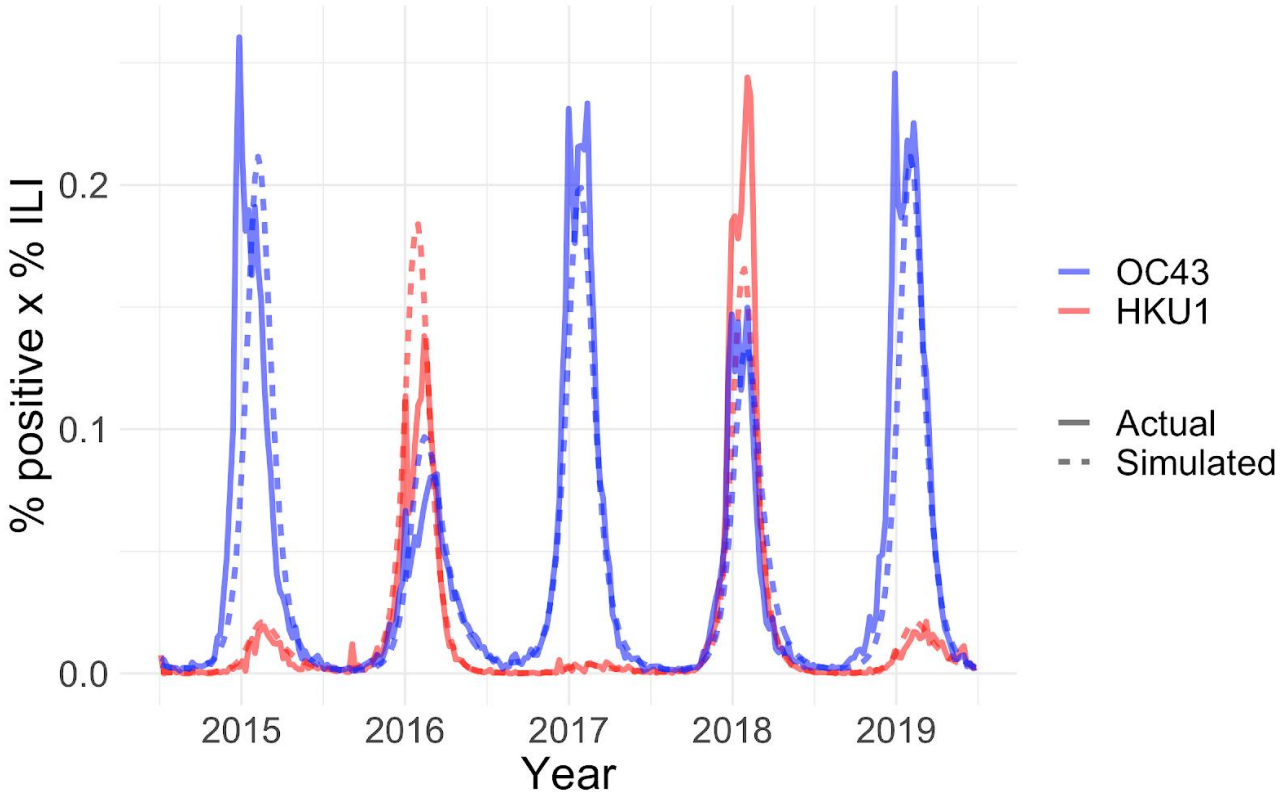
$$log(R_{sij}) = log(R_0 S_0) + \alpha_{sj} + \lambda_s d_{sij} + \delta_s d_{rij} + \sum_{n=1}^{10} \theta_n B_n(i) + \epsilon_{sij}$$

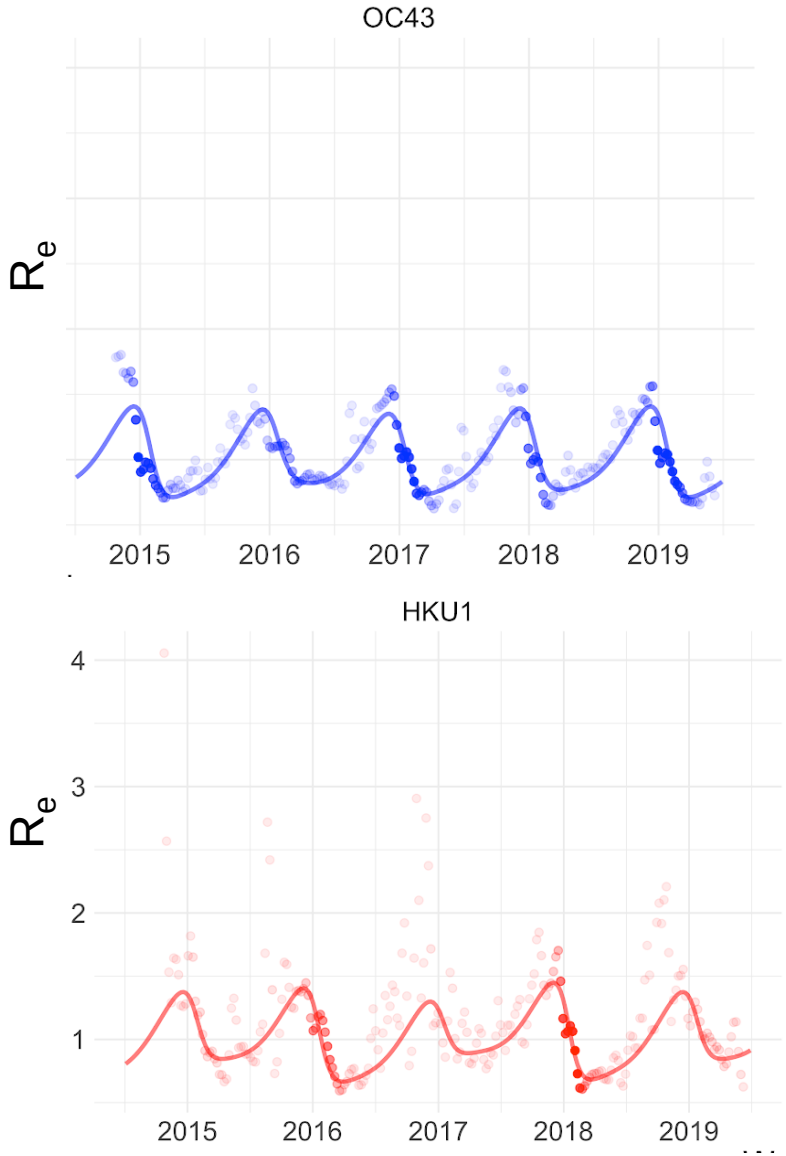
Transmission model





Model fit


% positive x % ILI
0.2
0.1
0.0
2015
2016
2017
2018
2019
Year
OC43
HKU1
Actual
Simulated


OC43
R_e
2015
2016
2017
2018
2019
HKU1
R_e
4
3
2
1
2015
2016
2017
2018
2019

Seasonality of betacoronaviruses

- 21% best fit amplitude of seasonal forcing
- Rest is accounted for by depletion of susceptibles
- This would not be enough alone to control SARS-CoV-2 in summer
- Limitations: incidence proxy, national data, lack of mechanism, not the same virus!

Other work uses less reliable but more relevant data on SARS-CoV-2 and reaches similar conclusions

Ultraviolet radiation decreases COVID-19 growth rates:
Global causal estimates and seasonal implications

Tamma Carleton, Jules Cornetet, Peter Huybers, Kyle C. Meng, and Jonathan Proctor*

This version: May 15, 2020
First version: April 20, 2020

The role of environmental factors on transmission rates of the COVID-19 outbreak: An initial assessment in two spatial scales.

Canelle Poirier[1,2], Wei Luo[1,2], Maimuna S. Majumder[1,2], Dianbo Liu[1,2], Kenneth D. Mandl[1,2,3], Todd A. Mooring[4], Mauricio Santillana[1,2,5,*]

Conclusions

- Much has been learned about the basic properties: this is a very hard virus to control due to variable clinical spectrum and high infectiousness early.
- Social factors affect infection risk, outcome. Need far more information on this in each part of the world.
- Some key issues we did not highlight in Feb (seasonality, seroprotection) are highly important
- Representative sampling is a repeated challenge
- Opportunities for comparison across countries and regions to understand risk predictors better.