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COVID-19 Infection Fatality Ratio:

Where we started, Where we were, Where we are

Nick Brazeau, *On Behalf of the Imperial College COVID-19 Response Team*

“Do you have a job yet…?”

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UNC SCHOOL OF MEDICINE

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MD 1-2 → PHD 1-4 (ideel) → Imperial College London → MD 3-4

Whose Work am I Presenting: ICL Severity Workstream

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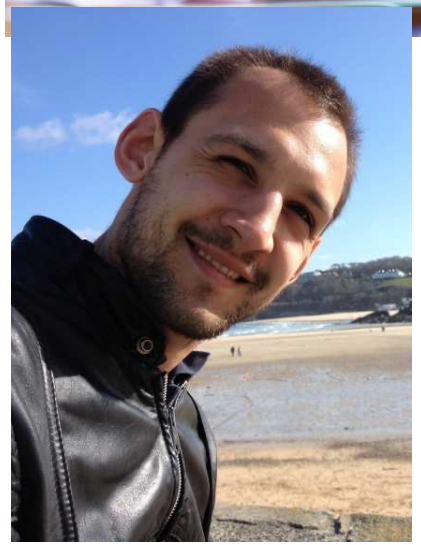
Lucy Okell

Azra Ghani

Ilaria Dorigatti **Pete Winskill** **Charlie Whittaker** **Patrick Walker**

& Imperial College COVID Response Team

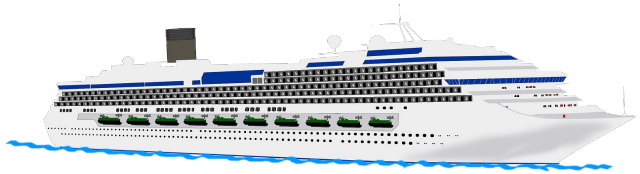


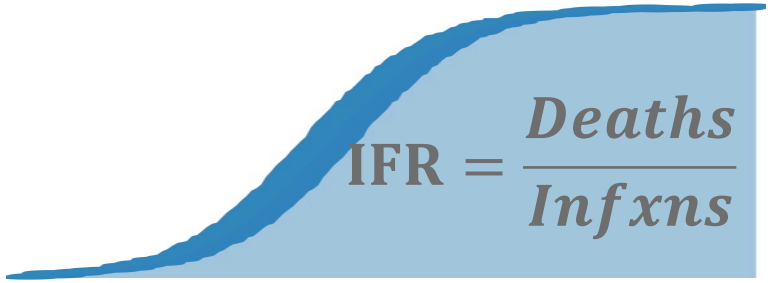
Bob Verity

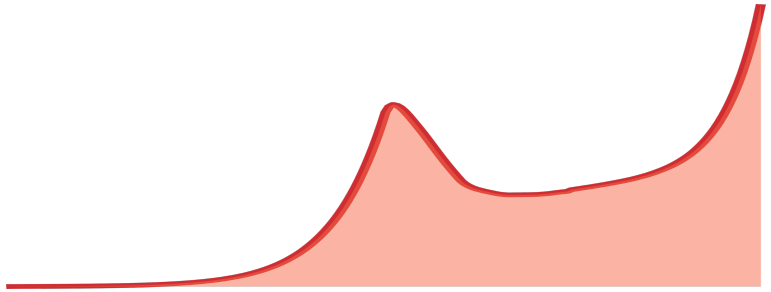
Neil Ferguson

Outline

- **Introduction**
- **"Beginning": Outbreak in Wuhan/Mainland China**
  - Limited data sources vs. High demand
- **"Middle": First Wave Analysis**
  - Infections: The Denominator
  - Deaths: The Numerator
  - Results
- **"Now": Has the IFR changed over time**
  - Evidence from hospitalization data
  - Future Work
- **Conclusions**







COVID-19 – Epidemiological Characteristics

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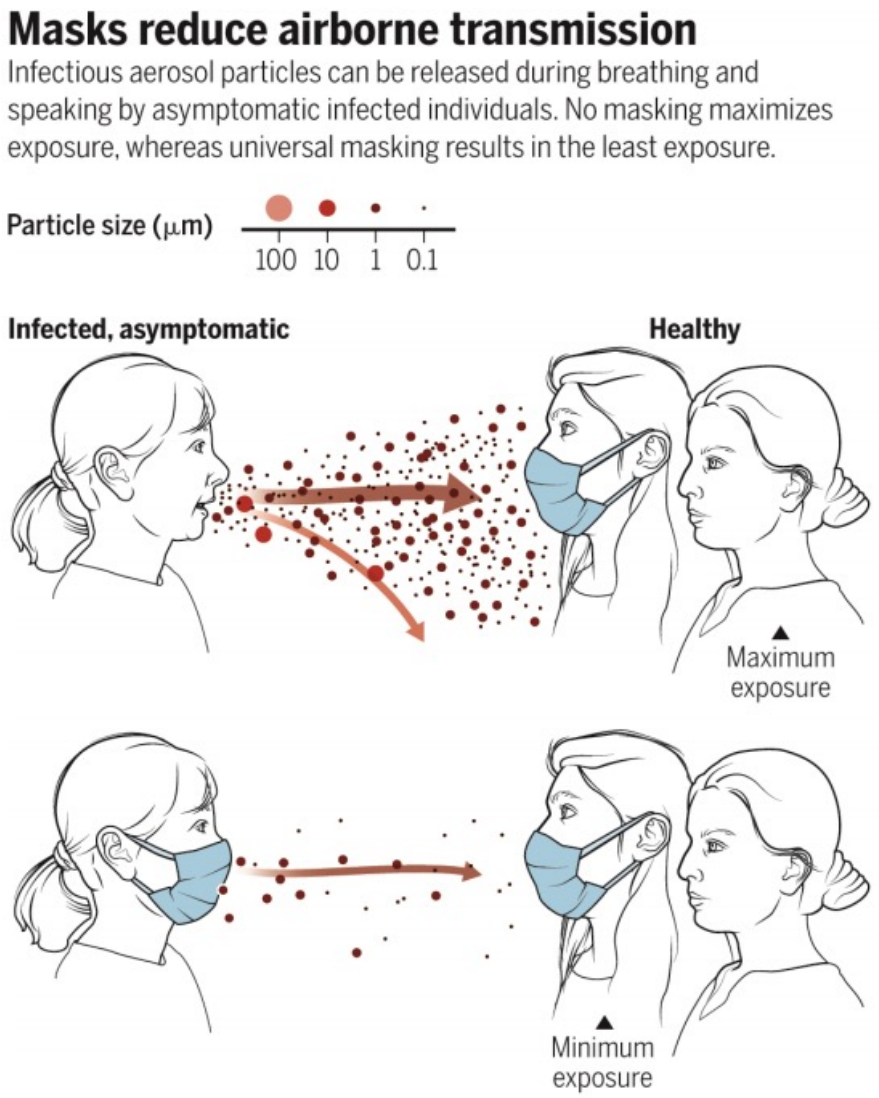
- Primarily mechanism appears to be droplet/aerosol
- Extensive pre-symptomatic transmission (approximately 40-50%)
  - Asymptomatic individuals thought less infectious, but extent remains unclear
- Basic Reproduction Number (R0) highly variable depending on the context, ranging from 2 – 4
  - 2009 H1N1 Influenza R_0 ~ 1.4 - 1.6
  - Measles R_0 ~ 12 - 18



COVID-19 – Disease Characteristics

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- Wide variety of symptoms elicited by infection with the virus
  - Although primary complications are respiratory
  - Asymptomatic fraction ~20% - some age-variation
- Severity of disease significantly influenced by age, biological sex, and comorbidities

COVID-19 – Disease Burden to Date

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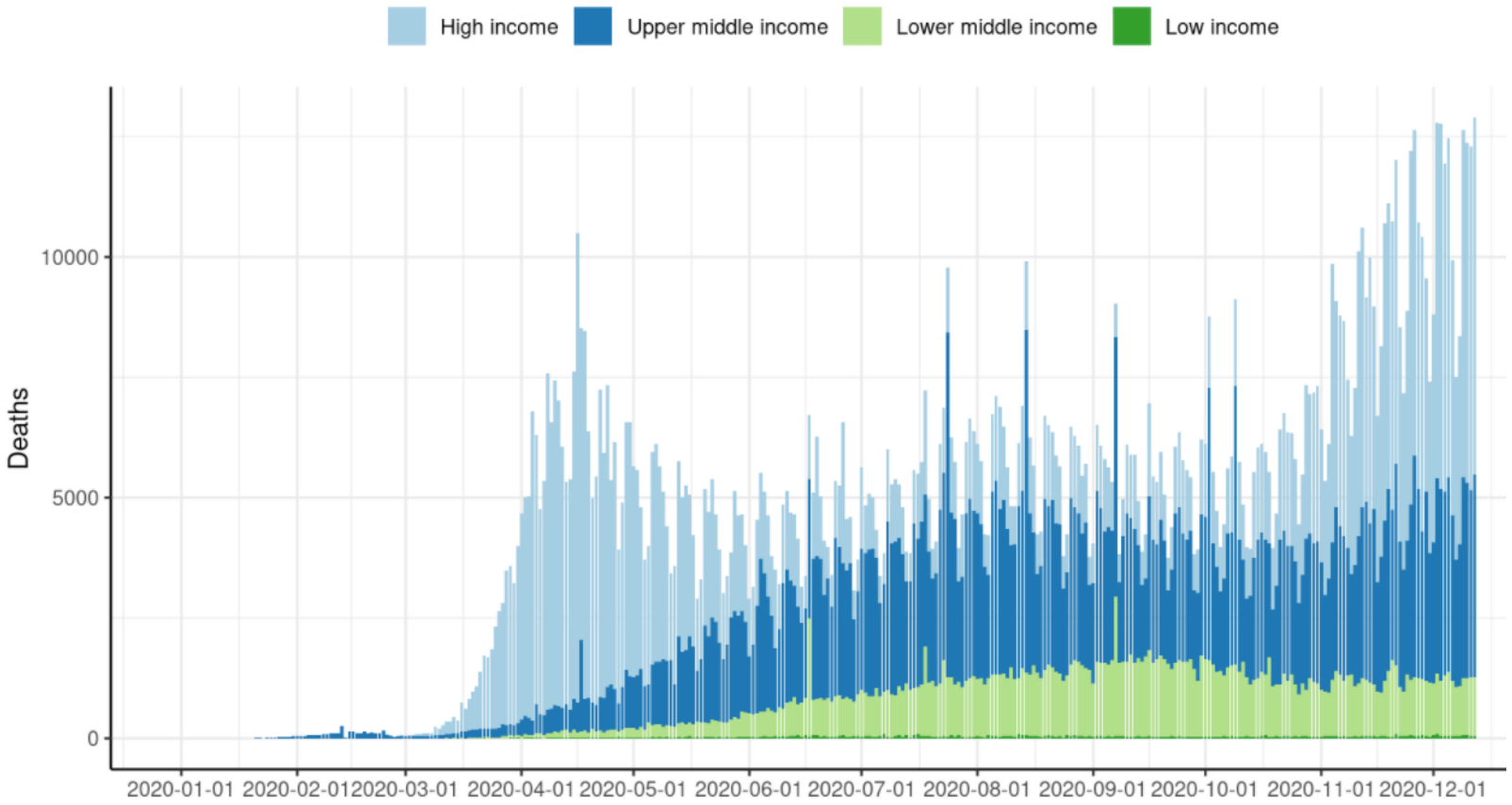
- ~72.8 million cases and 1.62 million deaths reported to date.
  - Likely to be significant underestimate.



COVID-19 Fatality Ratios

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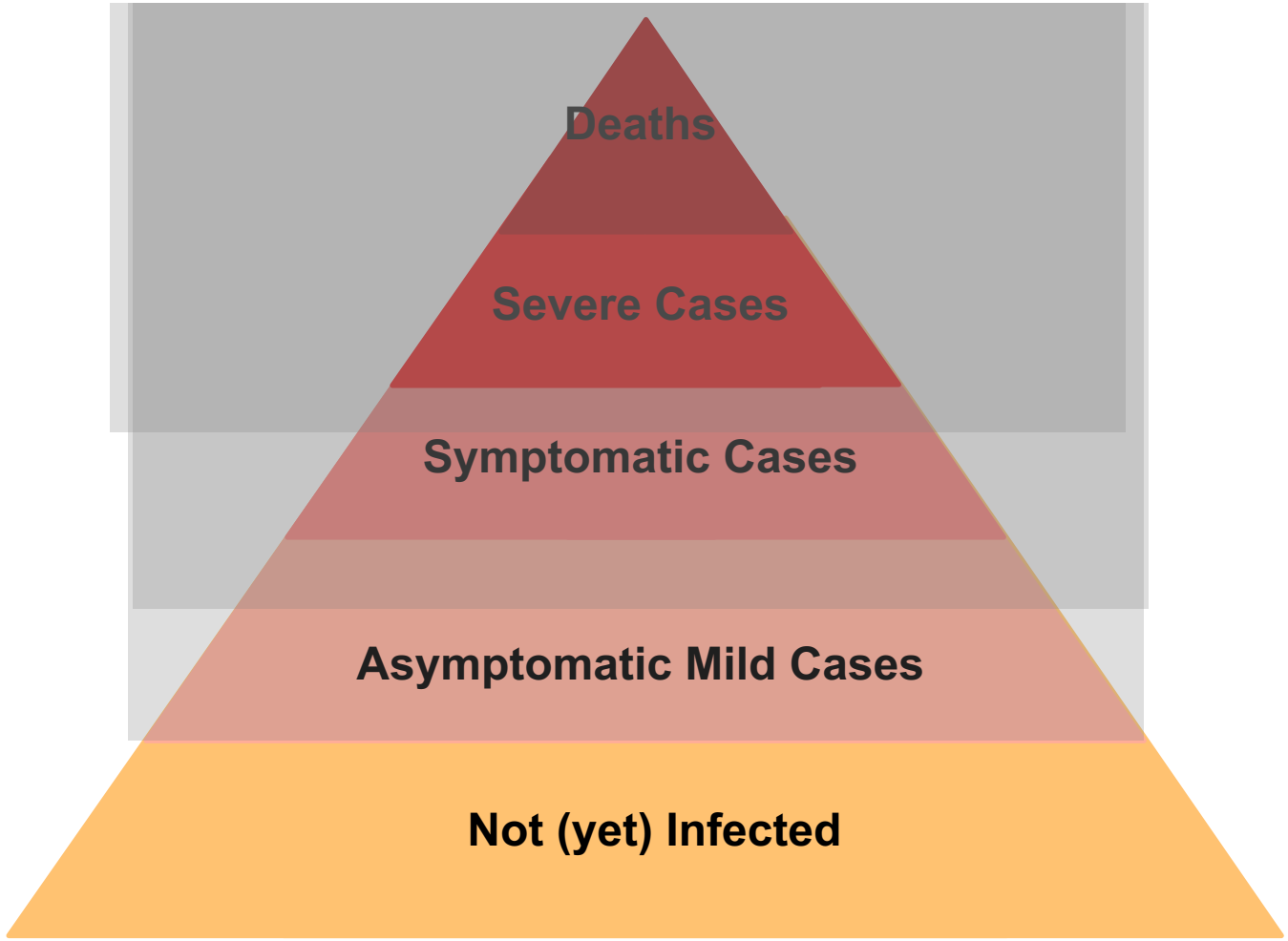
$$\text{Hospitalized Fatality Ratio} = \frac{\text{Deaths}}{\text{Hosp. Pop.}}$$

$$\text{Case Fatality Ratio} = \frac{\text{Deaths}}{\text{Cases}}$$

$$\text{Infection Fatality Ratio} = \frac{\text{Deaths}}{\text{Infxns}}$$

$$\text{“Per Capita” Fatality Ratio} = \frac{\text{Deaths}}{\text{Pop.}}$$



COVID-19 Infection Fatality Ratio

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- Probability of death given infection

$$\textbf{Infection Fatality Ratio} = \frac{\textbf{Deaths}}{\textbf{Infxns}}$$

- Contested statistics throughout the COVID-19 pandemic

- Estimates:
  - 0.09 – 0.53% (Ioannidis, 2020)
  - >2% based on Estimates from Italy

Why We Care about the COVID-19 IFR: Justification for Policy

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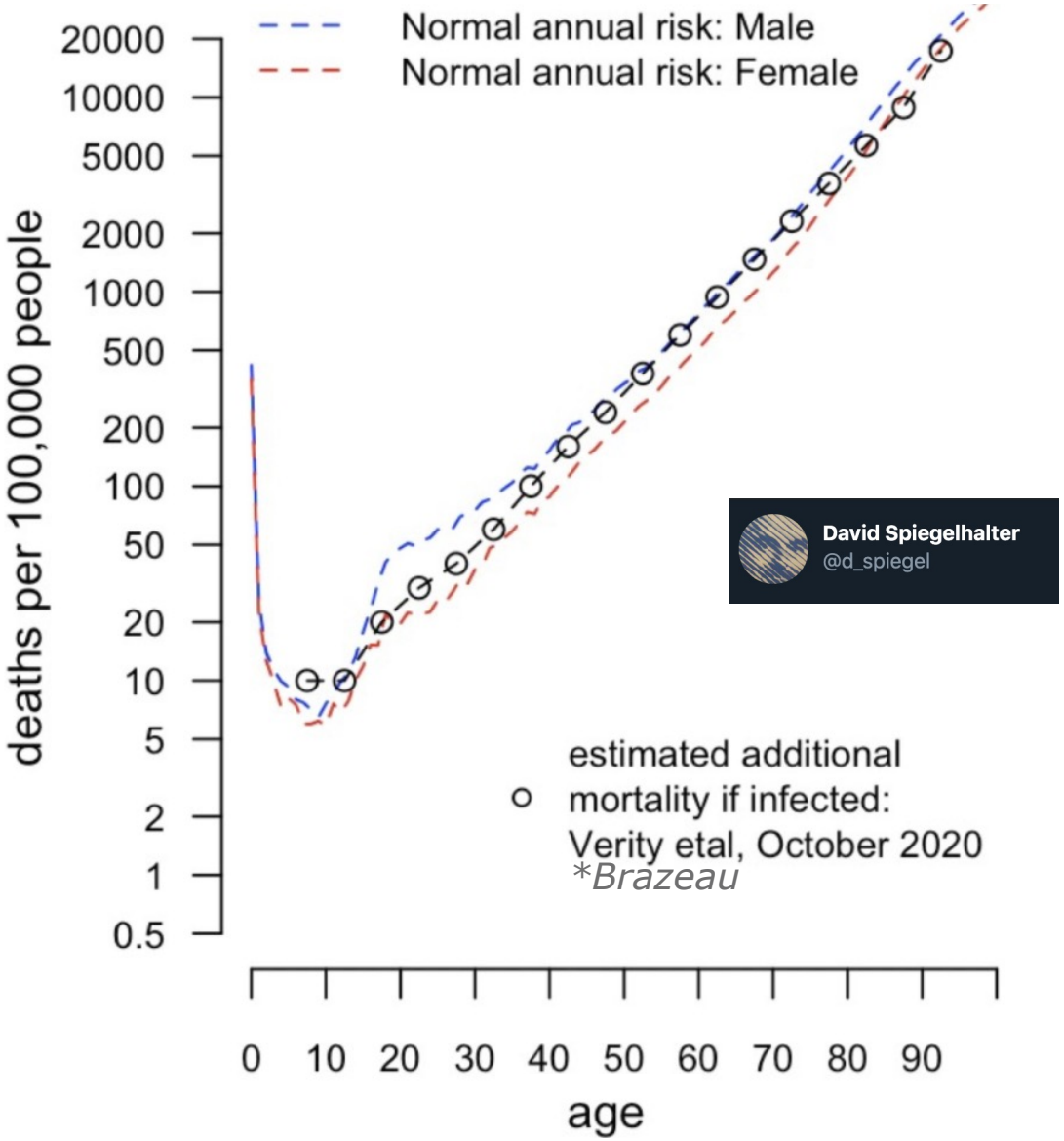

- Severity of the disease prompts public health urgency
- COVID-19 age-specific mortality closely matches annual risk of death

Why We Care about the COVID-19 IFR: S(E)IR Model Parameterization

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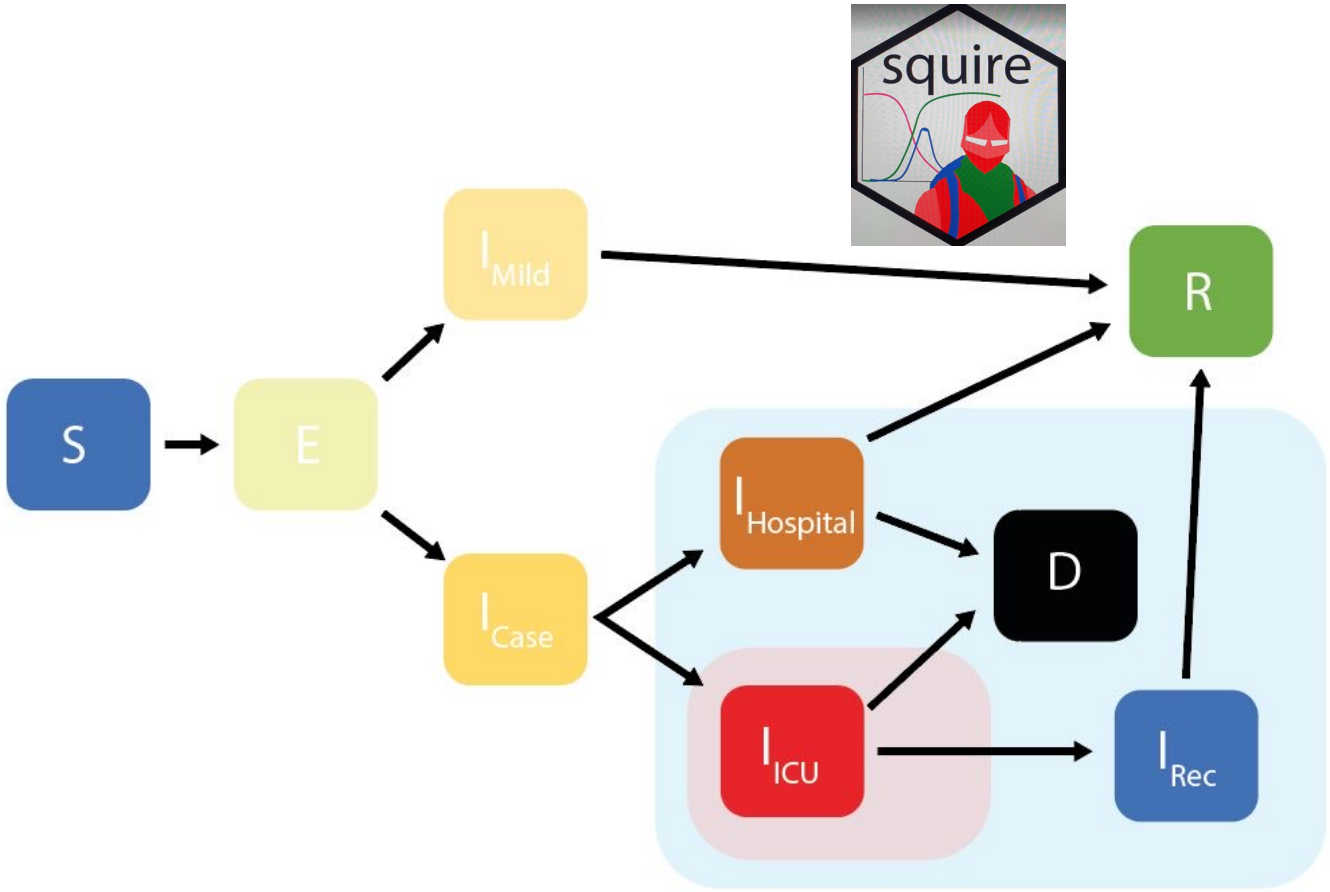
IFR Estimates



Lilith Whittles, Marc Baguelin, Rich Fitzjohn, Edward Knock, John Lees, OJ Watson, Charlie Whittaker, Peter Winskill, Alexandra Hogan, Nick Brazeau, Giovanni Charles

Why We Care about the COVID-19 IFR: S(E)IR Model Parameterization

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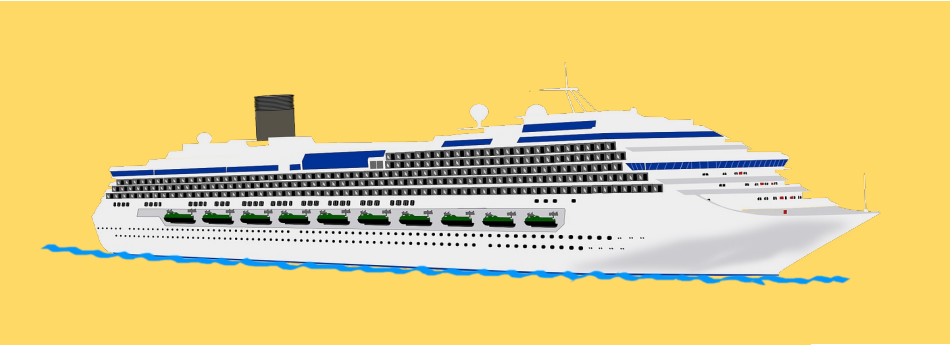
LMIC transmission dynamics: Report 12
Damascus Death Underreporting: Report 31
Sudan Under-ascertainment: Report 39
Vaccines: Report 33

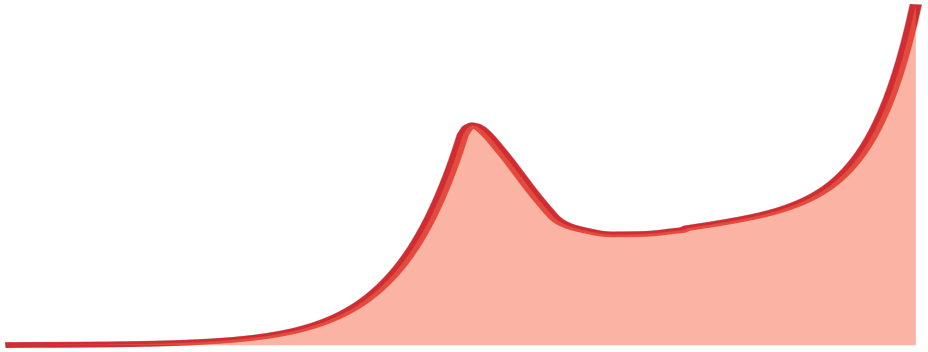
IFR Estimates → squire

Lilith Whittles, Marc Baguelin, Rich Fitzjohn, Edward Knock, John Lees, OJ Watson, Charlie Whittaker, Peter Winskill, Alexandra Hogan, Nick Brazeau, Giovanni Charles

Outline



$$\text{IFR} = \frac{\text{Deaths}}{\text{Infxns}}$$



Setting the Scene: Late Feb. 2020

- ***Situation in late Feb 2020…***
- USA: ~15 cases, 0 deaths
- UK: ~10 cases, 0 deaths
- Italy: ~100 cases, ~3 deaths
- China: ~70,000 cases, ~2000 deaths

Q. <u>If/When</u> this takes off in USA, how bad will it be?

- Is this a pandemic?
- What is severity of the disease (*i.e.* IFR)?
- How important is age?

Articles

Estimates of the severity of coronavirus disease 2019: a model-based analysis

Robert Verity*, Lucy C Okell*, Ilaria Dorigatti*, Peter Winskill*, Charles Whittaker*, Natsuko Imai, Gina Cuomo-Dannenburg, Hayley Thompson, Patrick G T Walker, Han Fu, Amy Dighe, Jamie T Griffin, Marc Baguelin, Sangeeta Bhatia, Adhiratha Boonyasiri, Anne Cori, Zulma Cucunubá, Rich FitzJohn, Katy Gaythorpe, Will Green, Arran Hamlet, Wes Hinsley, Daniel Laydon, Gemma Nedjati-Gilani, Steven Riley, Sabine van Elsland, Erik Volz, Haowei Wang, Yuanrong Wang, Xiaoyue Xi, Christl A Donnelly, Azra C Ghani, Neil M Ferguson*

Summary

Background In the face of rapidly changing data, a range of case fatality ratio estimates for coronavirus disease 2019 (COVID-19) have been produced that differ substantially in magnitude. We aimed to provide robust estimates, accounting for censoring and ascertainment biases.

Methods We collected individual-case data for patients who died from COVID-19 in Hubei, mainland China (reported by national and provincial health commissions to Feb 8, 2020), and for cases outside of mainland China (from government or ministry of health websites and media reports for 37 countries, as well as Hong Kong and Macau, until Feb 25, 2020). These individual-case data were used to estimate the time between onset of symptoms and outcome (death or discharge from hospital). We next obtained age-stratified estimates of the case fatality ratio by relating the aggregate distribution of cases to the observed cumulative deaths in China, assuming a constant attack rate by age and adjusting for demography and age-based and location-based under-ascertainment. We also estimated the case fatality ratio from individual line-list data on 1334 cases identified outside of mainland China. Using data on the prevalence of PCR-confirmed cases in international residents repatriated from China, we obtained age-stratified estimates of the infection fatality ratio. Furthermore, data on age-stratified severity in a subset of 3665 cases from China were used to estimate the proportion of infected individuals who are likely to require hospitalisation.

Lancet Infect Dis 2020
Published Online March 30, 2020 https://doi.org/10.1016/S1473-3099(20)30243-7
See Online/Comment https://doi.org/10.1016/S1473-3099(20)30257-7

*Contributed equally
MRC Centre for Global Infectious Disease Analysis, Abdul Latif Jameel Institute for Disease and Emergency Analytics, and Department of Infectious Disease Epidemiology, Imperial College London, London, UK (R Verity PhD, L C Okell PhD, I Dorigatti PhD, P Winskill PhD,

In the beginning, there was Verity *et al.*

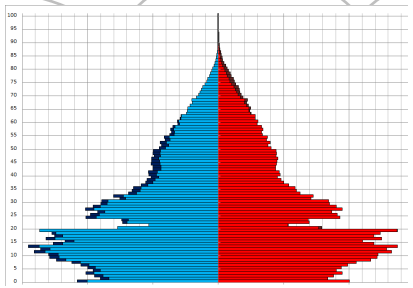
Data sources

Expected total deaths by

- **Age**
- **Location**

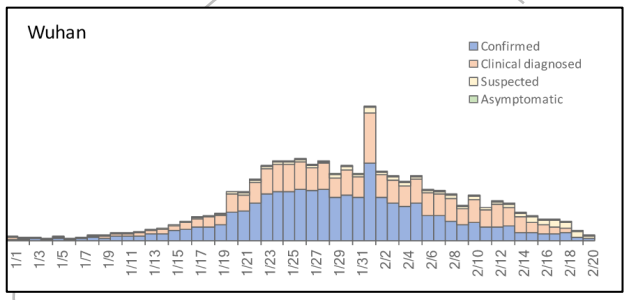
Time onset to death

Demography



China deaths line list

Cases over time



International line list

Repatriation flight data

Diamond Princess

Point estimate of infection prevalence

Point estimates of CFR and IFR, validation

Calculating the IFR in the beginning

- **Death Data**
  - Age-stratified counts deaths from WHO-China Report
- **Case Data**
  - Aggregate data on cases in China
  - Aggregate data on cases outside of China
- **Infection Data**
  - Repatriated flight data

Simplified Approach to get IFR and CFR (performed jointly)

1. Estimate CFR
   - From aggregate data
   - Given some set of onset-outcome delays
2. "Adjust" data for delays and ascertainment to get "true cases"
3. Assume infections can be determined from "true cases"
   - *Estimate IFR*

Estimating IFR in the beginning

- Imperfect data; imperfect estimate → urgency to know the relative magnitude of severity → prompt action

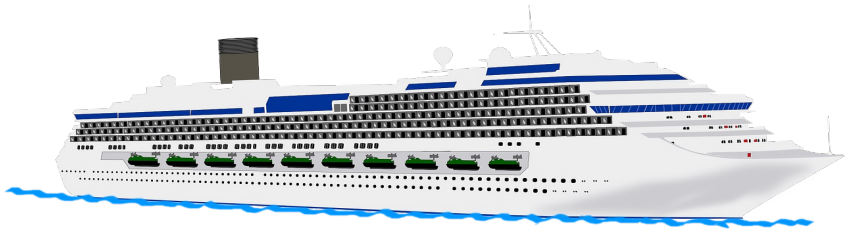
- Michael Ryan, executive director of the WHO Health Emergencies Programme: "[P]erfection is the enemy of the good when it comes to emergency management. Speed trumps perfection."

Estimating IFR in the beginning

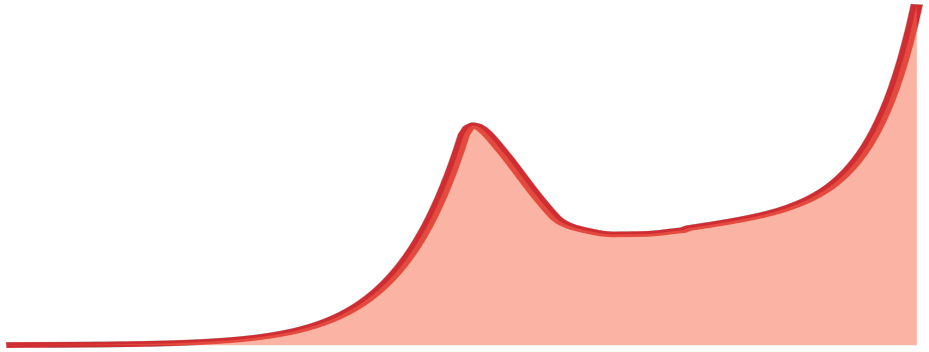
	Deaths	Laboratory-confirmed cases*	Case fatality ratio			Infection fatality ratio†
			Crude	Adjusted for censoring	Adjusted for censoring, demography, and under-ascertainment‡	
Overall	1023	44 672	2·29% (2·15–2·43)	3·67% (3·56–3·80)	1·38% (1·23–1·53)	0·657% (0·389–1·33)
Age group, years						
0–9	0	416	0·000% (0·000–0·883)	0·0954% (0·0110–1·34)	0·00260% (0·000312–0·0382)	0·00161% (0·000185–0·0249)
10–19	1	549	0·182% (0·00461–1·01)	0·352% (0·0663–1·74)	0·0148% (0·00288–0·0759)	0·00695% (0·00149–0·0502)
20–29	7	3619	0·193% (0·0778–0·398)	0·296% (0·158–0·662)	0·0600% (0·0317–0·132)	0·0309% (0·0138–0·0923)
30–39	18	7600	0·237% (0·140–0·374)	0·348% (0·241–0·577)	0·146% (0·103–0·255)	0·0844% (0·0408–0·185)
40–49	38	8571	0·443% (0·314–0·608)	0·711% (0·521–0·966)	0·295% (0·221–0·422)	0·161% (0·0764–0·323)
50–59	130	10 008	1·30% (1·09–1·54)	2·06% (1·74–2·43)	1·25% (1·03–1·55)	0·595% (0·344–1·28)
60–69	309	8583	3·60% (3·22–4·02)	5·79% (5·20–6·34)	3·99% (3·41–4·55)	1·93% (1·11–3·89)
70–79	312	3918	7·96% (7·13–8·86)	12·7% (11·5–13·9)	8·61% (7·48–9·99)	4·28% (2·45–8·44)
≥80	208	1408	14·8% (13·0–16·7)	23·3% (20·3–26·7)	13·4% (11·2–15·9)	7·80% (3·80–13·3)
Age category (binary), years						
<60	194	30 763	0·631% (0·545–0·726)	1·01% (0·900–1·17)	0·318% (0·274–0·378)	0·145% (0·0883–0·317)
≥60	829	13 909	5·96% (5·57–6·37)	9·49% (9·11–9·95)	6·38% (5·70–7·17)	3·28% (1·82–6·18)

Verity *et al.* 2020 Lancet ID: 1,618 citations

Outline



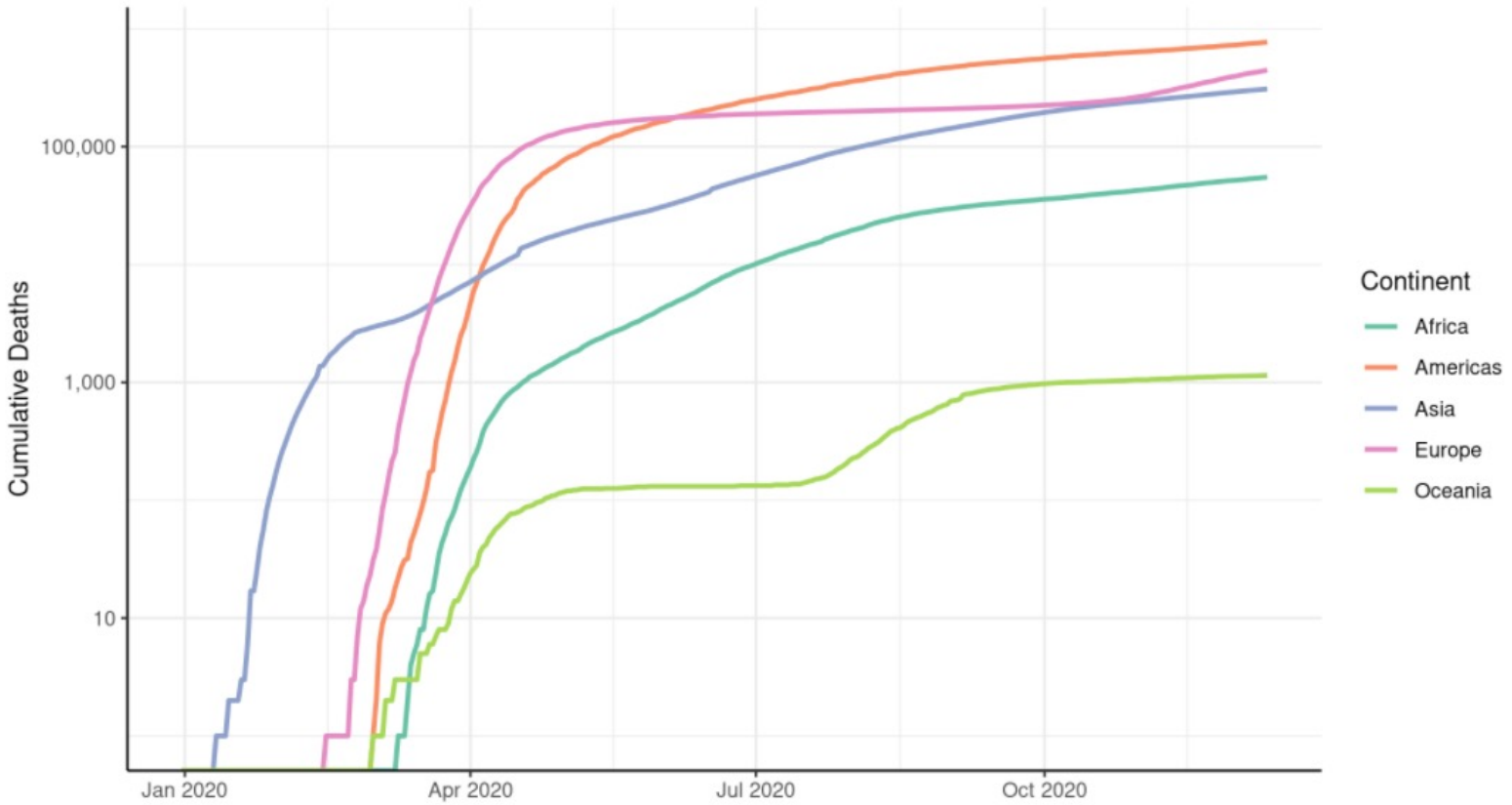
$$\text{IFR} = \frac{Deaths}{Infxns}$$



Data from the First Wave: Death Data

"Line List Data"
(Individual Outcome Data)

Aggregate Data
(Totals/Counts)

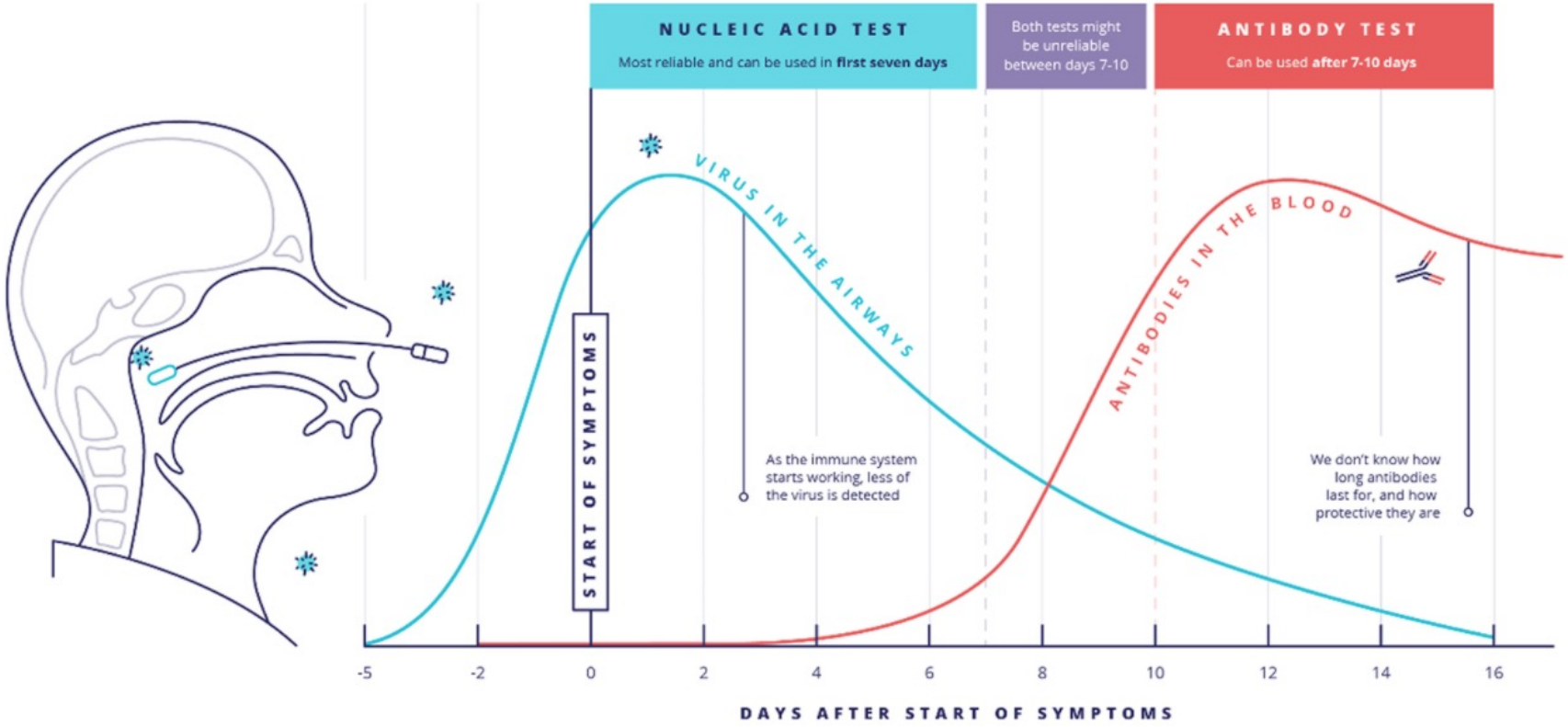


Cumulative or daily death counts from Ministries of Health, NGOs, or John Hopkin's Dashboard (if not otherwise available)

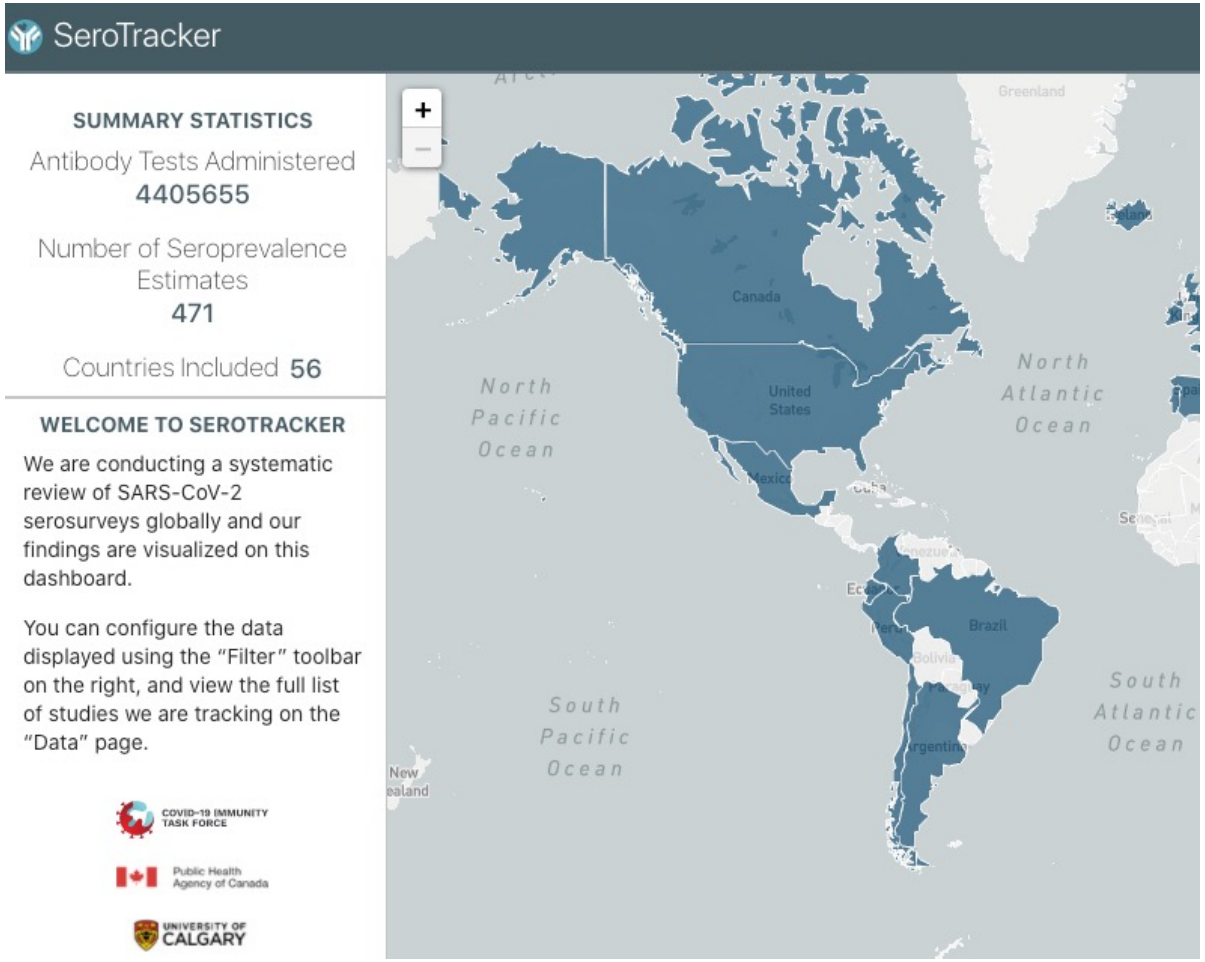
Data from the First Wave: Infection Data

Serology

- Testing for antibodies
- Assays
  - Sensitivity
  - Specificity



Data from the First Wave: Infection Data



175 "First Wave" Studies Screened

Estimation Without Representation: Early Severe Acute Respiratory Syndrome Coronavirus 2 Seroprevalence Studies and the Path Forward

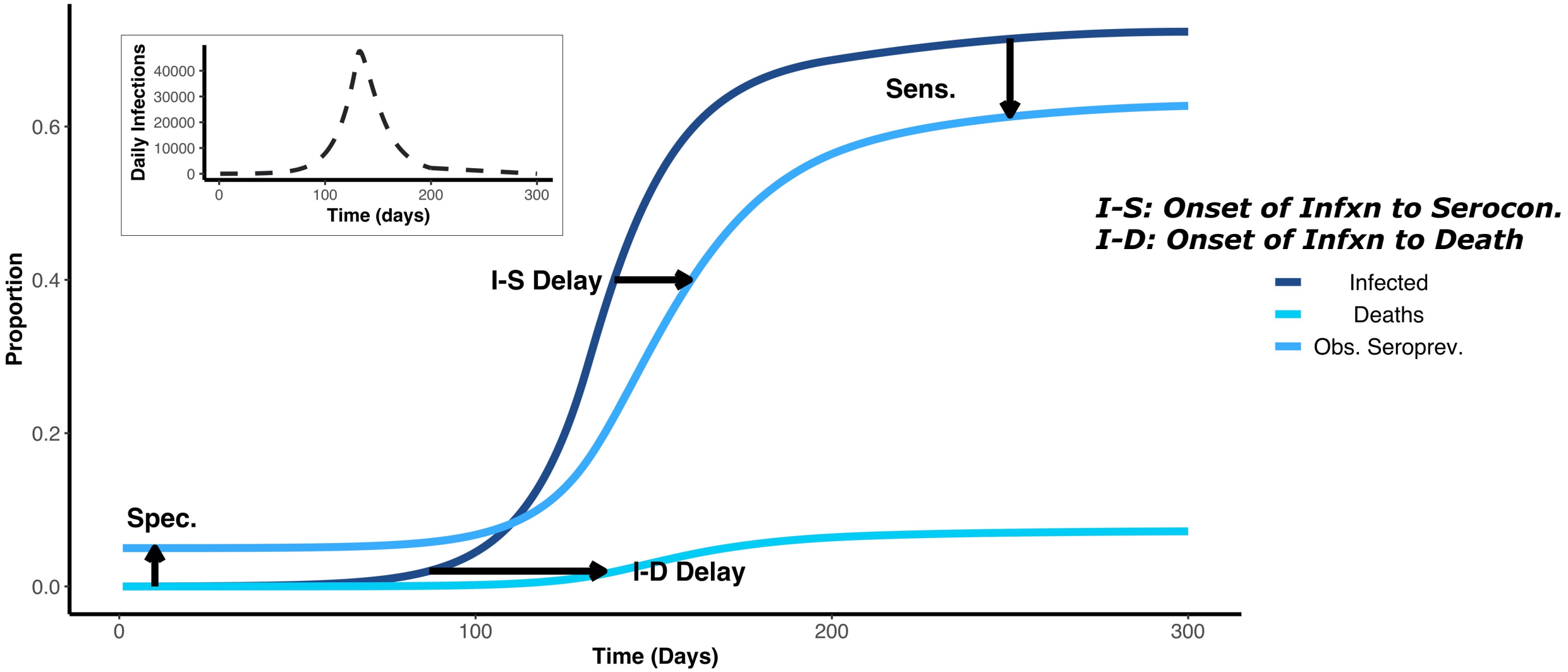
Bonnie E Shook-Sa, Ross M Boyce, Allison E Aiello

The Journal of Infectious Diseases, Volume 222, Issue 7, 1 October 2020, Pages 1086–1089, https://doi.org/10.1093/infdis/jiaa429

Published: 16 July 2020 **Article history**

10 Studies Included

Calculating the IFR for the First Wave



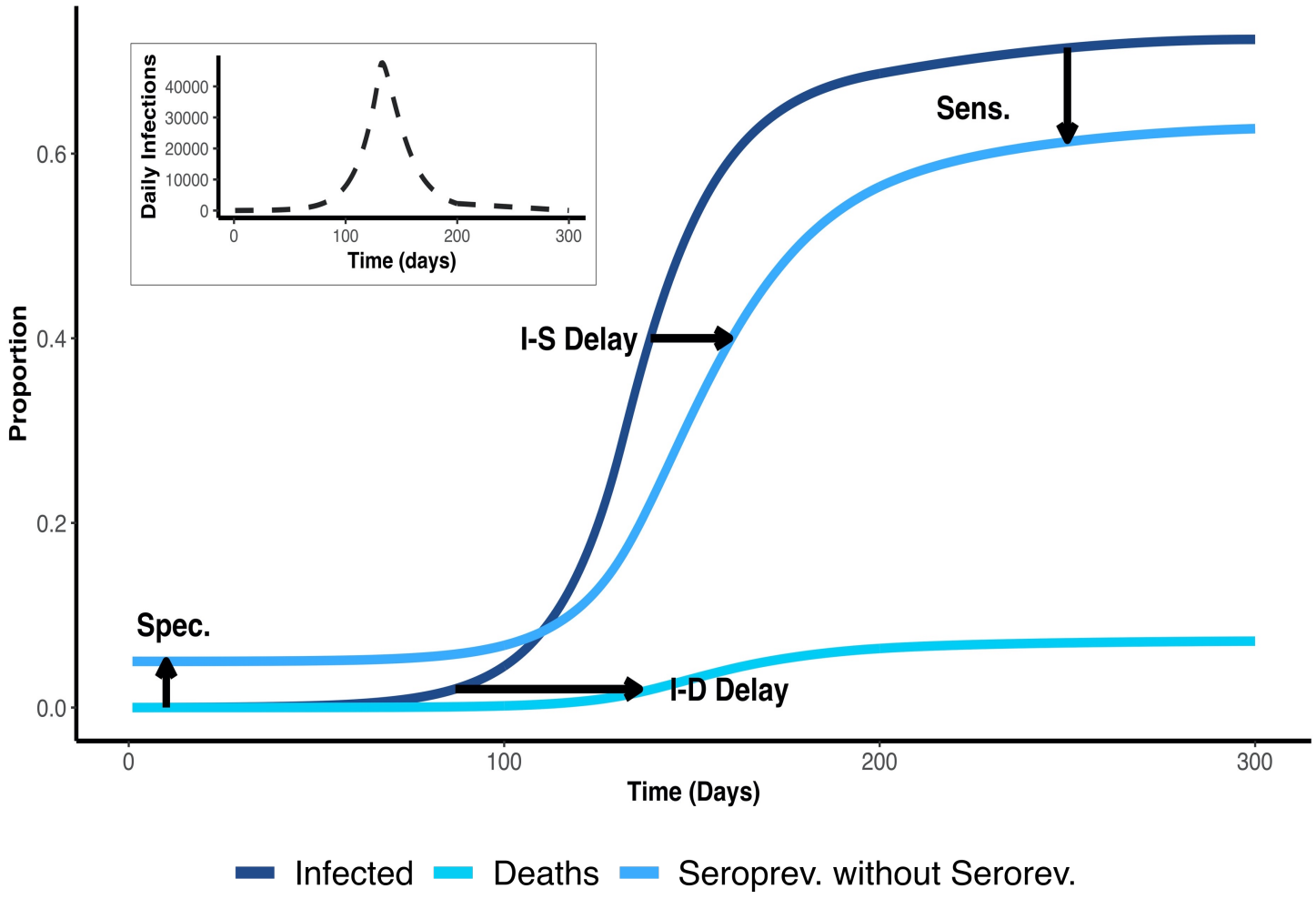
Calculating the "middle" IFR: Simple Maths

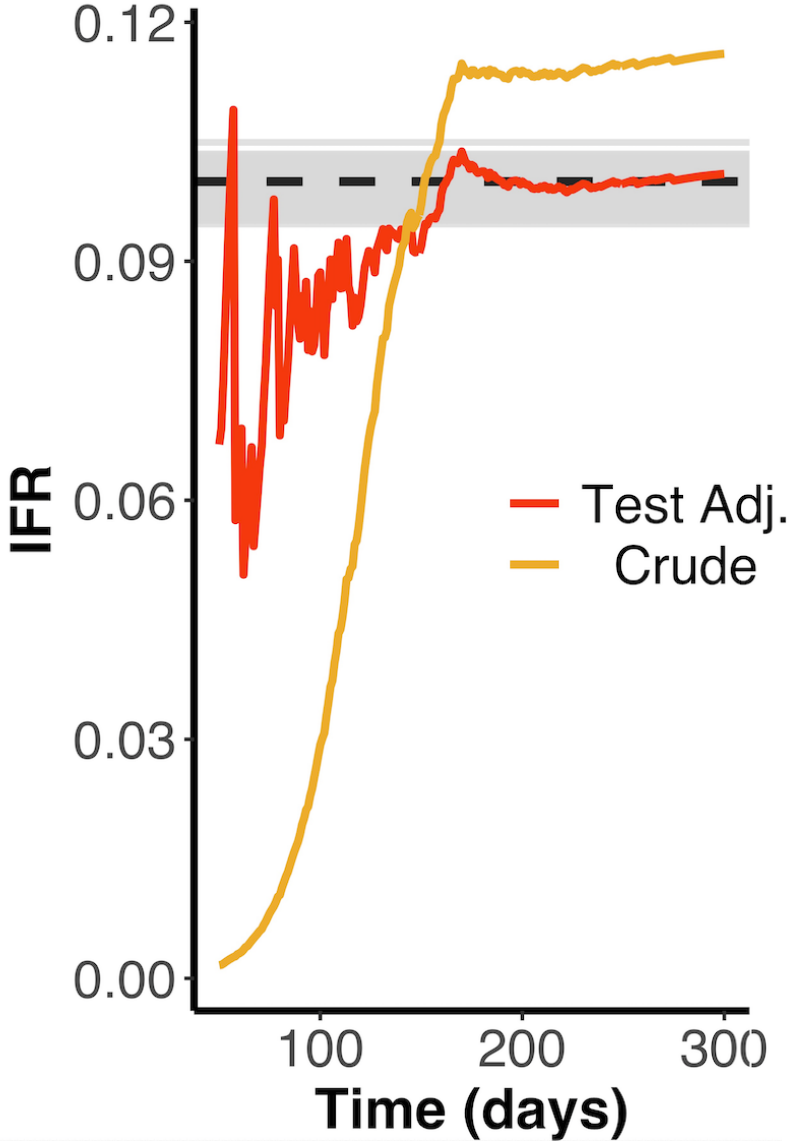
- **Goal:** Infer age-specific infection fatality ratios in a "simple" framework

- **Data Input**
  - Stratified "aggregate" deaths
  - Stratified seroprevalence

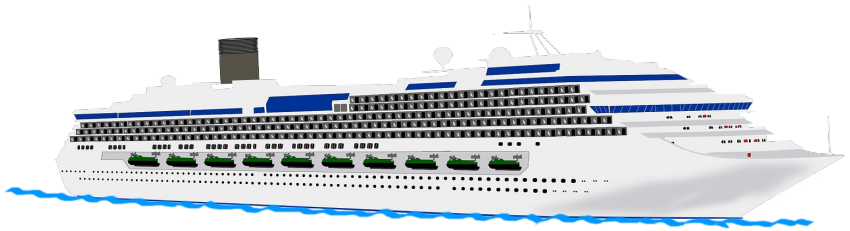
- **Approach**
  - Likelihood two pieces:
    - "***Shape***" determined by throwing forward the incidence curve to account for time-of-onset to time-of-death lag
    - ***"Pin***" the AUC of the incidence curve with serology
      - Age-specific "attack rate" effects
  - Estimated within Bayesian Framework
    - Metropolis Coupled MCMC

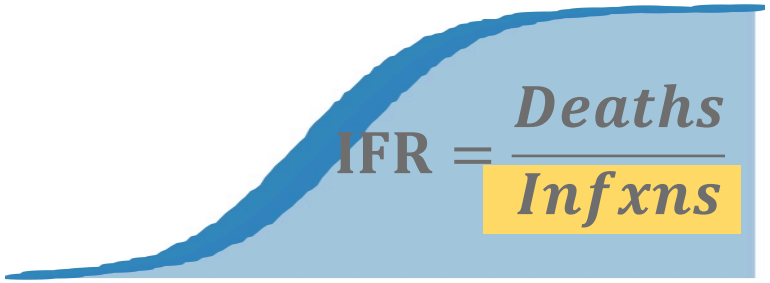
Justification for a modeling approach

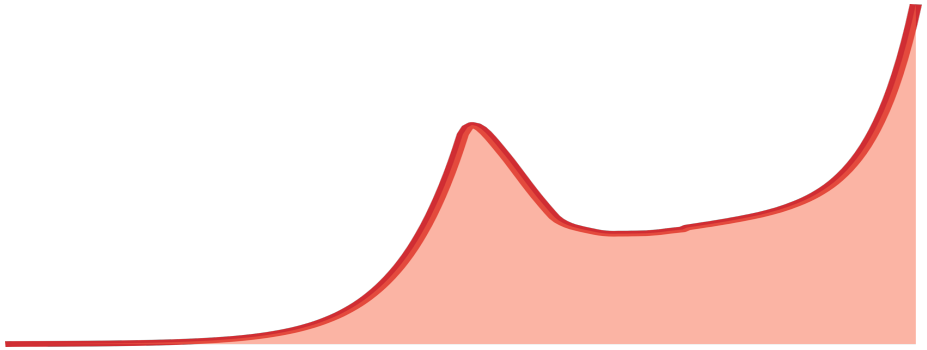




Outline







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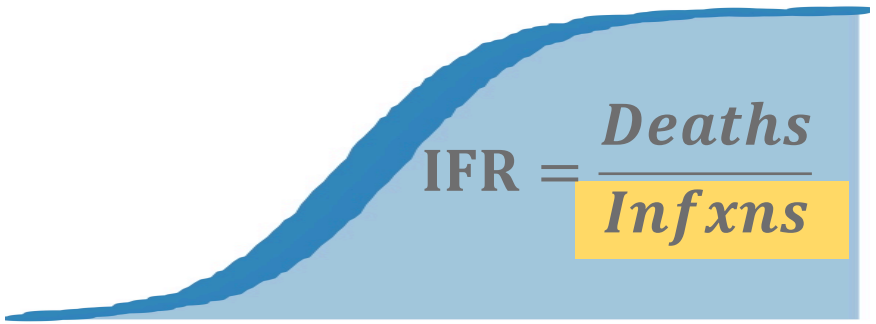
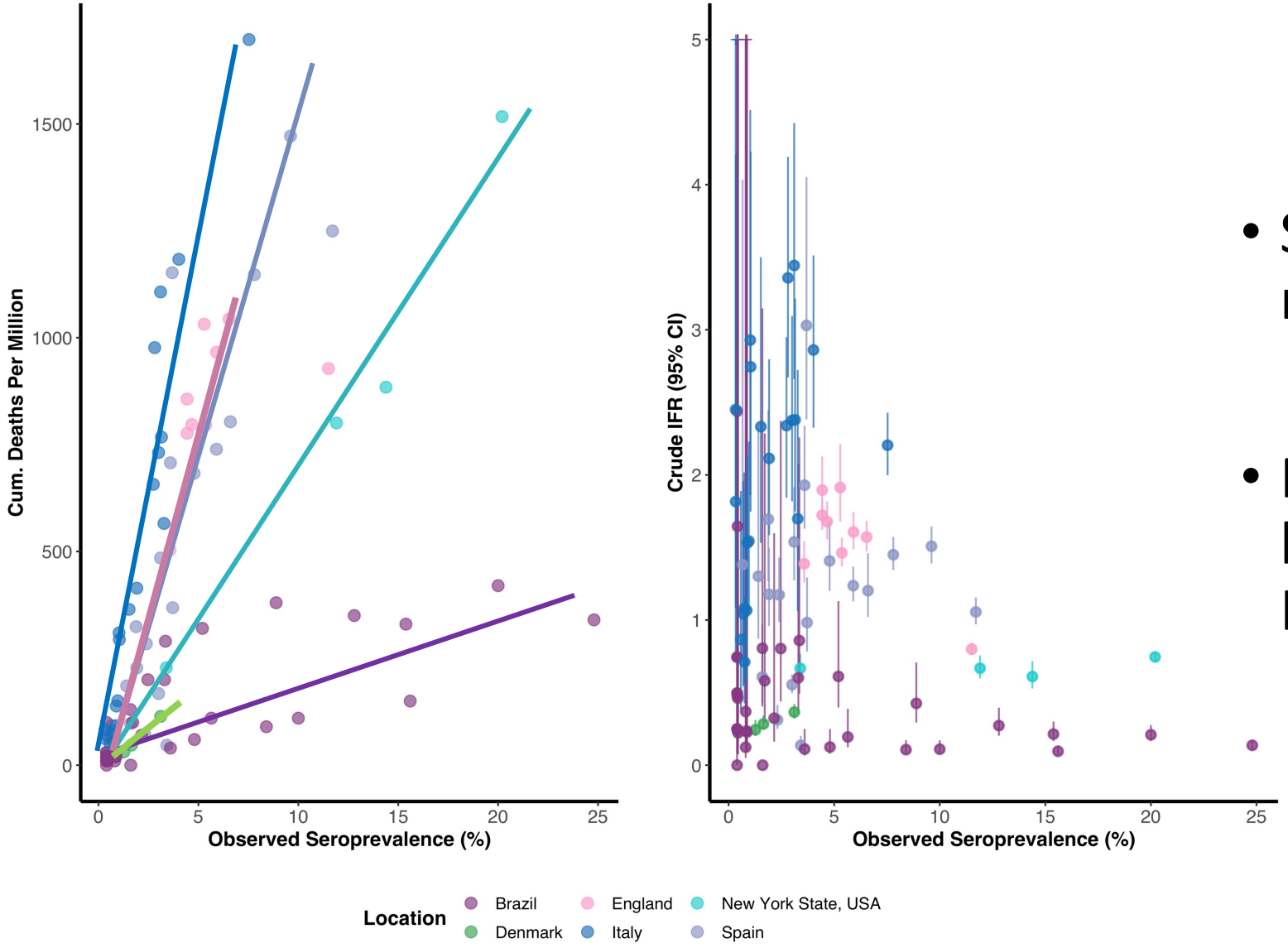


Serology is Useful

Re-estimating Specificity
(***results not shown***)

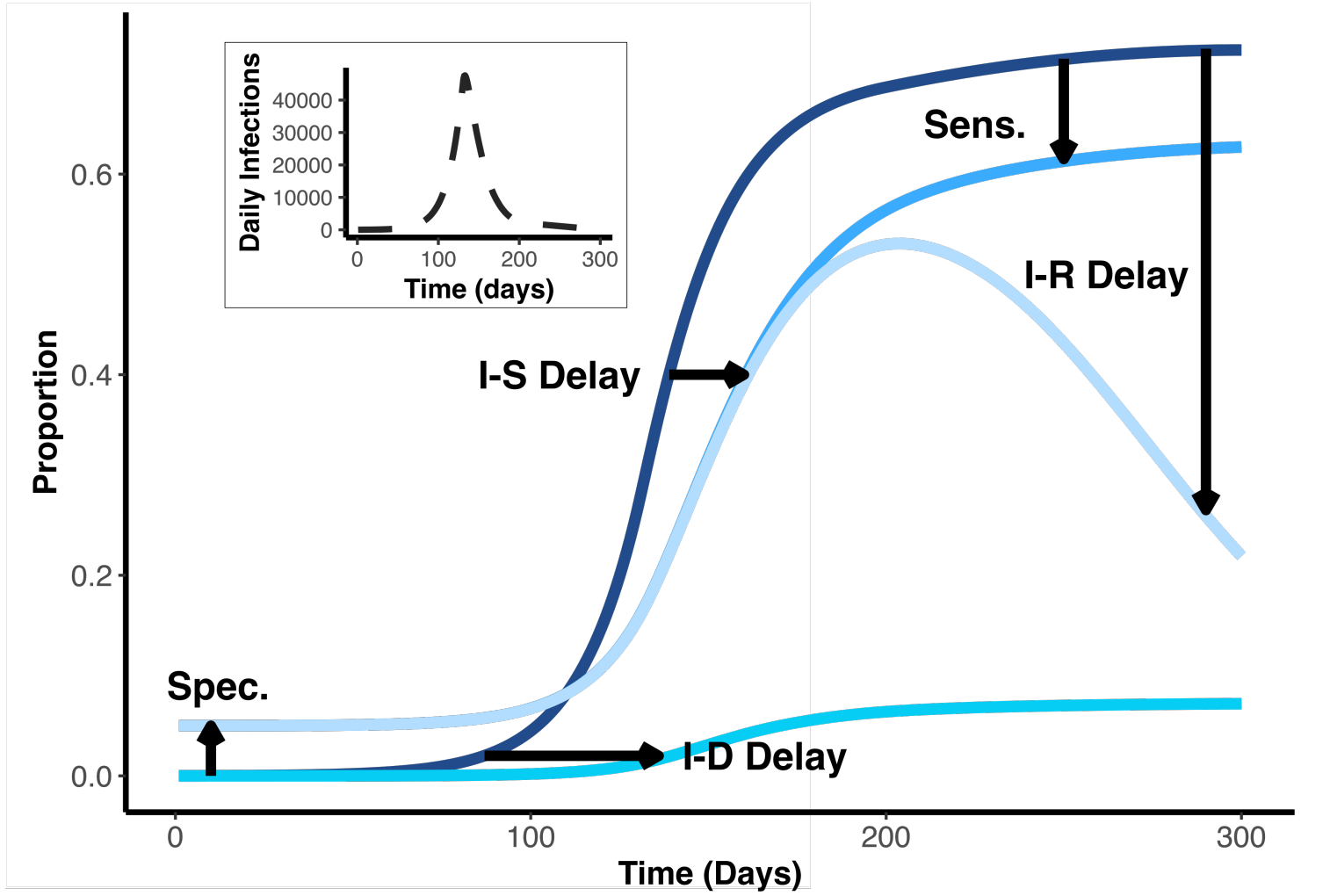
SeroREVersion

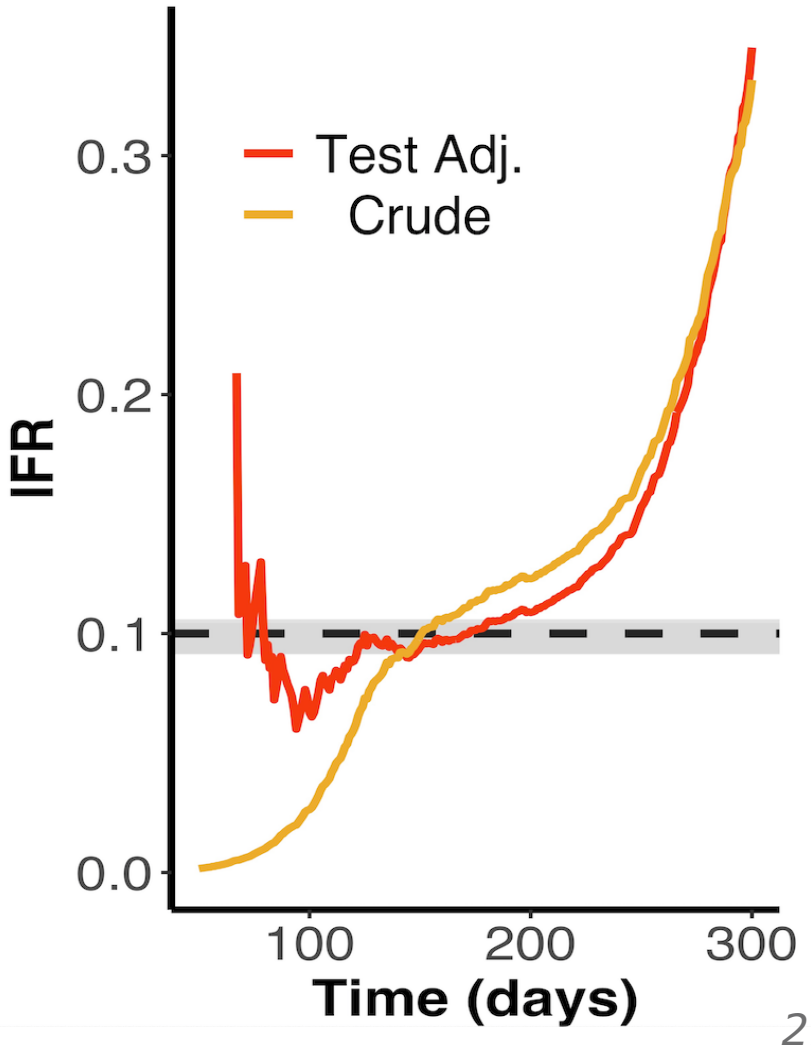
Serology as a Useful Metric



- Serology correlated with mortality (within study site)
- Regions hit harder, do not have a systematically different IFR

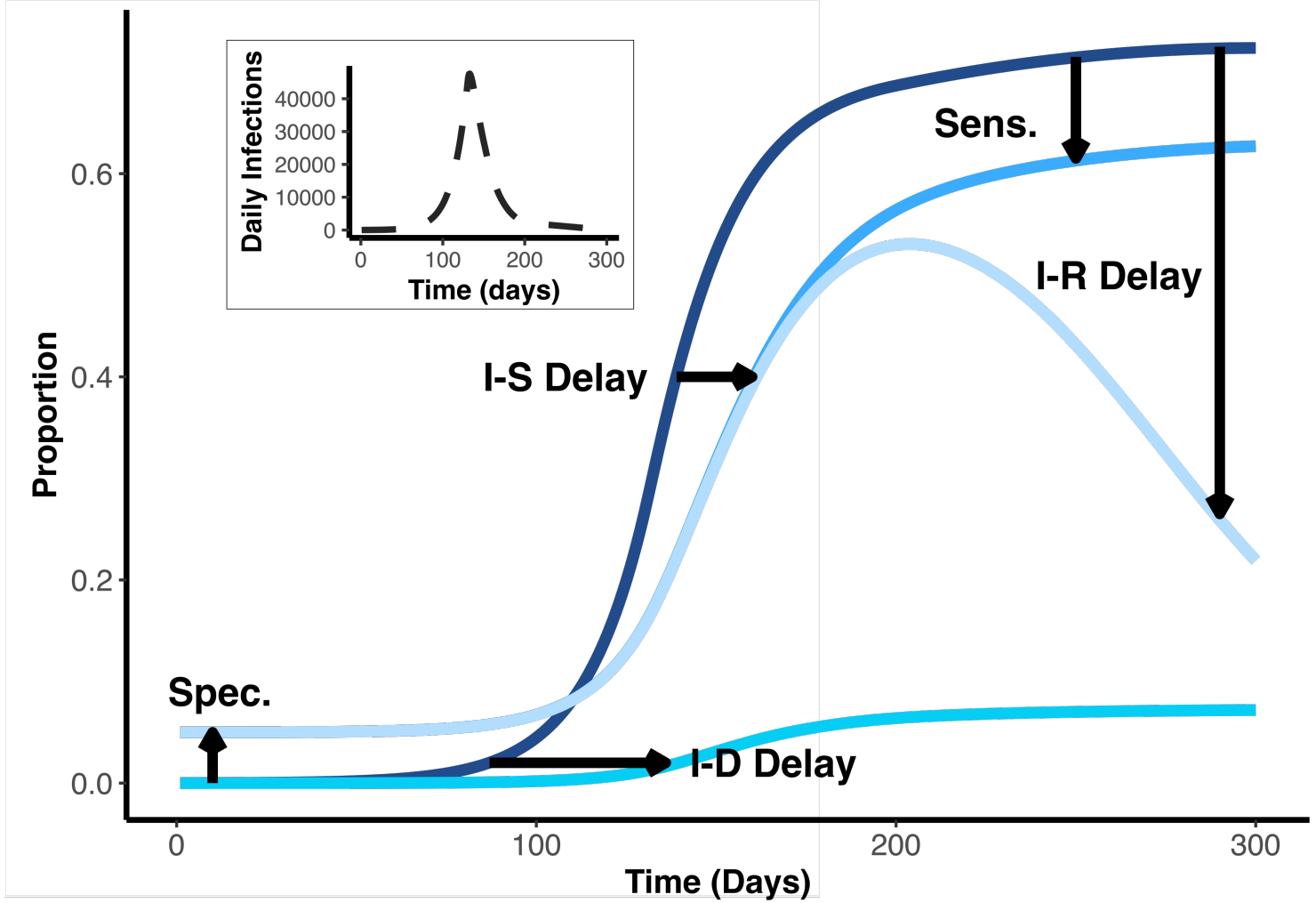
Accounting for Seroreversion

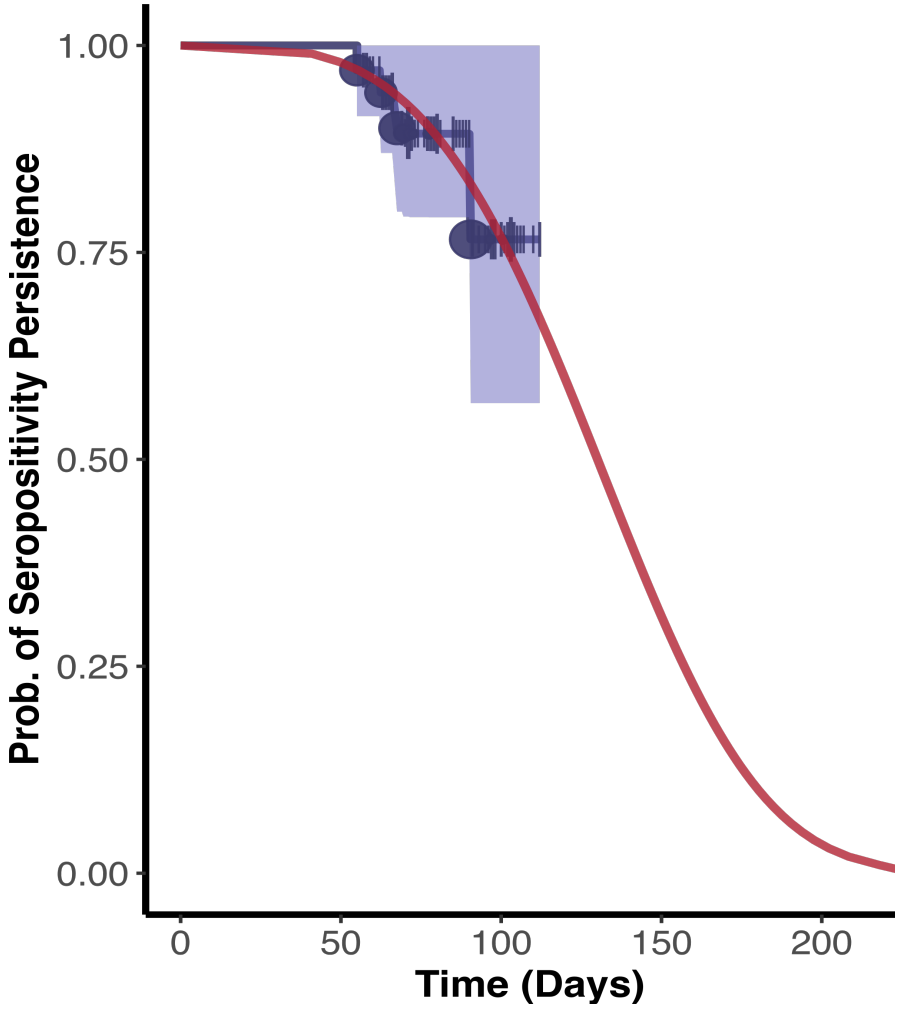




Infected Deaths Seroprev. without Serorev. Seroprev. with Serorev.

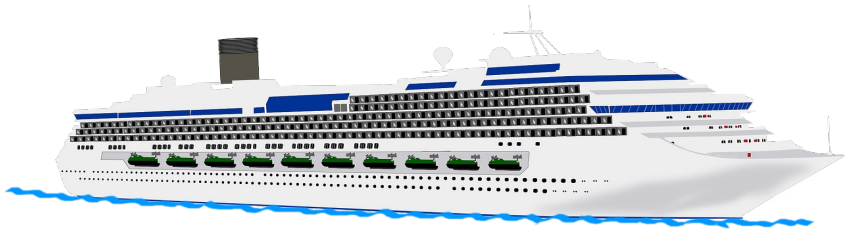
Accounting for Seroreversion

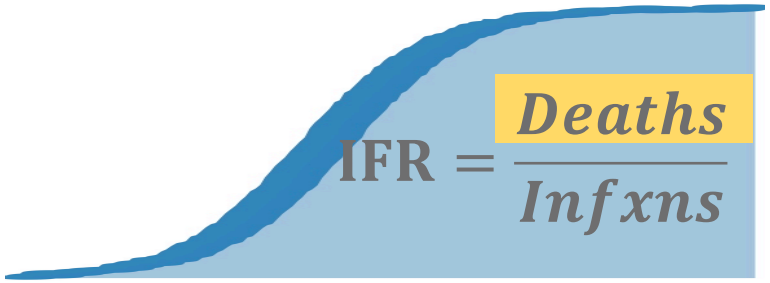


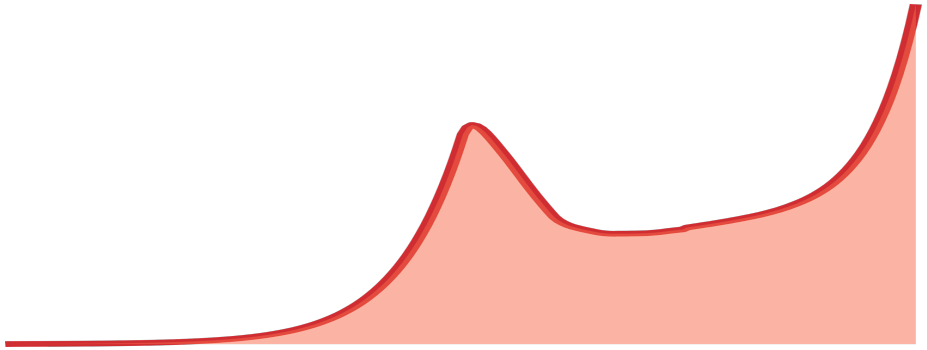


Infected Deaths Seroprev. without Serorev. Seroprev. with Serorev.

Outline







Deaths

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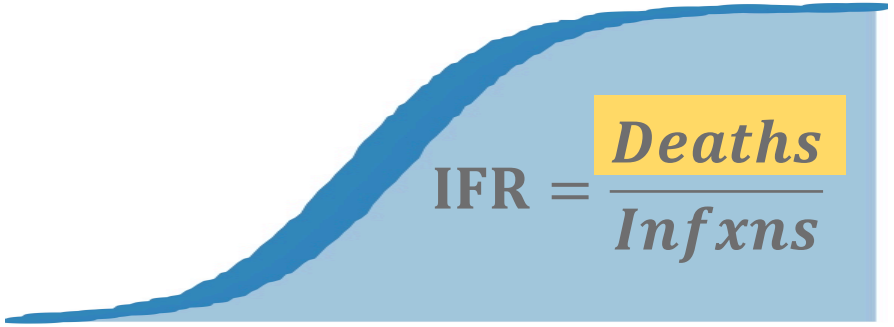


$$\text{IFR} = \frac{Deaths}{Infxns}$$

Underreporting

Care Homes

Dr. [redacted] **MD** [redacted] · Oct 29

Replying to @MRC_Outbreak [redacted]

These are alleged IFRs!

If we remove those who died FROM influenza, heart attack, cancer, accident, suicide, etc. from the deceased WITH SARS-CoV-2, the real IFR is much lower than influenza's, in the range of other corona cold viruses.

End this BS!

Mounting Evidence of COVID-19 Death Underreporting

Spain's COVID-19 death toll could be 60% higher than official count, says El Pais

By Reuters Staff 2 MIN READ

26th July 2020

WORLD, AFRICA

'Mysterious deaths' being probed in Nigeria's Kano

So far there has been nothing to suggest that deaths are linked with coronavirus, says state governor

28.04.2020

28th April 2020

Fears over hidden Covid-19 outbreak in Lebanon, Iraq and Syria

Number of cases may far exceed official figures amid claims of quarantining by non-state actors

31st March 2020

At least half of mystery deaths in Nigeria's Kano due to COVID-19 - minister

By Reuters Staff 2 MIN READ

2nd June 2020

I work as a medic in Syria, where an unreported Covid-19 crisis is unfolding

Anonymous

The shattered health system is unable to cope with the pandemic, and we are scared to speak out about its spread

24th August 2020

THE LANCET Log in

WORLD REPORT | VOLUME 396, ISSUE 10252, P657, SEPTEMBER 05, 2020

Is India missing COVID-19 deaths?

Patralekha Chatterjee

Published: September 05, 2020

DOI: https://doi.org/10.1016/S0140-6736(20)31857-2

The Washington Post

Democracy Dies in Darkness

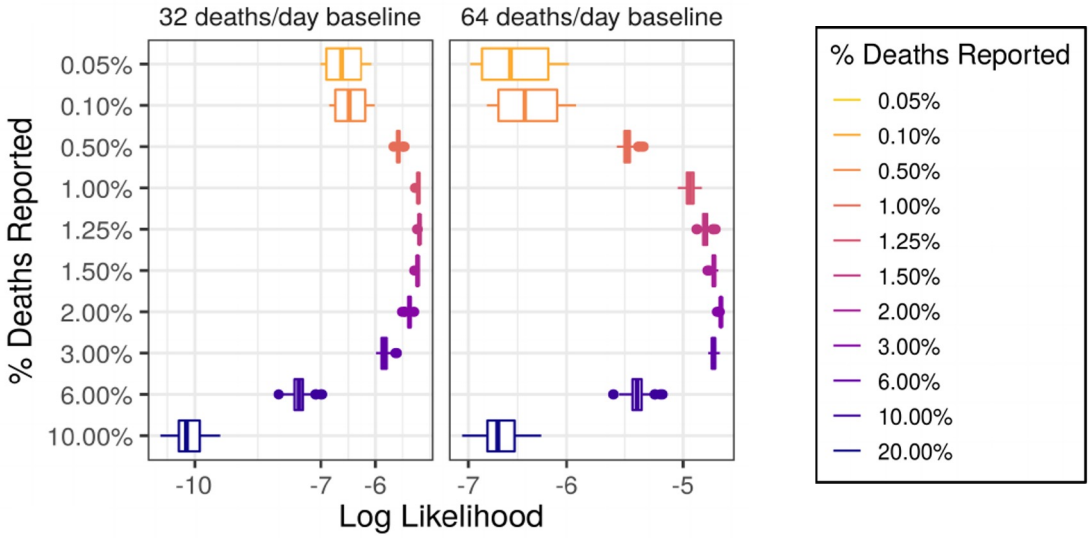
World Africa Americas Asia Europe Middle East Fore

The Americas

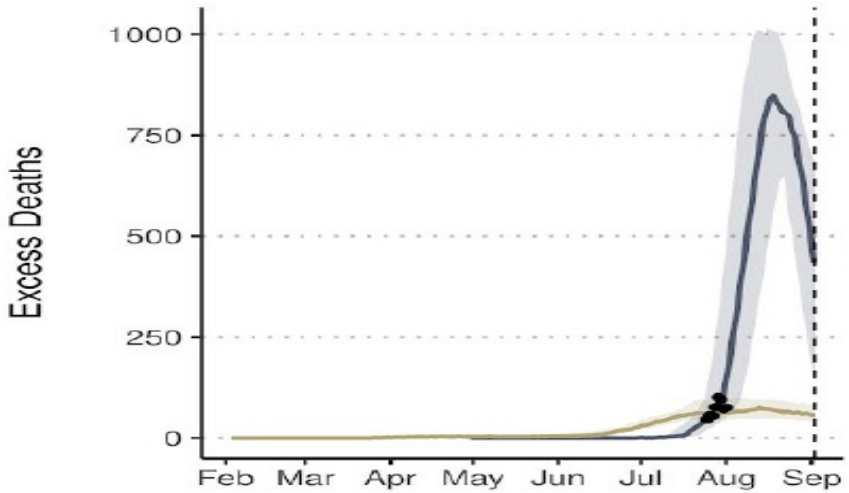
Peru probes whether 27,253 coronavirus deaths uncounted

Case Study: Damascus, Syria

- Fit `squire` SEIR compartment model to death data (assuming deaths not full captured)
- Sensitivity analysis fit to excess mortality
- ***Between 1% - 3% of deaths reported provides best fit to excess mortality***



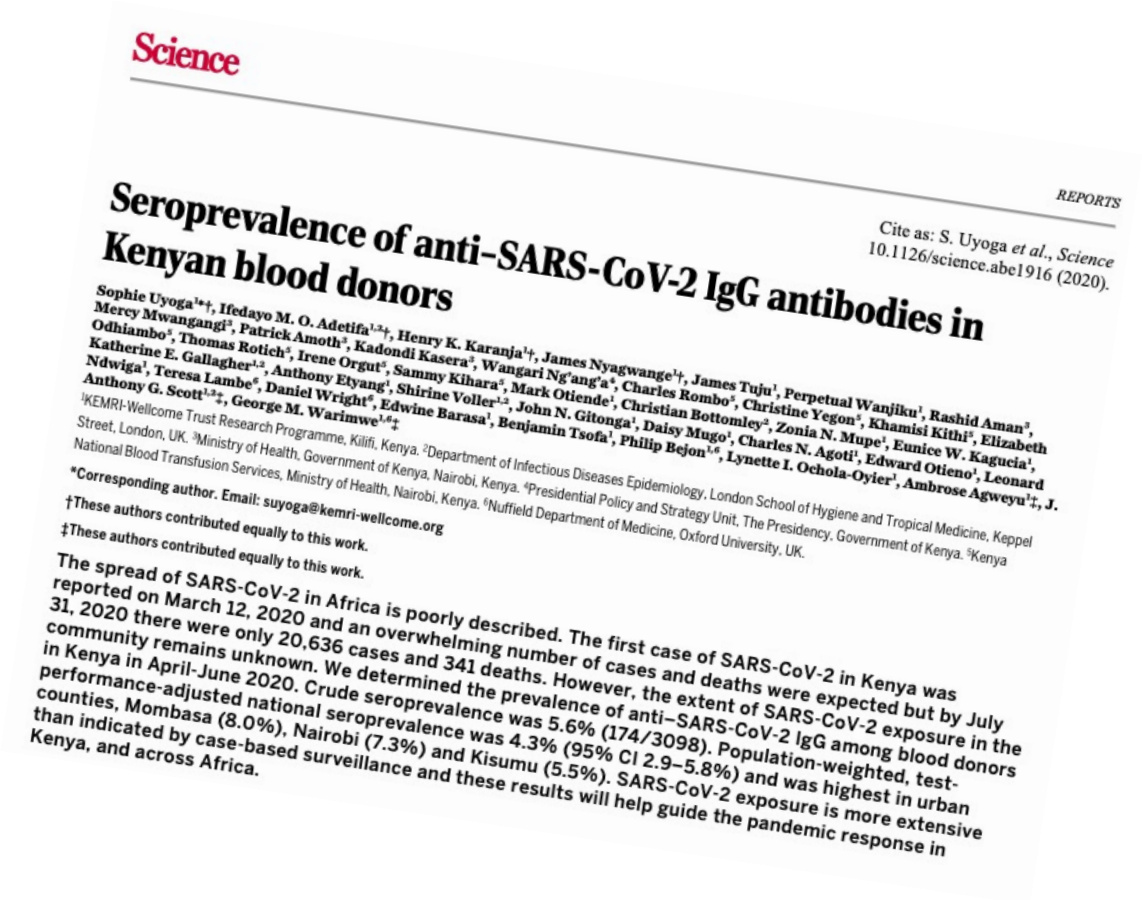
OJ Watson



Report 31

“Back of Envelope” Case Study: Kenya

- Very nice study assessing seropositivity among blood donors across Kenya
- National seroprevalence: 4.3% (95% CI 2.9–5.8%) from April 30 – June 16
- 71 deaths reported by May 30 (median sample date reported)



Science

REPORTS

Cite as: S. Uyoga *et al.*, *Science* 10.1126/science.abe1916 (2020).

Seroprevalence of anti–SARS-CoV-2 IgG antibodies in Kenyan blood donors

Sophie Uyoga[1*†], Ifedayo M. O. Adetifa[1,2†], Henry K. Karanja[1†], James Nyagwange[1†], James Tuju[1], Perpetual Wanjiku[1], Rashid Aman[3], Mercy Mwangangi[3], Patrick Amoth[3], Kadondi Kasera[3], Wangari Ng'ang'a[4], Charles Rombo[5], Christine Yegon[5], Khamisi Kithi[5], Elizabeth Odhiambo[5], Thomas Rotich[5], Irene Orgut[5], Sammy Kihara[5], Mark Otiende[1], Christian Bottomley[2], Zonia N. Mupe[1], Eunice W. Kagucia[1], Katherine E. Gallagher[1,2], Anthony Etyang[1], Shirine Voller[1,2], John N. Gitonga[1], Daisy Mugo[1], Charles N. Agoti[1], Edward Otieno[1], Leonard Ndwiga[1], Teresa Lambe[6], Daniel Wright[6], Edwine Barasa[1], Benjamin Tsofa[1], Philip Bejon[1,6], Lynette I. Ochola-Oyier[1], Ambrose Agweyu[1‡], J. Anthony G. Scott[1,2‡], George M. Warimwe[1,6‡]

[1]KEMRI-Wellcome Trust Research Programme, Kilifi, Kenya. [2]Department of Infectious Diseases Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London, UK. [3]Ministry of Health, Government of Kenya, Nairobi, Kenya. [4]Presidential Policy and Strategy Unit, The Presidency, Government of Kenya. [5]Kenya National Blood Transfusion Services, Ministry of Health, Nairobi, Kenya. [6]Nuffield Department of Medicine, Oxford University, UK.

*Corresponding author. Email: suyoga@kemri-wellcome.org

†These authors contributed equally to this work.

‡These authors contributed equally to this work.

The spread of SARS-CoV-2 in Africa is poorly described. The first case of SARS-CoV-2 in Kenya was reported on March 12, 2020 and an overwhelming number of cases and deaths were expected but by July 31, 2020 there were only 20,636 cases and 341 deaths. However, the extent of SARS-CoV-2 exposure in the community remains unknown. We determined the prevalence of anti–SARS-CoV-2 IgG among blood donors in Kenya in April-June 2020. Crude seroprevalence was 5.6% (174/3098). Population-weighted, test-performance-adjusted national seroprevalence was 4.3% (95% CI 2.9–5.8%) and was highest in urban counties, Mombasa (8.0%), Nairobi (7.3%) and Kisumu (5.5%). SARS-CoV-2 exposure is more extensive than indicated by case-based surveillance and these results will help guide the pandemic response in Kenya, and across Africa.

“Back of Envelope” Case Study: Kenya

- Kenyan Population ~ 50 Million

- 4% seroprevalence * ~ 50 million = 2 million infections
  - IFR = 0.0036%

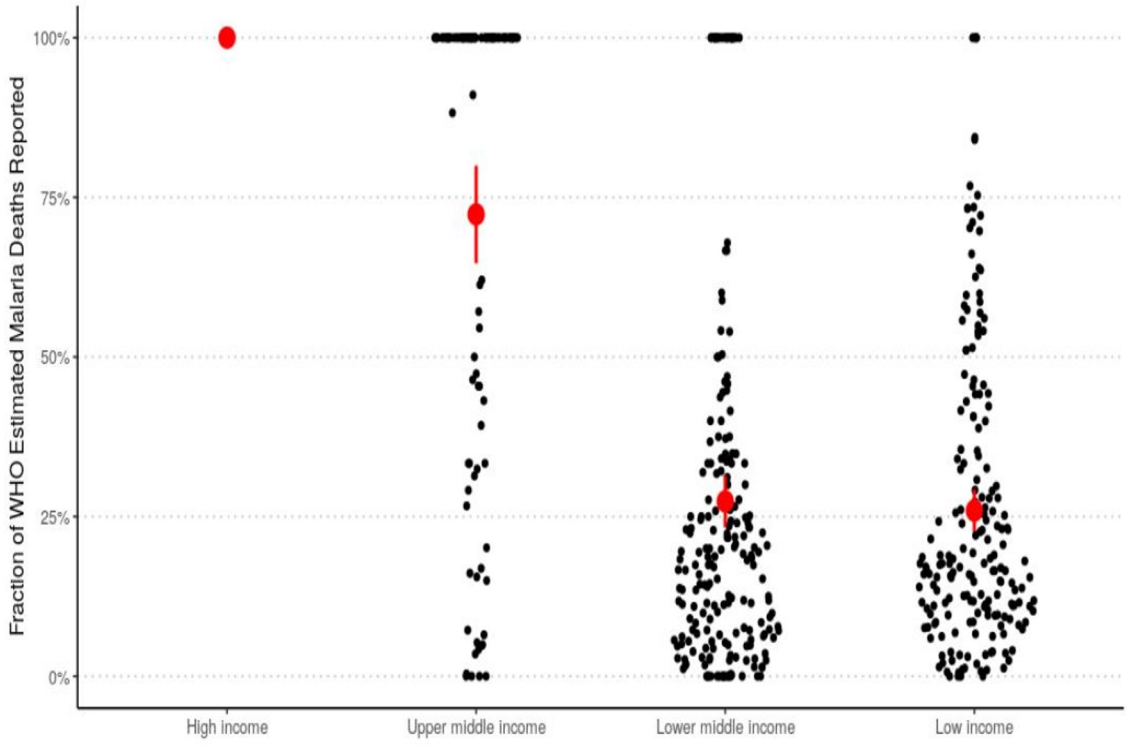
$$\text{Num. Infxns} = \frac{Deaths}{IFR} = \frac{1,604}{0.000036} \approx 44.5 \text{ Million}$$

- Today: 1,604 deaths

- ~90% of population infection (>>Herd Immunity Estimates)

Should We Be Surprised?

- From WHO records, it is estimated that approximately 1 in every 4 malaria deaths appear in official national statistics.[1]
- For yellow fever, less than 1% of the predicted 50,000 deaths a year across Africa are successfully diagnosed and reported.[2]



1. https://www.who.int/data/gho/data/indicators/indicator-details/GHO/estimated-number-of-malaria-deaths
2. The global burden of yellow fever. Katy A. M. Gaythorpe, Arran T. P. Hamlet, Kevin Jean, Daniel Garkauskas Ramos, Laurence Cibrelus, Tini Garske, Neil M. Ferguson medRxiv 2020.10.14.20212472; doi: https://doi.org/10.1101/2020.10.14.20212472

Care Home Deaths

- Extreme burden in the first wave
- “Separate” epidemic
- Excluding these deaths greatly reduces the IFR (results later)
- “Type” of *deaths* matter

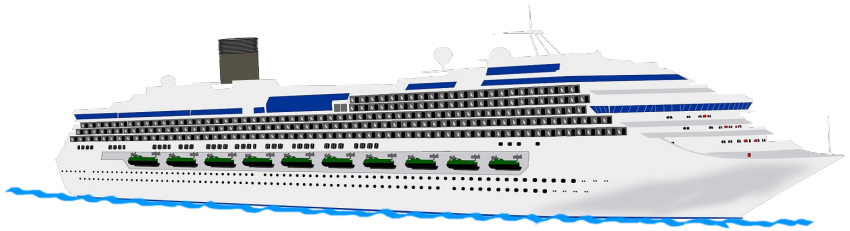
Share of COVID-19 Deaths Care Homes Non-Care Homes

Country	Care Home Deaths	Non-Care Home Deaths	Share of Deaths in Care Homes	Share of Deaths in Care Homes (Stacked Bar)
Canada	166.5	29.1	85.1%	
Slovenia	40.8	9.6	81.0%	
New Zealand	3.2	1.2	72.7%	
Belgium	542.1	303.9	64.1%	
Ireland	223.6	129.9	63.2%	
Norway	27	18.8	59.0%	
France	214.1	227	48.5%	
Sweden	222.5	246.9	47.4%	
Finland	26.6	32.6	45.0%	
U.S.	**164.5**	**204.1**	**44.6%**	
Israel	15.2	18.8	44.6%	
U.K.	331.4	477.2	41.0%	
Portugal	43.7	65.6	40.0%	
Germany	42.1	65.1	39.2%	
Denmark	36.3	66.7	35.3%	
Austria	25.1	47.9	34.4%	
Spain	207.1	398.8	34.2%	
South Korea	1.6	3.1	34.0%	
Australia	1.1	2.9	28.4%	
Hungary	13	41.4	23.9%	
Singapore	0.4	4.3	07.7%	
Hong Kong	0	0.5	0.0%	

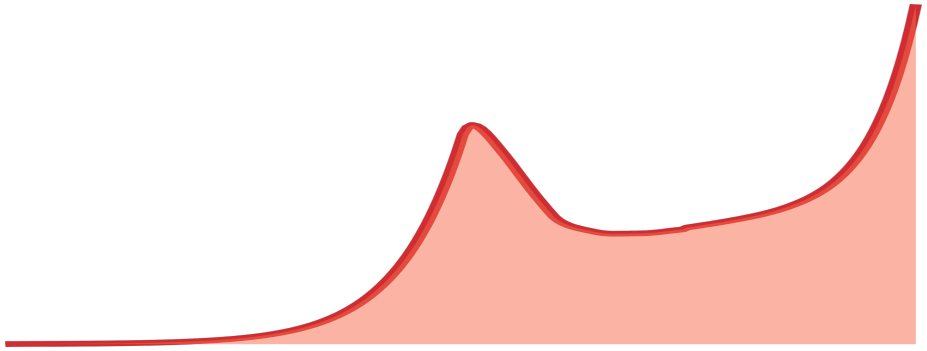
Sources: International Long Term Care Policy Network, Avik Roy • Data as of June 26, 2020
Note: Finland, Ireland, New Zealand, & Norway do not report deaths of care home residents outside of LTC facilities

WIHI FREOPP.org

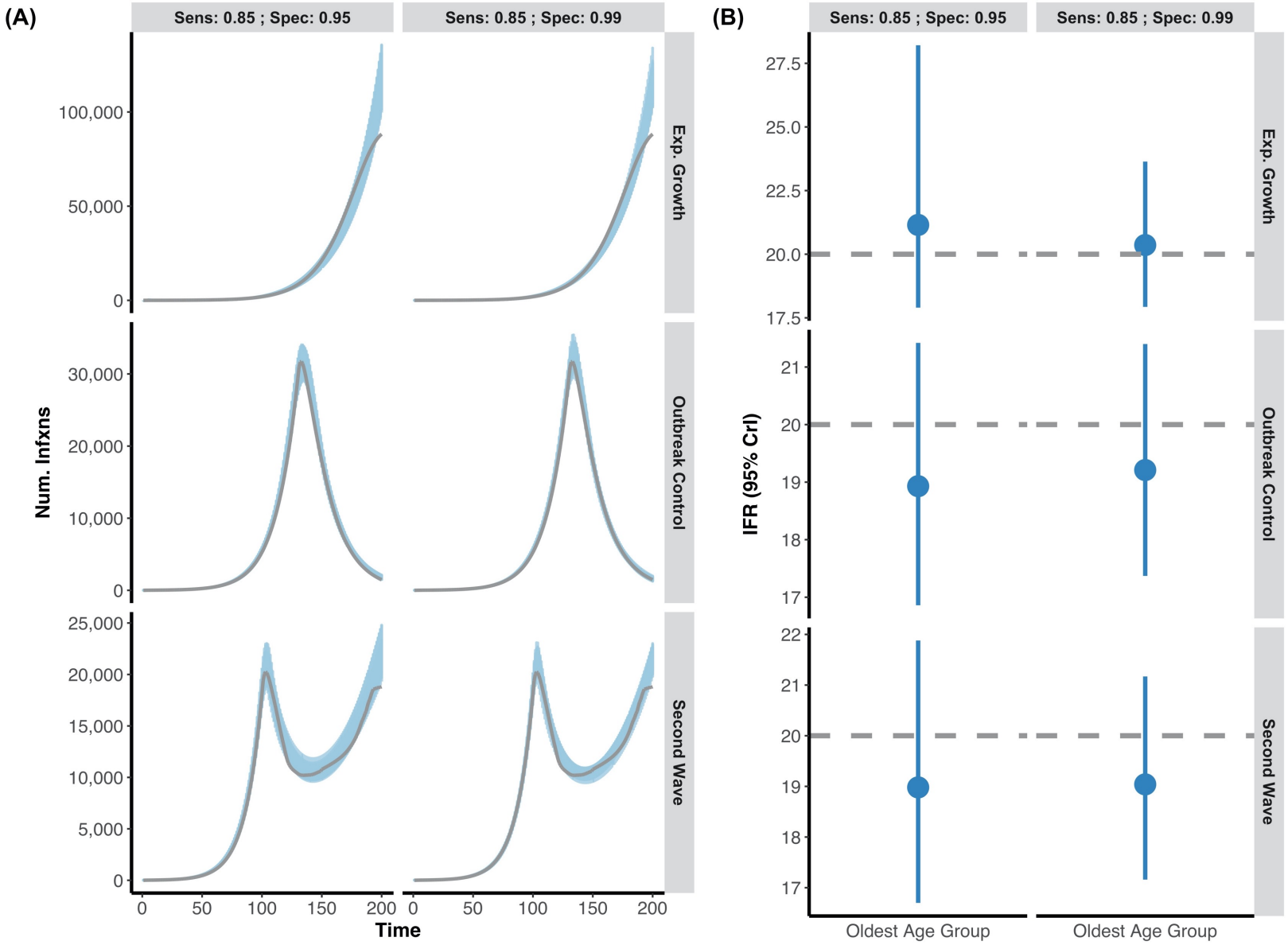
Outline



$$\text{IFR} = \frac{Deaths}{Infxns}$$



Simulations: Evidence the Model Works

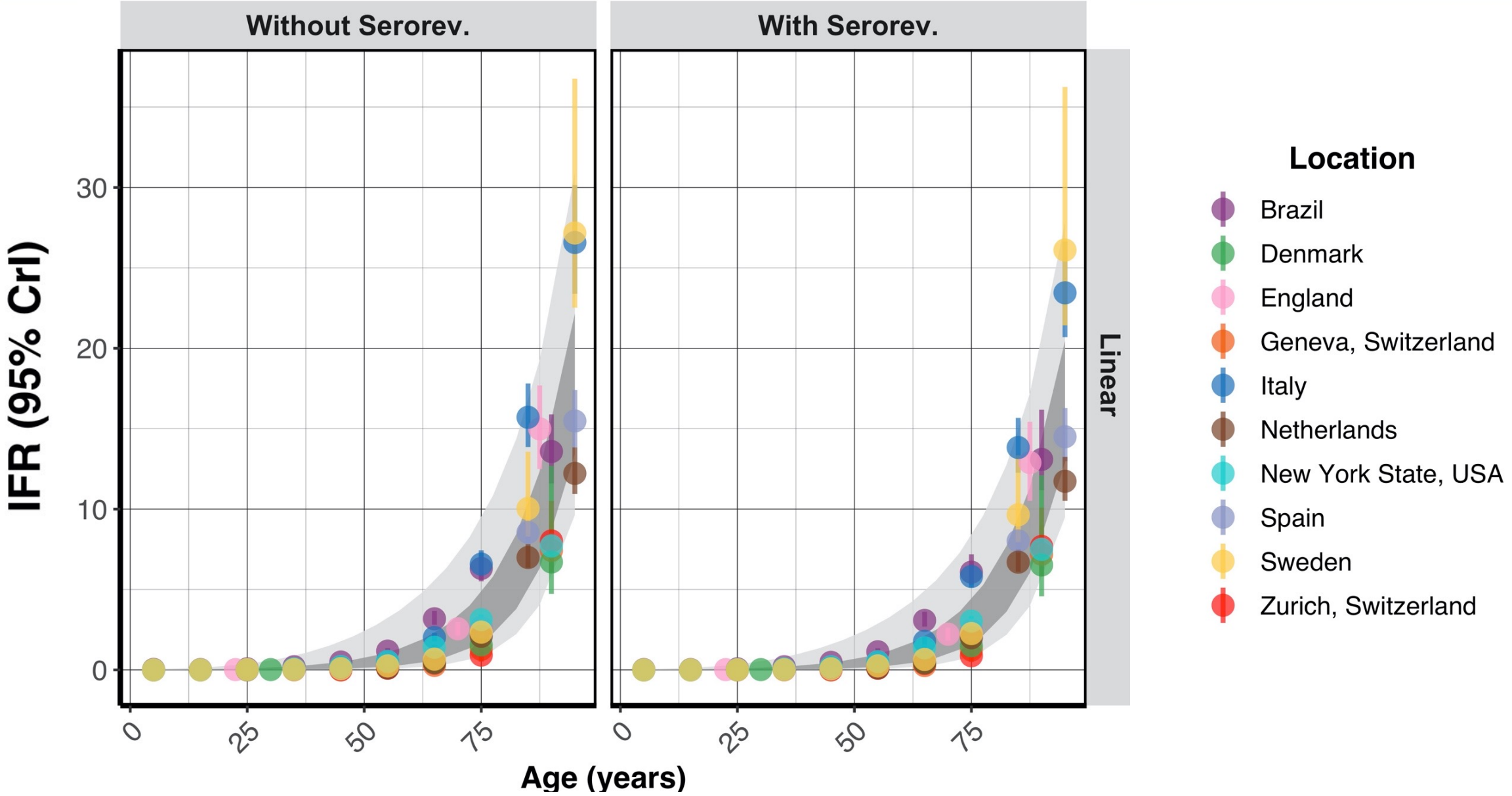


- Fit to complex infection curve shapes
- IFRs w/in 95% credible intervals

Results: Study Specific IFRs

	Data					*Model Estimates*				
Study Location	**Cumulative COVID-19 Deaths**	**Reported Seroprevalence (dates)**	**Serostudy Sensitivity (%)** (T+/D+ or 95% CrI)	**Serostudy Specificity (%)** (T-/D- or 95% CrI)	**Crude IFR** (95 CI%)	**Sensitivity (%)** (95% CrI)	**Specificity (%)** (95% CrI)	**IFR without Seroreversion** (95% CrI)	**IFR with Seroreversion** (95% CrI)	**IFR: Care Home Deaths Excluded, no seroreversion** (95% CrI)
Brazil*	51,179	2.42% (Jun. 04 - Jun. 07)	85.14 (81.93, 87.97)	99.72 (99.55, 99.85)	0.99 (0.92, 1.06)	85.32 (82.25, 88.22)	99.75 (99.61, 99.86)	1.03 (0.93, 1.16)	0.99 (0.89, 1.15)	
Denmark*	463	2.4% (Apr. 27 - May 03)	82.09 (75.51, 87.58)	99.25 (98.94, 99.56)	0.33 (0.23, 0.48)	82.41 (75.88, 87.88)	99.16 (98.73, 99.46)	0.53 (0.38, 1)	0.52 (0.37, 0.96)	0.33 (0.23, 0.6)
England*	47,954	5.94% (Jun. 20 - Jul. 03)	78.4 (65.68, 88.15)	99.44 (99.11, 99.71)	1.41 (1.38, 1.45)	79.79 (67.69, 89.31)	99.6 (99.34, 99.77)	1.18 (0.99, 1.34)	1.02 (0.85, 1.18)	0.73 (0.61, 0.83)
Italy*,α	34,610	2.44% (May 25 - Jul. 15)	96.04 (89.84, 99.05)	99.7 (99.59, 99.79)	2.3 (1.94, 2.72)	96.47 (90.79, 99.16)	99.69 (99.57, 99.78)	2.53 (2.3, 2.77)	2.23 (2.03, 2.44)	
Netherlands	5,767	5.5% (May 10 - May 20)	98.28 (171/174)	99.65 (281/282)	0.6 (0.58, 0.63)	98.25 (95.64, 99.53)	99.83 (99.43, 99.98)	0.62 (0.58, 0.68)	0.59 (0.55, 0.65)	
Spain*	28,116	5.27% (Jun. 08 - Jun. 22)	81.84 (75.67, 87.01)	98.79 (98.55, 99.02)	1.12 (1.08, 1.16)	84.72 (83.07, 88.52)	99.04 (98.86, 99.21)	1.14 (1.08, 1.21)	1.07 (1.01, 1.14)	0.75 (0.71, 0.8)
Sweden	4,992	7.1% (Jun. 08 - Jun. 12)	99.36 (156/157)	98.89 (267/270)	0.68 (0.46, 1)	99.29 (97.19, 99.93)	99.17 (98.13, 99.77)	1.03 (0.87, 1.37)	0.99 (0.84, 1.37)	0.55 (0.46, 1.2)
Geneva, Switzerland	262	10.84% (May 03 - May 10)	91.16 (165/181)	100 (176/176)	0.48 (0.42, 0.56)	91.49 (86.89, 94.96)	99.89 (98.76, 100)	0.49 (0.42, 0.6)	0.48 (0.4, 0.57)	0.22 (0.18, 0.27)
Zurich, Switzerland	124	1.59% (May 01 - May 31)	90.74 (49/54)	99.89 (5,497/5,503)	0.51 (0.45, 0.58)	91.8 (83.36, 96.86)	99.87 (99.74, 99.95)	0.52 (0.41, 0.67)	0.5 (0.39, 0.64)	
New York State, USA*	17,718	12.1% (Apr. 19 - Apr. 28)	89.39 (85.57, 92.55)	98.73 (98.15, 99.27)	0.75 (0.74, 0.76)	89.67 (85.99, 92.69)	98.7 (98.02, 99.19)	0.77 (0.72, 0.83)	0.75 (0.7, 0.8)	0.61 (0.58, 0.66)

Results: Age-Specific IFRs



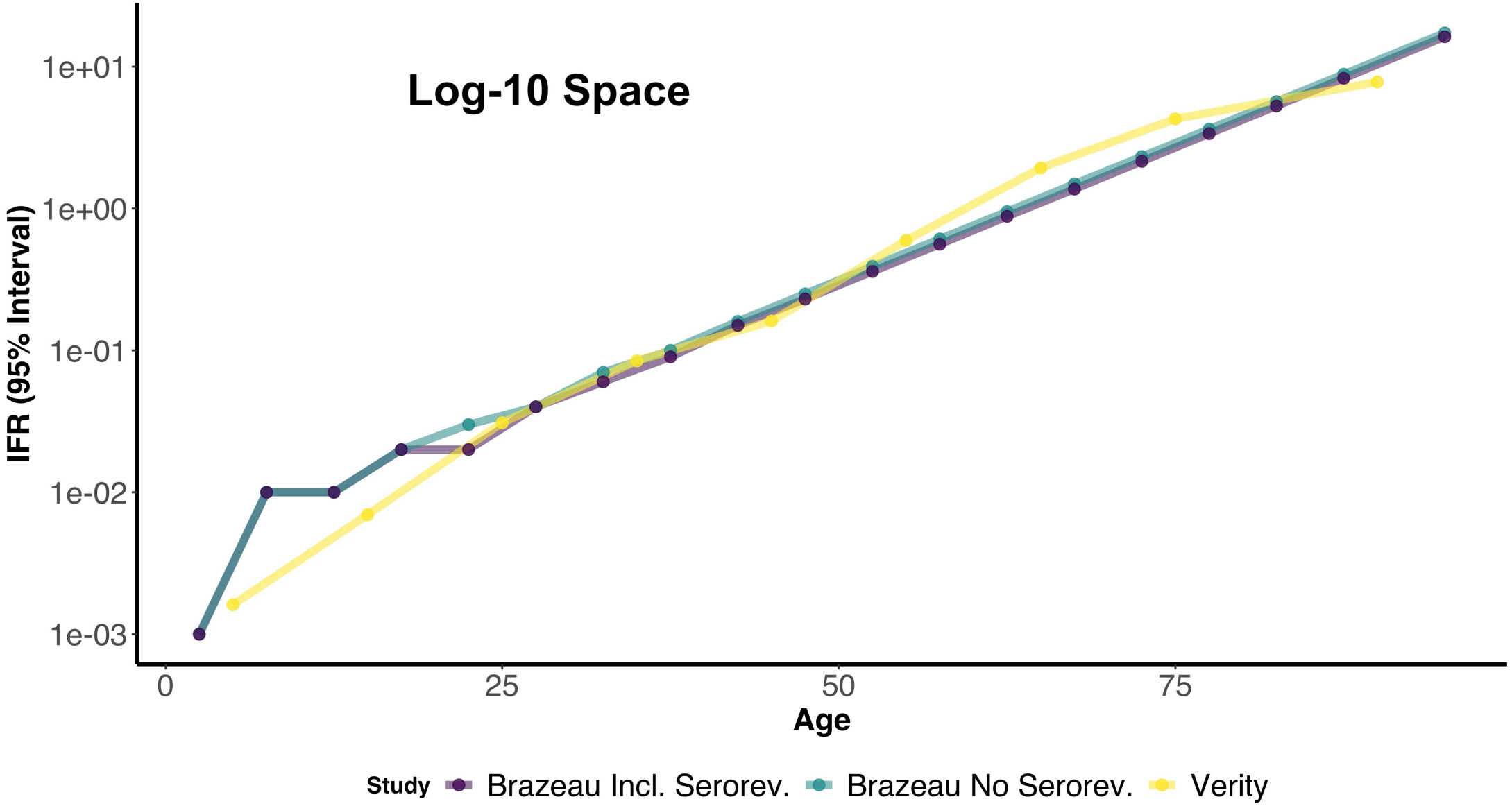
Results: Best Guesses of the IFR

Age-Band (years)	IFR (%) without Seroreversion (95% PI)	IFR (%) with Seroreversion (95% PI)
0-4	0 (0, 0.04)	0 (0, 0.03)
5-9	0.01 (0, 0.06)	0.01 (0, 0.06)
10-14	0.01 (0, 0.11)	0.01 (0, 0.1)
15-19	0.02 (0, 0.19)	0.02 (0, 0.17)
20-24	0.03 (0, 0.31)	0.02 (0, 0.28)
25-29	0.04 (0, 0.48)	0.04 (0, 0.43)
30-34	0.07 (0.01, 0.73)	0.06 (0.01, 0.66)
35-39	0.1 (0.01, 1.06)	0.09 (0.01, 0.96)
40-44	0.16 (0.02, 1.5)	0.15 (0.02, 1.35)
45-49	0.25 (0.03, 2.07)	0.23 (0.03, 1.85)
50-54	0.39 (0.05, 2.79)	0.36 (0.05, 2.48)
55-59	0.61 (0.1, 3.7)	0.56 (0.1, 3.28)
60-64	0.95 (0.19, 4.84)	0.88 (0.18, 4.28)
65-69	1.49 (0.35, 6.32)	1.37 (0.34, 5.58)
70-74	2.32 (0.65, 8.25)	2.15 (0.63, 7.29)
75-79	3.62 (1.21, 10.84)	3.37 (1.18, 9.59)
80-84	5.66 (2.23, 14.37)	5.28 (2.19, 12.75)
85-89	8.84 (4.05, 19.3)	8.27 (3.98, 17.21)
90+	17.25 (9.63, 30.9)	16.23 (9.48, 27.81)

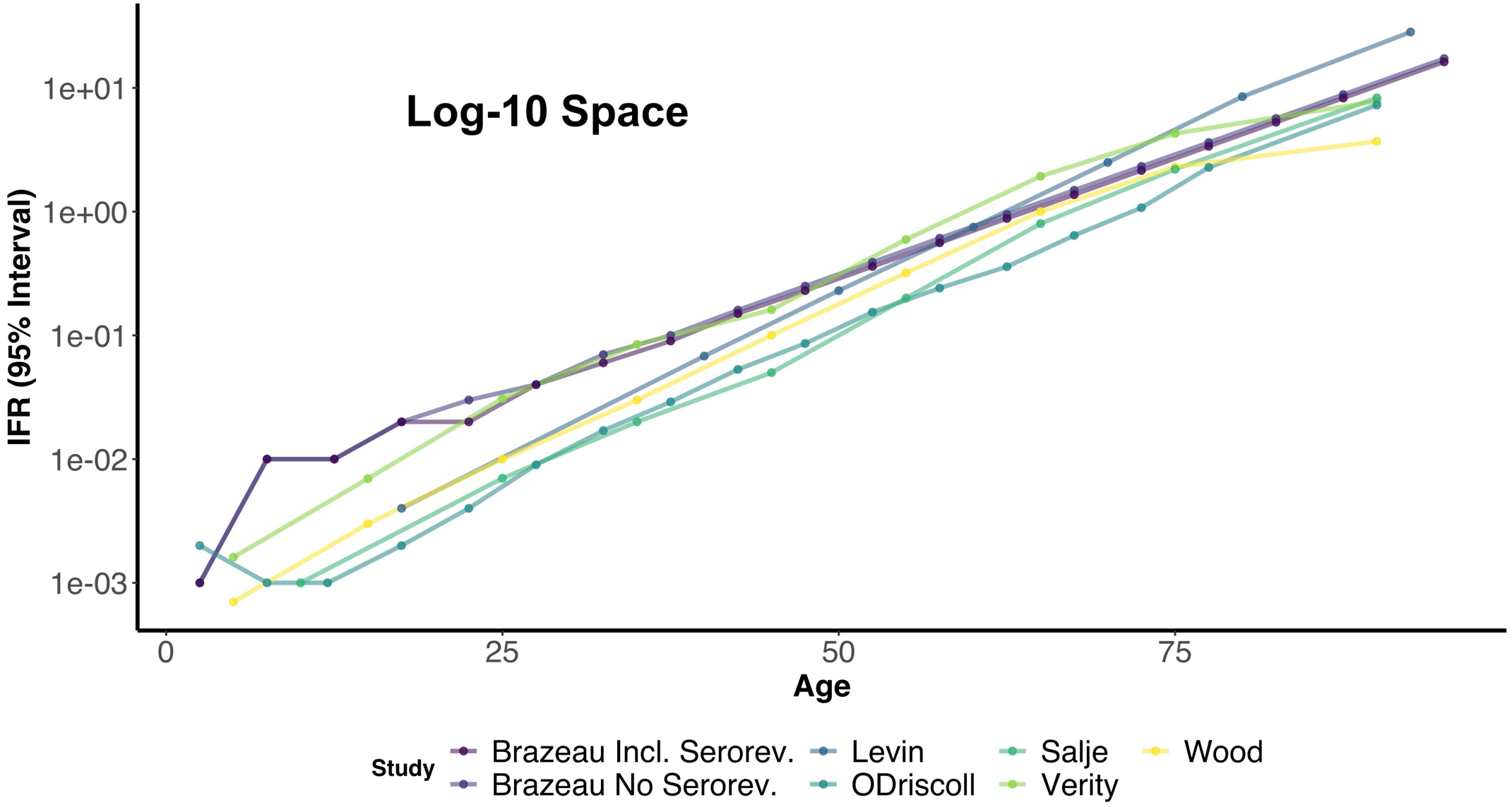
Overall (LIC)	0.24 (0.15, 0.43)	0.21 (0.14, 0.38)
Overall (LMIC)	0.4 (0.26, 0.67)	0.37 (0.24, 0.61)
Overall (UMIC)	0.62 (0.41, 1)	0.56 (0.38, 0.91)
Overall (HIC)	1.15 (0.78, 1.8)	1.06 (0.73, 1.62)

- "Risk" of death doubles every eight years of age
- IFR ranges from 0.15 – 0.43% in LIC
- IFR ranges from 0.78 – 1.8% in HIC

Verity *et al.* Holding up to the Test of Time



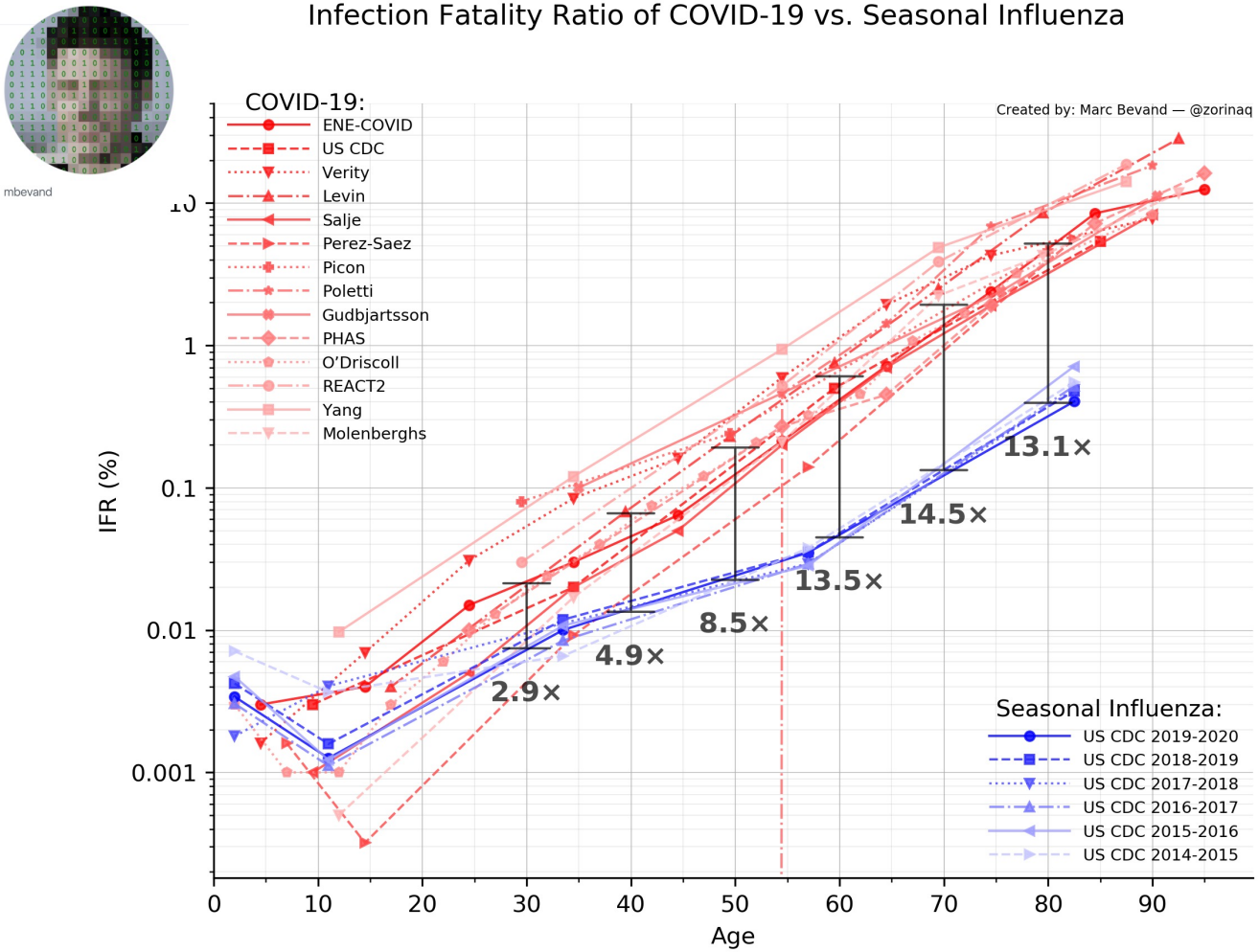
Contrasting the IFR Across Studies



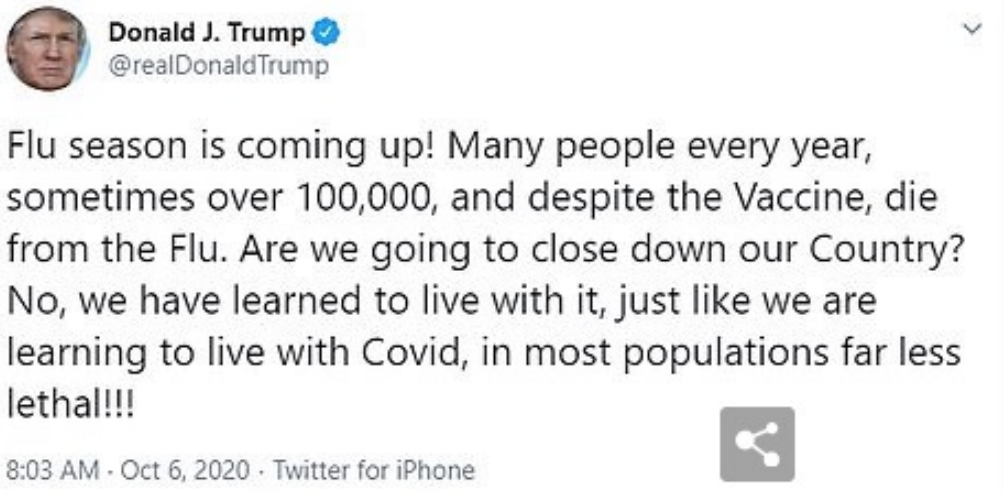
IFR Estimates in the “Wild”

MRC Centre for Global Infectious Disease Analysis

Imperial College London

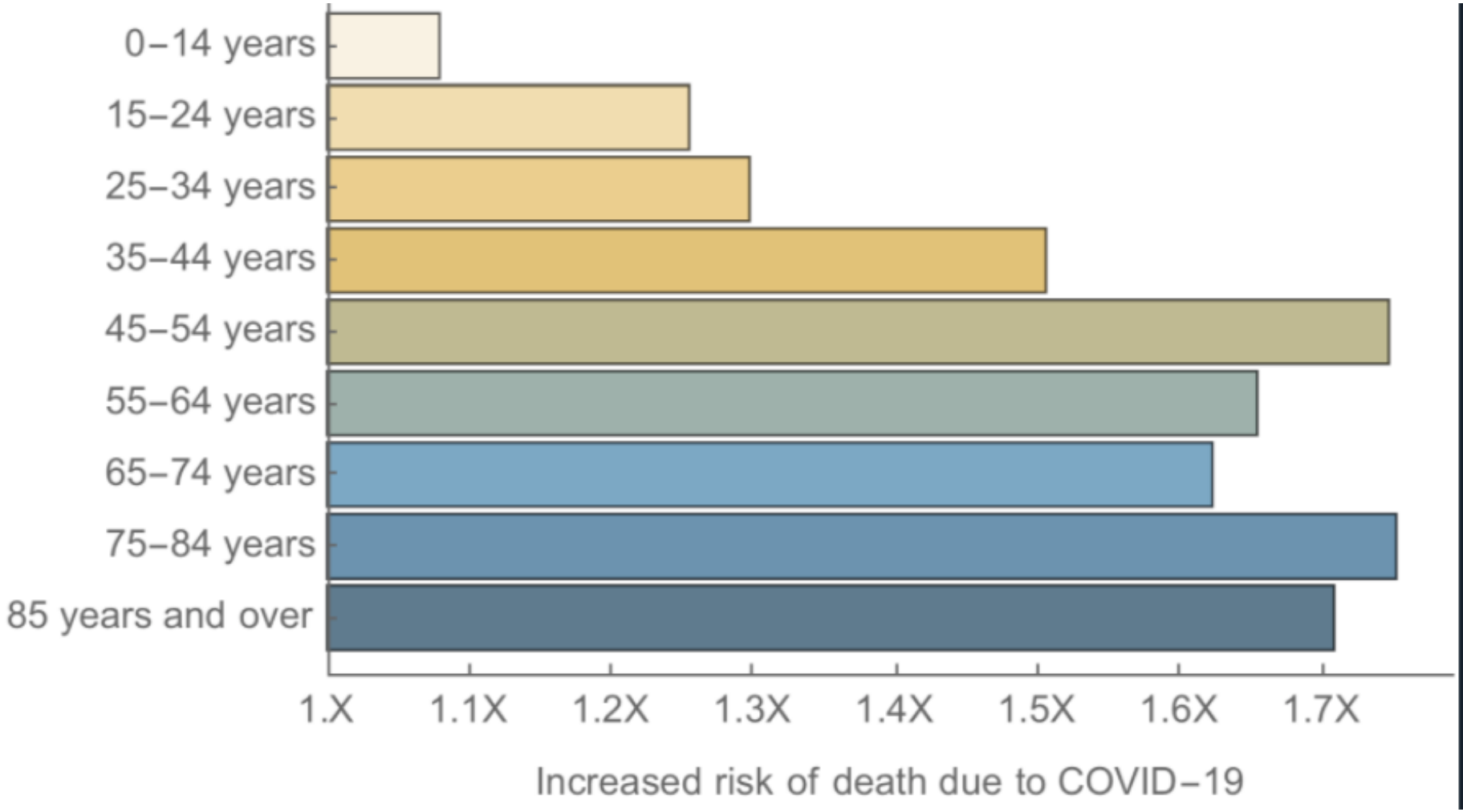


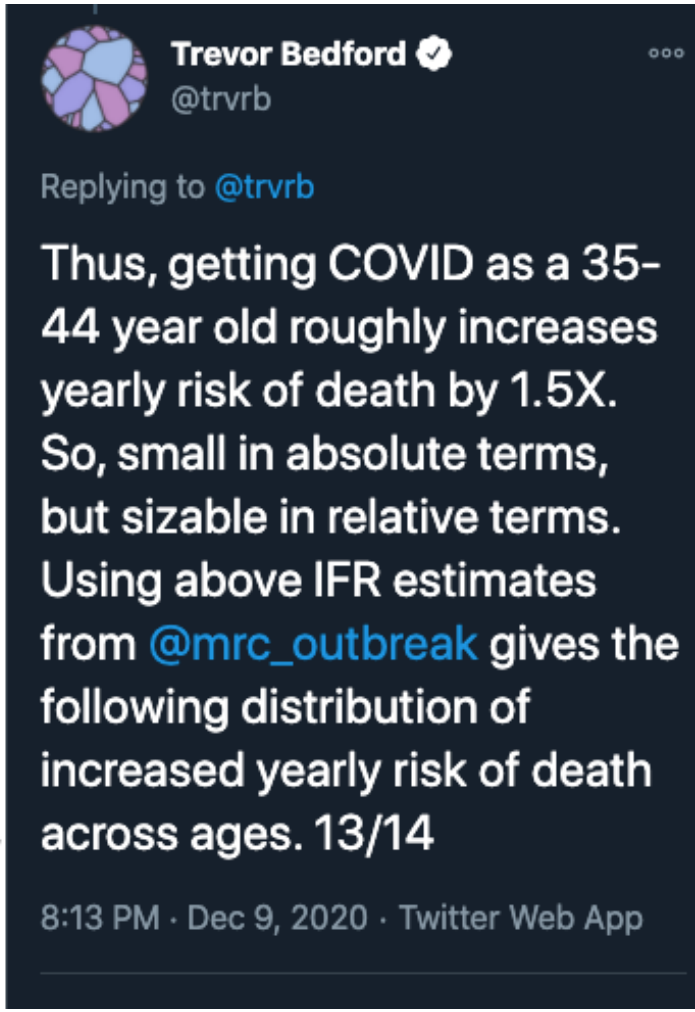
Source: https://github.com/mbevand/covid19-age-stratified-ifr
Note: the vertical lines on one COVID-19 IFR curve (Poletti) are caused by the IFR being estimated to be zero for age groups 0-19 and 20-49.



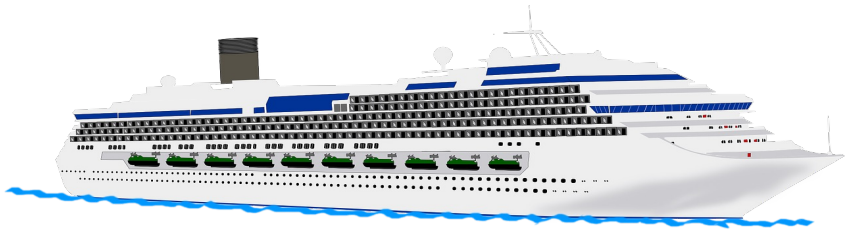
- Not the flu

IFR Estimates in the “Wild”

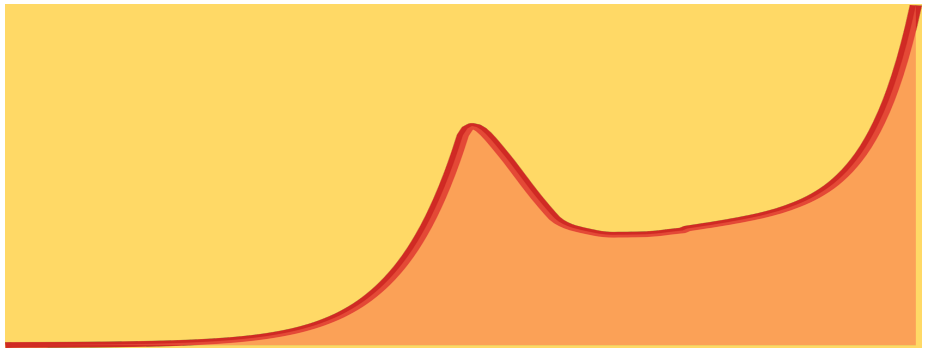




Outline



$$\mathrm{IFR} = \frac{Deaths}{Infxns}$$



Has the IFR changed over time

nature

NEWS FEATURE · 11 NOVEMBER 2020

Why do COVID death rates seem to be falling?

Hard-won experience, changing demographics and reduced strain on hospitals are all possibilities – but no one knows how long the change will last.

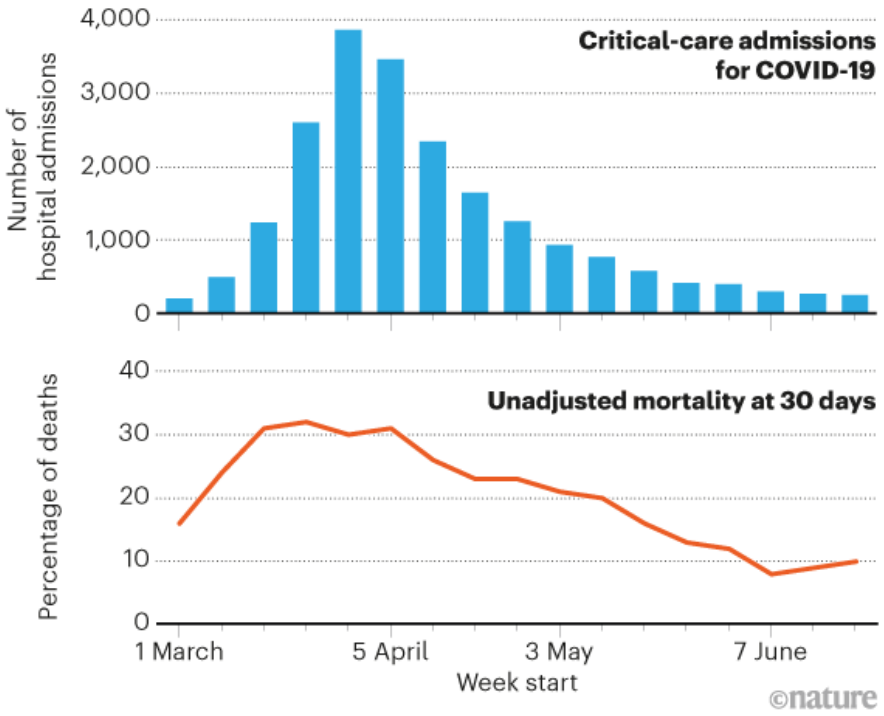
Has the IFR changed over time?

OPEN

Improving Survival of Critical Care Patients With Coronavirus Disease 2019 in England: A National Cohort Study, March to June 2020

John M. Dennis, PhD[1]
Andrew P. McGovern, MD (Res)[1]
Sebastian J. Vollmer, PhD[2,3]
Bilal A. Mateen, MBBS[3,4]

The COVID-19 death rate dropped in about 21,000 people admitted to critical-care units in England between March and June 2020. Reductions in mortality were apparent even after adjusting for age, sex, ethnicity and pre-existing health conditions.



October 26, 2020

ONLINE FIRST OCTOBER 23, 2020—BRIEF REPORT

Trends in COVID-19 Risk-Adjusted Mortality Rates

Leora I Horwitz, MD, MHS[1,2,3]*, Simon A Jones, PhD[1,2], Robert J Cerfolio, MD[4], Fritz Francois, MD[3], Joseph Greco, MD[5], Bret Rudy, MD[6], Christopher M Petrilli, MD[3]

[1]Center for Healthcare Innovation and Delivery Science, NYU Langone Health, New York, New York; [2]Department of Population Health, NYU Grossman School of Medicine, New York, New York; [3]Department of Medicine, NYU Grossman School of Medicine, New York, New York; [4]Department of Surgery, NYU Grossman School of Medicine, New York, New York; [5]NYU Winthrop Hospital, Mineola, New York; [6]Department of Pediatrics, NYU Grossman School of Medicine, New York, New York.

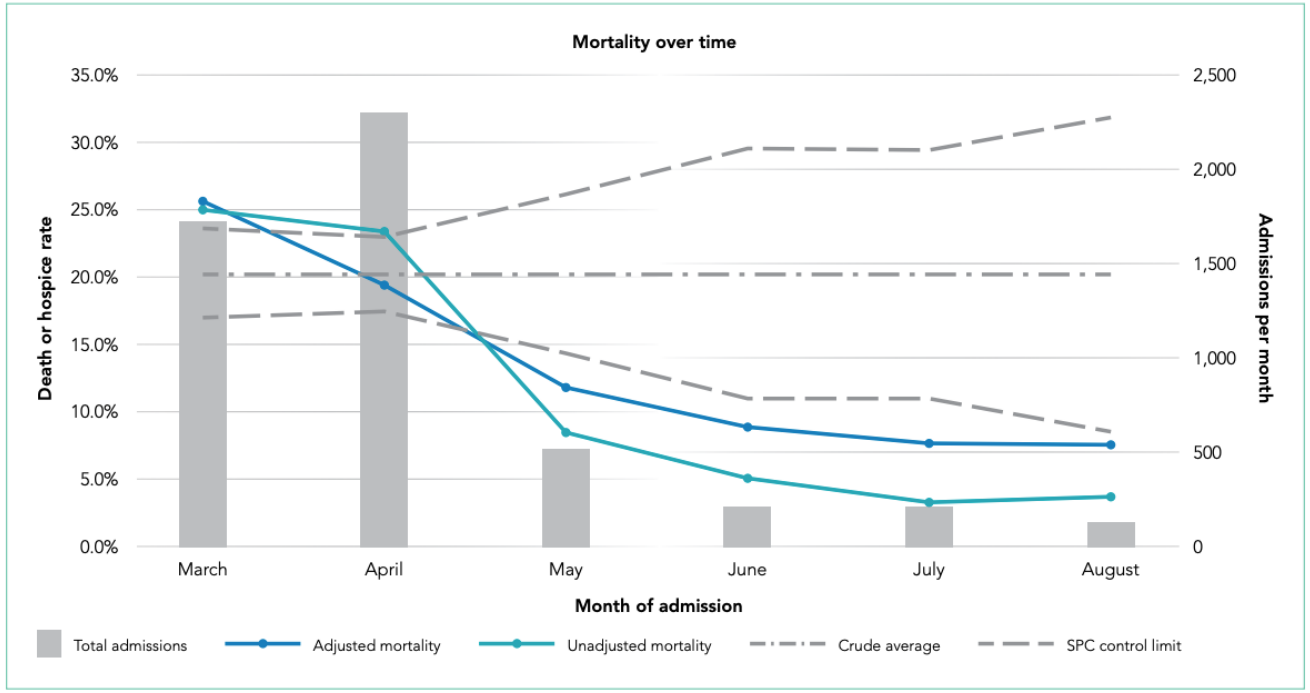
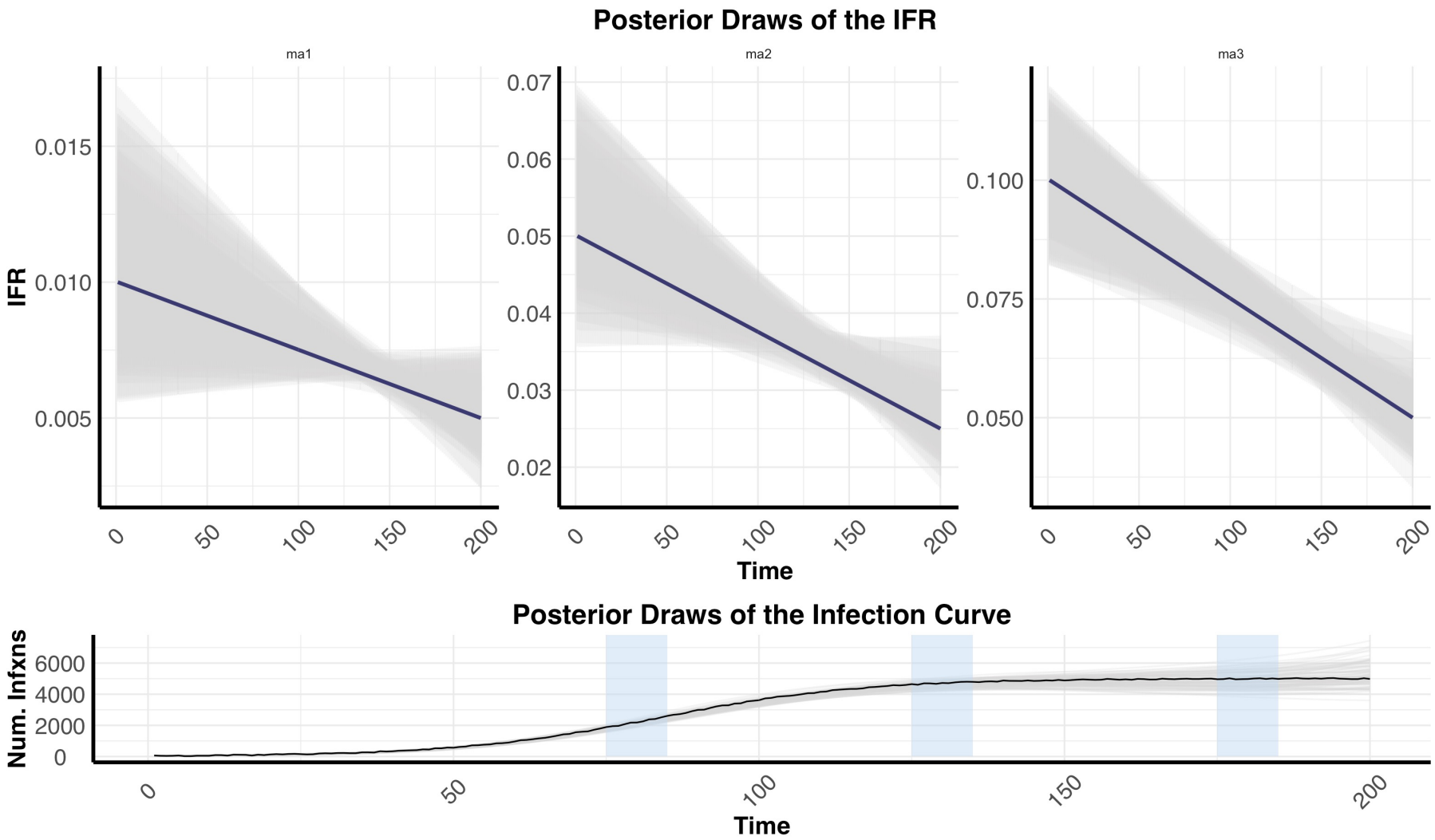


FIG. Adjusted and Unadjusted Mortality or Hospice Rate, by Month of Admission.

October 23, 2020

⚠️ Same Shape, Same Pin, New IFR approach



⚠️ Heavy work in progress (*i.e.* model still may fail)

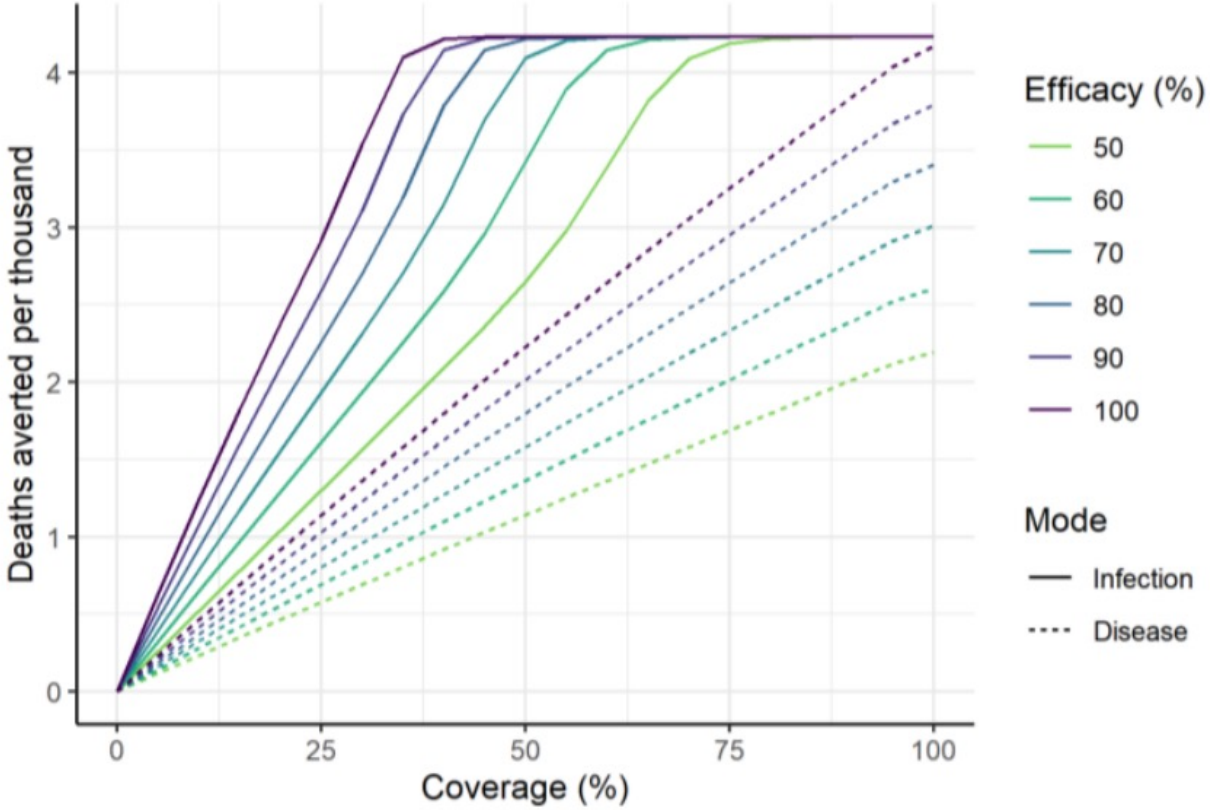
Comments on Vaccines & the IFR

- Do COVID-19 Vaccines Block Transmission or just Dz
  - *Transmission*
    - IFR will change in complicated ways
  - *Only Dz*:
    - IFR will drop along with deaths (removing from numerator *but not* denominator)

- Moving forward, interested in:
  - IFR in vaccinated
  - IFR in unvaccinated
  - (IFR before vaccination)

Alexandra Hogan ***Pete Winskill***

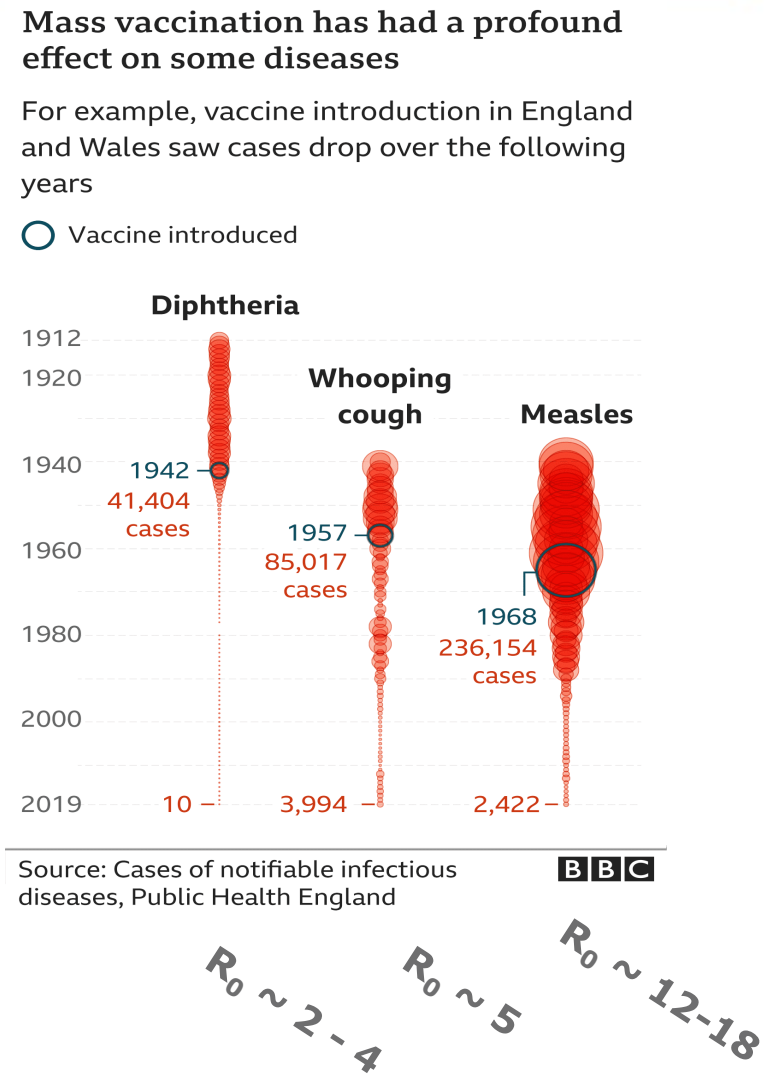
Report 33



Comments on Vaccines & the IFR

- IFR is only on piece of the puzzle
  - Herd Immunity Thresholds
    - 2009 H1N1 Influenza R_0 ~ 1.4 – 1.6 (PMC3735127; PMC3084966)
      - (20-40% of population immune for control*)
    - COVID-19 R_0 ~ 2 - 4
      - (50-75% of population immune for control*)

- Huge success stories with improvements in care/treatment *(to be further described)* and available vaccines
  - Good place because of action, not in spite of it



⚠️ Simple assumptions at play

Take-Aways

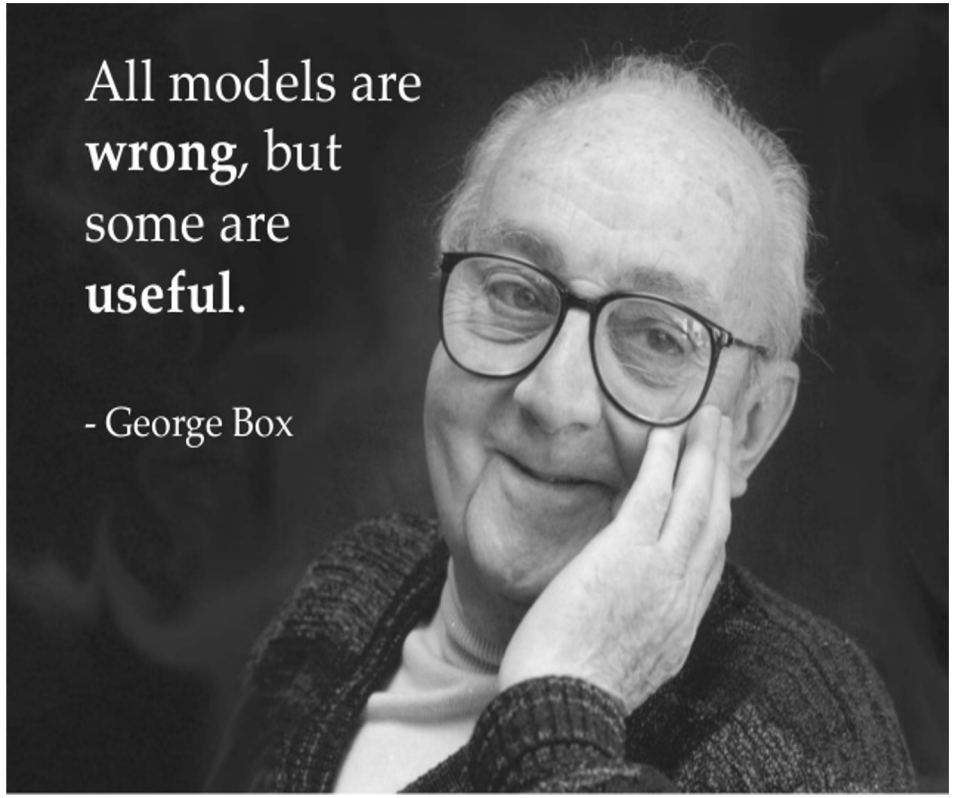
MRC Centre for Global Infectious Disease Analysis

Imperial College London

- **Serologic Data**
  - Useful metric for disease burden
  - Need to account for sens, spec, and seroreversion

- **"First Wave" IFR Estimates**
  - Significant pattern by age ("risk" doubles every 8 years)
  - 10-15x higher than seasonal influenza
    - Not considering long-term sequalae
  - Large variation in IFRs even in similar wealth brackets/demographics

- **The IFR has *likely* decreased over time**
  - ⚠️ Future work needed



Acknowledgements

MRC Centre for Global Infectious Disease Analysis

Imperial College London

& Imperial College COVID Response Team

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- **Imperial College London**
- F30AI143172
- UNC MD/PhD Program

National Institute of Allergy and Infectious Diseases

Acknowledgements

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ideel

@IDEELlabs

https://www.med.unc.edu/medicine/infdis/ideel/

MRC Centre for Global Infectious Disease Analysis

Imperial College London

QUESTIONS & Discussion

Reproducibility & Data Availability

- *Software Package: mrc-ide/COVIDCurve*
- *Analyses: mrc-ide/reestimate_covidIFR_analysis*

GitHub

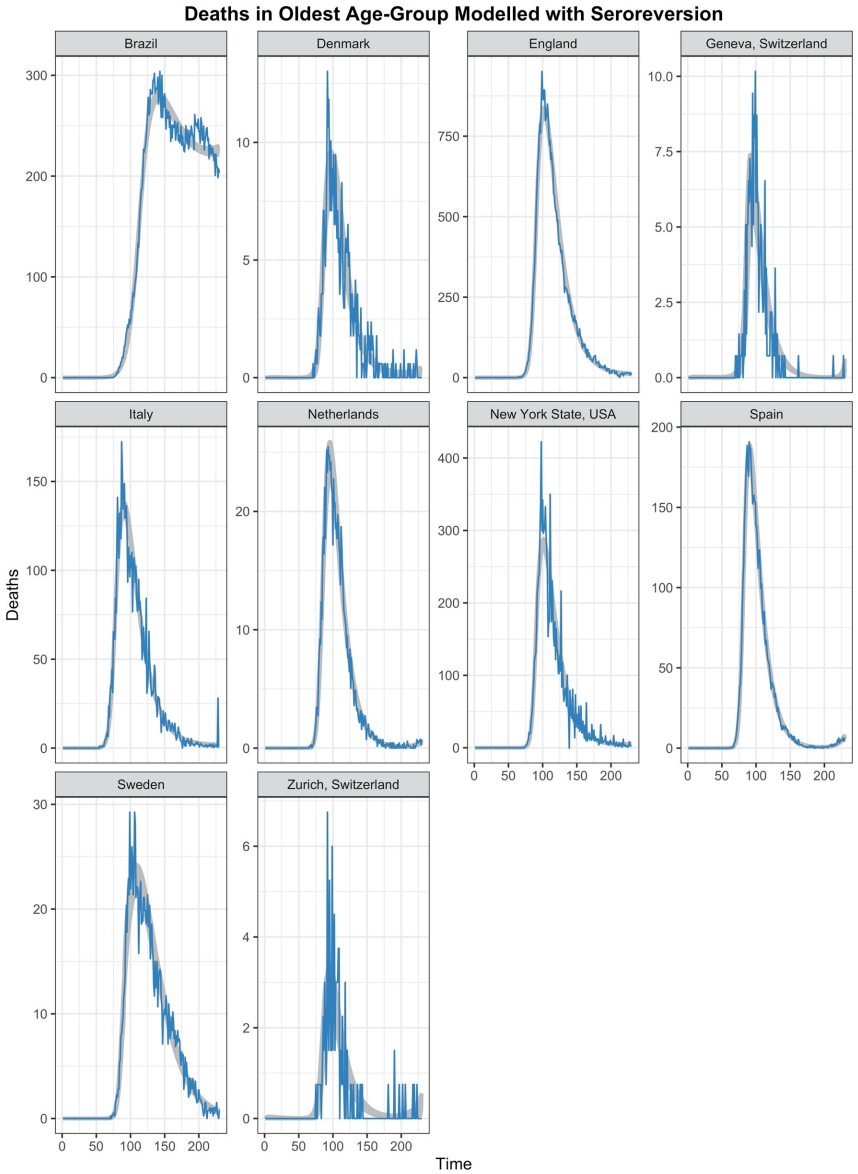
Reports Available Online (link below or google "Imperial COVID Reports")

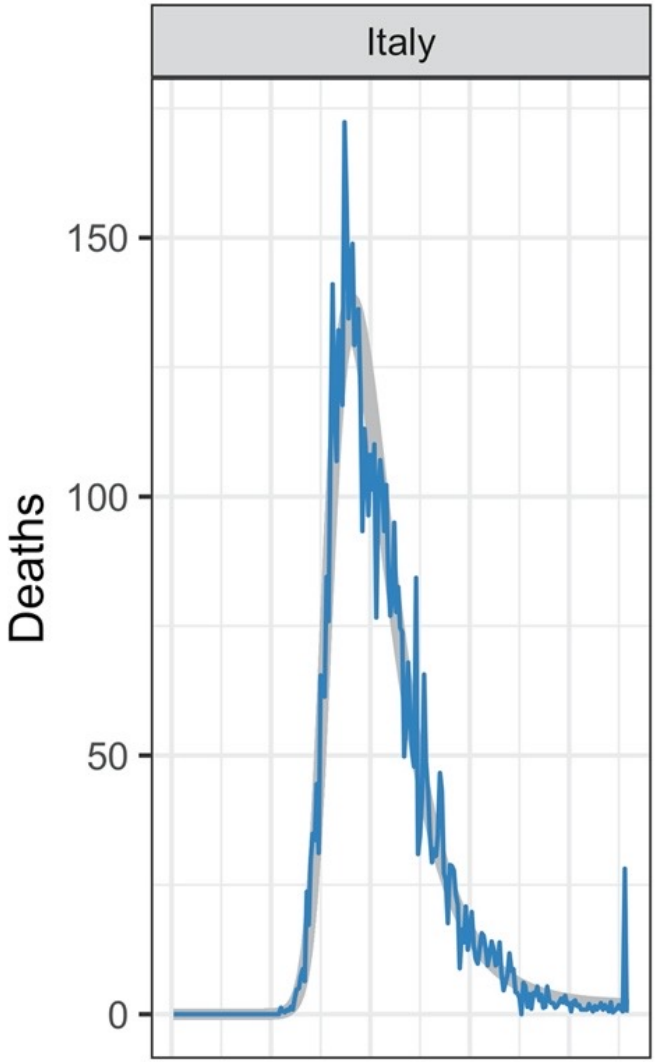
- *https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/covid-19-reports*
- Report 34: IFR Analyses from Serologic Data

Nick Brazeau, MD/PhD Candidate
nbrazeau@med.unc.edu
@NFBrazeau

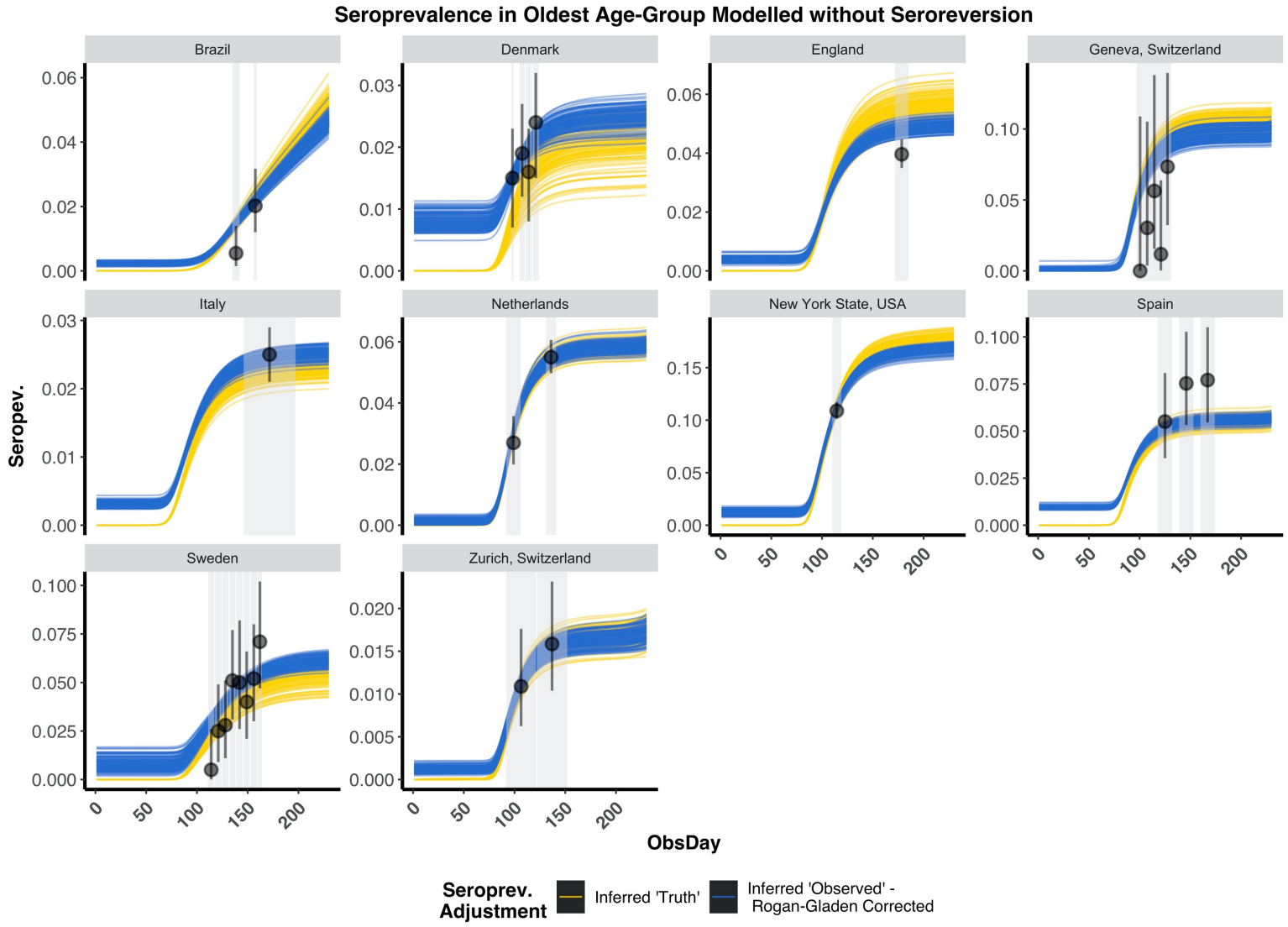
Posterior Predictive Checks

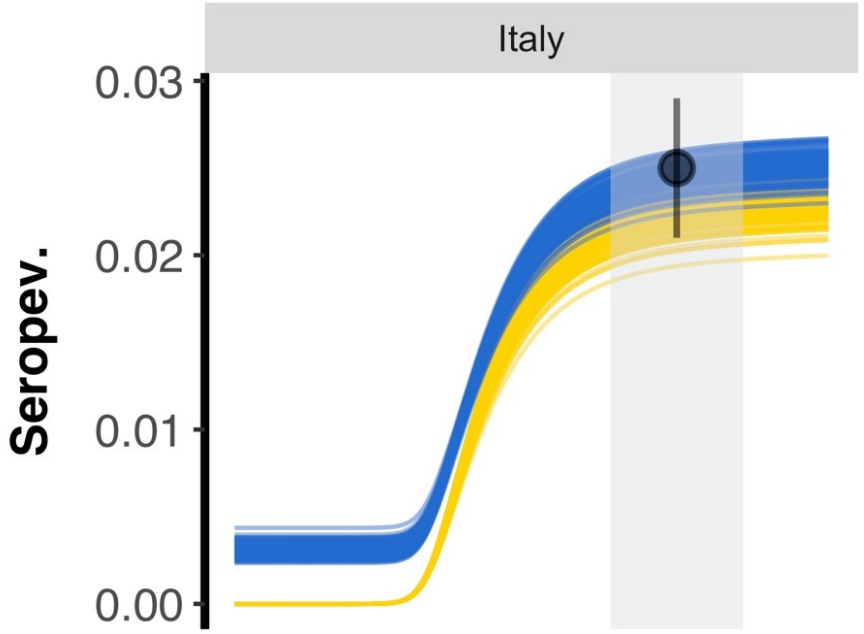
Results: Posterior Predictive Checks - Deaths





Results: Posterior Predictive Checks - Serology





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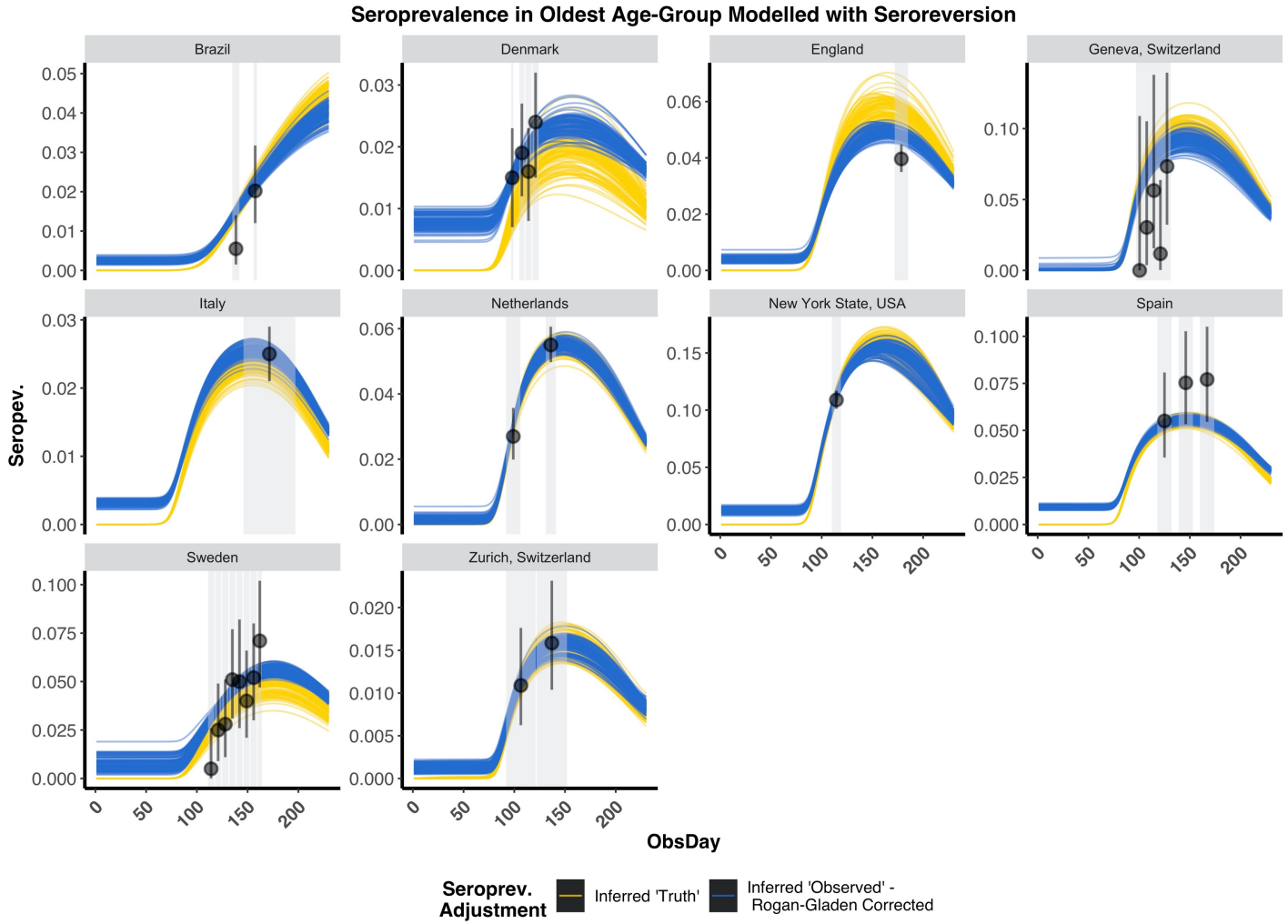
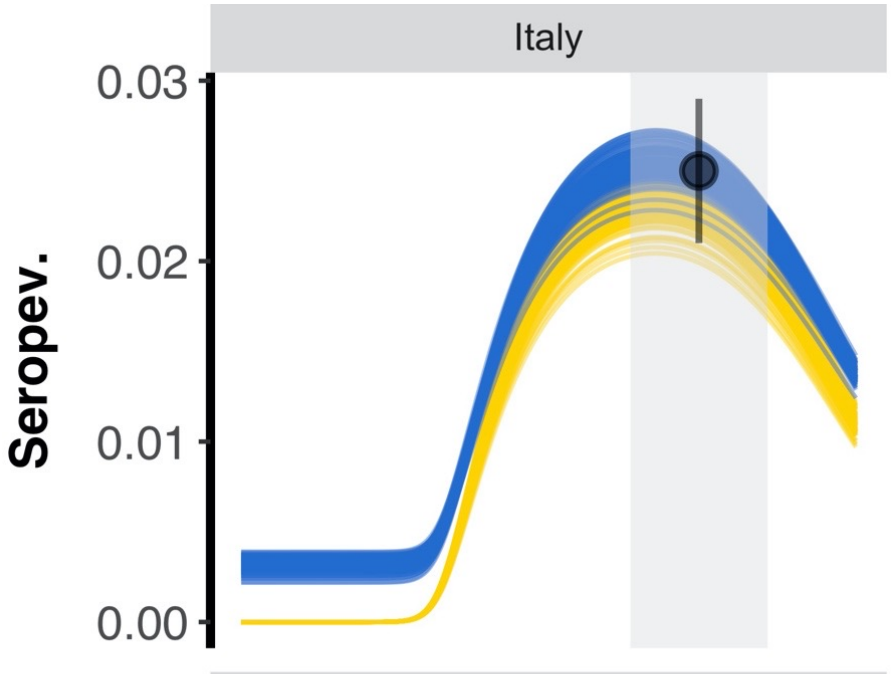


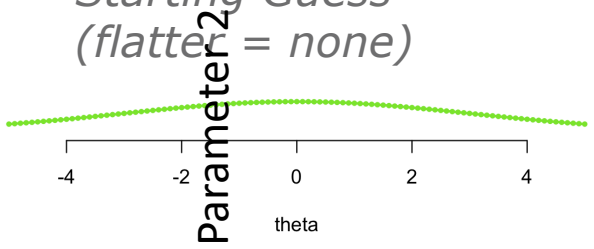


Bayesian Approach

MCMC (one slide)

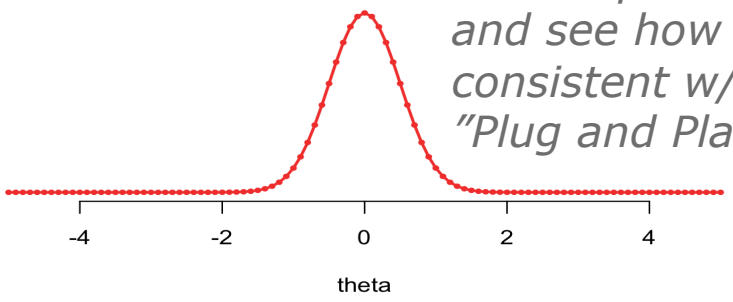
Prior

Starting Guess
(flatter = none)

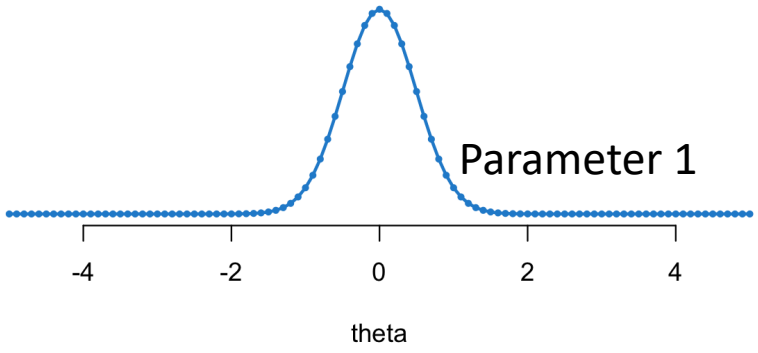


Likelihood

Draw a parameter, and see how consistent w/ data "Plug and Play"

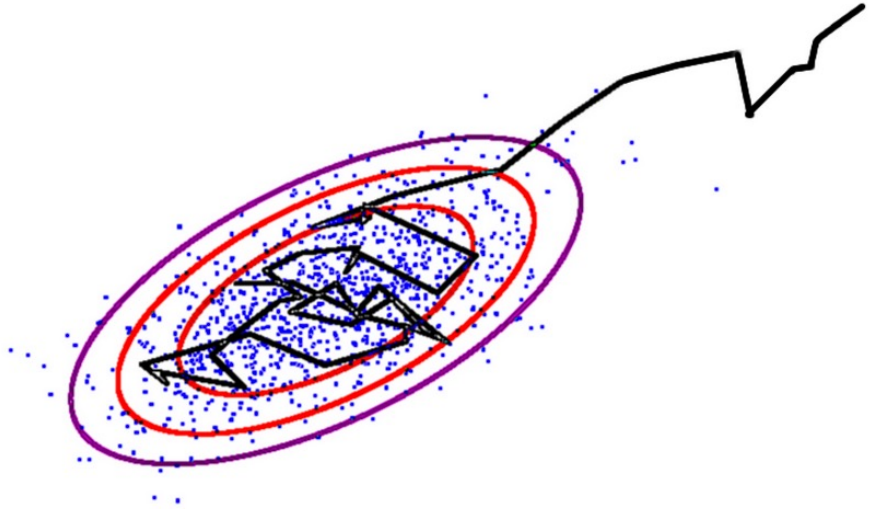


Posterior

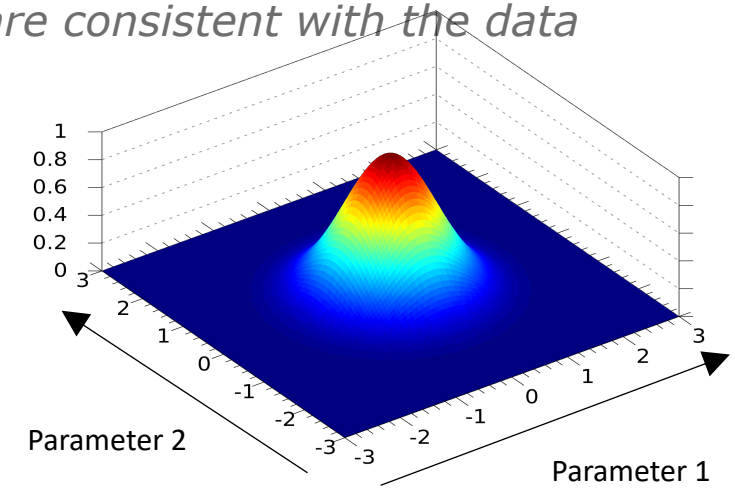


Combination is the posterior, or the probability of parameter given data ("evidence")

i.e. it's what you want statistics to be



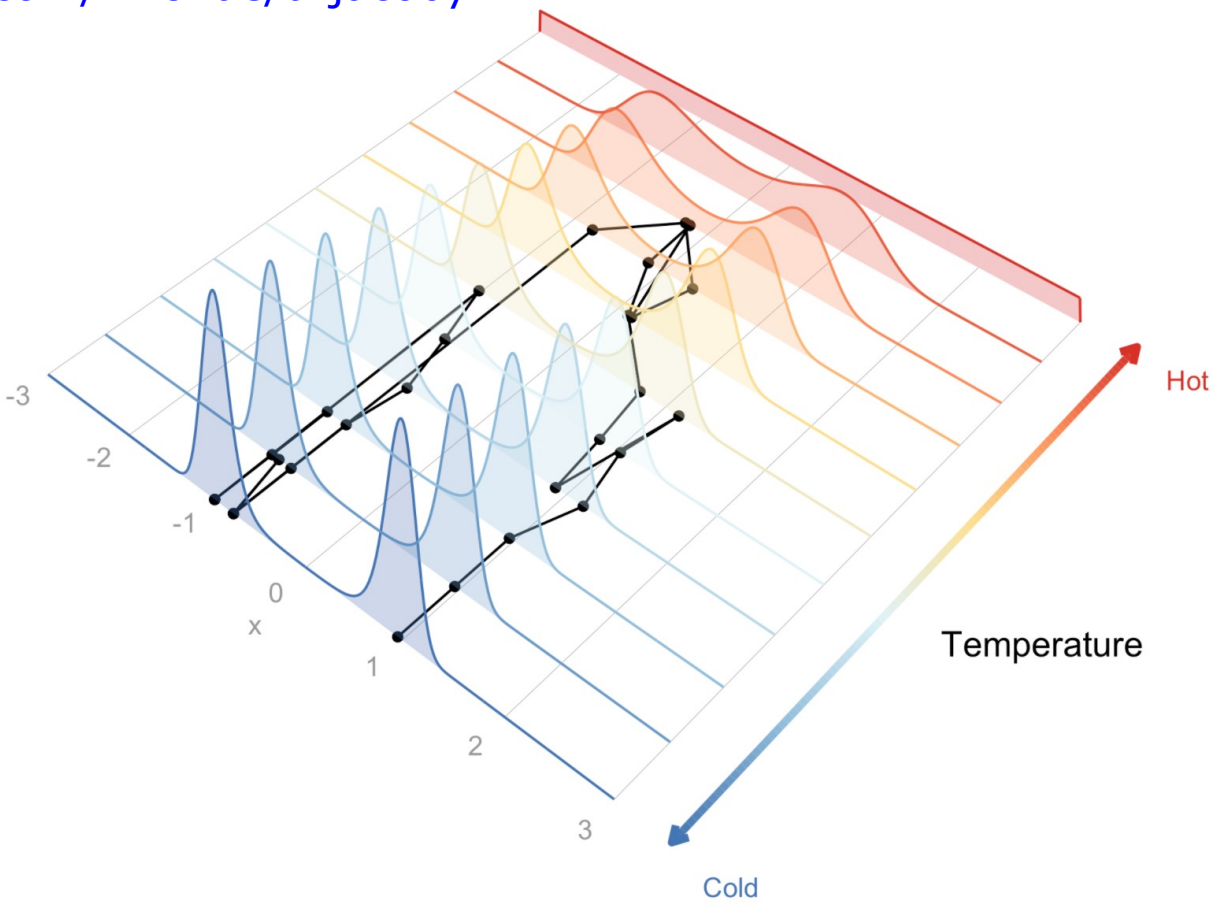
We ask the Markov Chain Monte Carlo to wander around in a specific way until it seems to find a set of parameters that are consistent with the data



Acknowledgements: DrJ

drjacoby

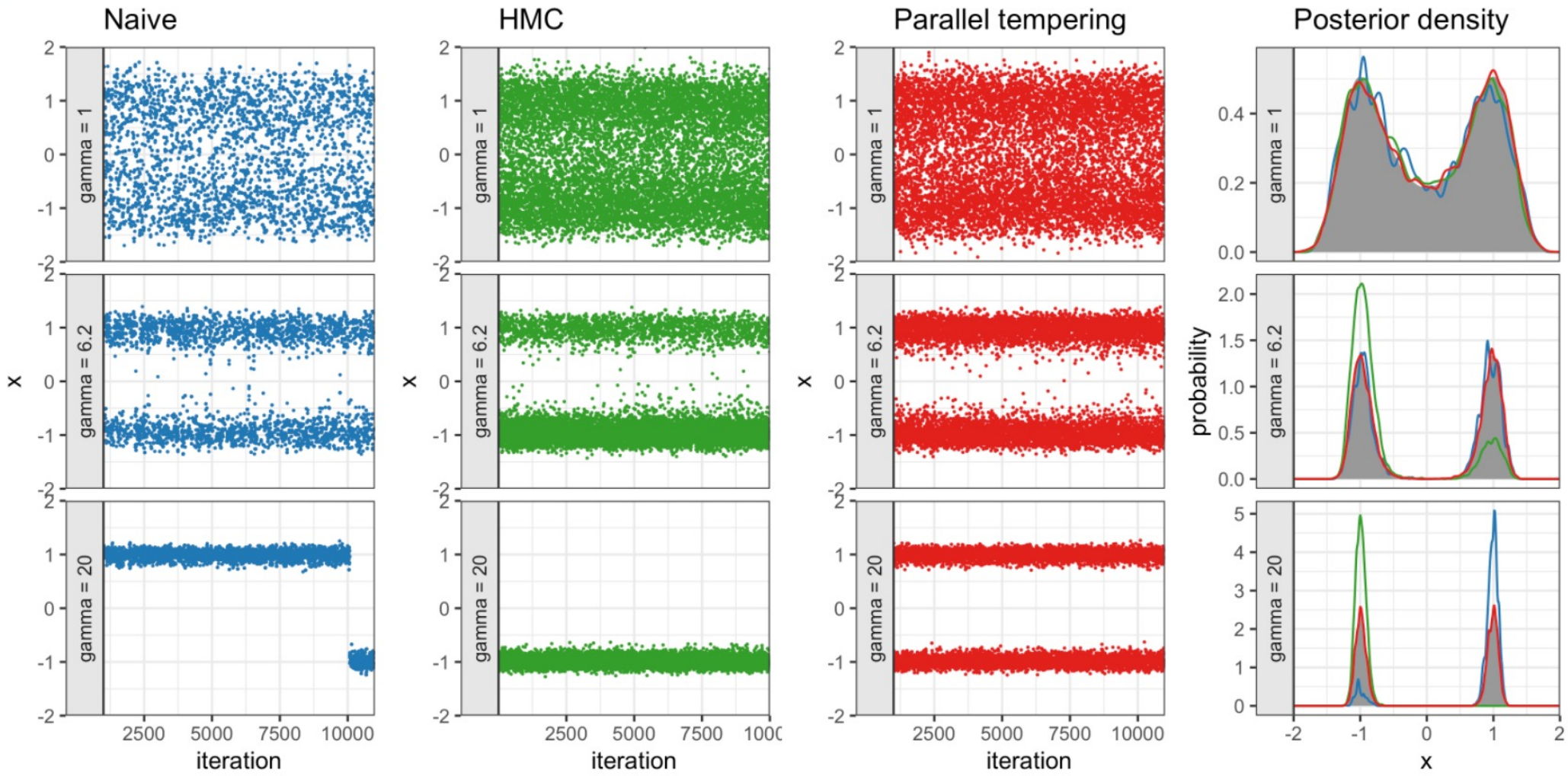
https://github.com/mrc-ide/drjacoby



Bob Verity

Pete Winskill

MCMCMC: Cheaper Lunch



<u>Takeaway</u>: Better algorithms → better sampling → better exploration of parameter space (thereby allowing us to have fewer assumptions at start)

Study Inclusion/Exclusion

Supplementary Table 1 - Inclusion and Exclusion Criteria for Seroprevalence Studies: We assumed that dexamethasone treatment was considered routine clinical practice approximately one-month after the RECOVERY trial results were released (*; PMID: 32678530). Studies conducted after the introduction of dexamethasone were excluded, as we assumed that this change in clinical practice caused shifts in the IFR that were not comparable to pre-treatment periods.

Inclusion Criteria	Exclusion Criteria
• Serosurvey in a defined geographic area representing a national or subnational geographic unit for which data on COVID deaths in all age groups are also available up to the date of the serosurvey. • Sampling framework is defined. • Sample sizes available for serosurvey, or uncertainty in the seroprevalence is explicitly quantified. • Sero-assay sensitivity and specificity estimates available. • At least 100 COVID-19 deaths observed in the study area by the serosurvey midpoint. • First date of the serosurvey is before the introduction and widespread use of dexamethasone treatment (August 17, 2020)*	• Study participants selected based on being healthcare workers, having symptoms of COVID, referring themselves for a test or self-selection into the study (for example, choosing to go for an antibody test in a clinic or responding to an advert). • Studies of outbreaks within a confined setting that does not include a representative sample of the general population (e.g. a school, a military ship). • Studies exclusively or primarily in a narrow age group (e.g. school survey). • Surveys of patients in clinical settings (assumed higher contact with health systems and healthcare workers).

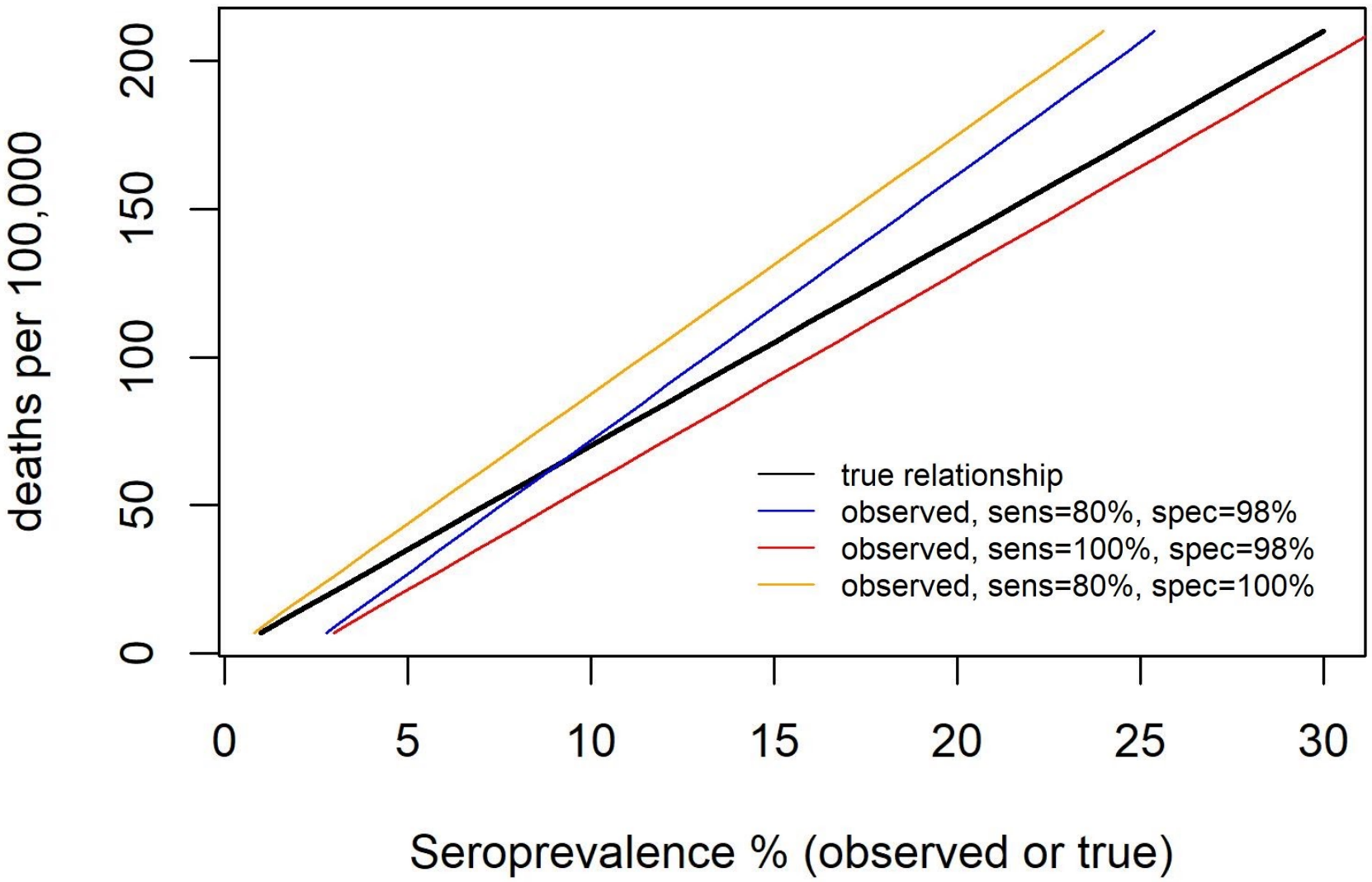
Vaccines and Flu vs. COVID

- Assuming random distribution → no immediate effect
- Does vaccine block infxn or severe dz
  - Muddy the waters → who knows bc serology doesn't work
  - Major modifier

- IFR in non-vaccinated population vs. population
- Covid not less dangerous → just mitigated infxns/control
  - Not dying because of control measures → not necessarily covid less bad
  - Waning of VE
- IFR is one part of the puzzle
- R0 between flu and COVID huge (1.3 vs 2.5)
- Optimism – but even if IFR has halved and we just lifted everything, we are still not even 50% of deaths → good place bc of action not in spite of

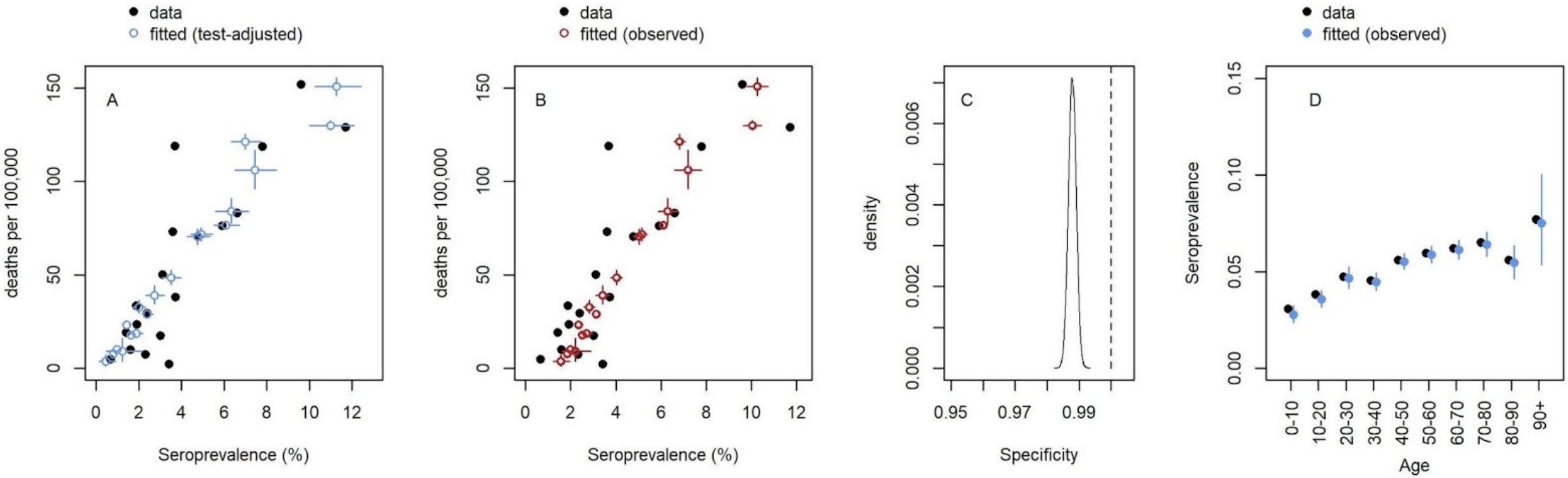
Re-estimating Specificity from Regional Data

Re-estimating Specificity



- Regional surveys allow for “true” estimation of specificity in the general population
- At zero deaths (assume zero infections), FPR

Re-estimating Specificity



Propagating Uncertainty

Propagating Uncertainty

- Know test characteristics but not true Sens/Spec
  - Know serovalidation numbers
- No idea what the true IFR is
- Know the infection curve should look similar to the death curve but no idea exactly how that relates (i.e. onset to outcome distribution changes)

Why Bother?

↓

Bayesian analysis of tests with unknown specificity and sensitivity*

Andrew Gelman† and Bob Carpenter‡

8 July 2020

Santa Clara Cautionary Tale

↓

Bayesian Approach

Parameters: ”No free lunches”

Parameter	Count	Distribution
Age-Specific IFRs	Number of Age Groups	Uniform(0,1); Uniform(0, 0.4)
Knots	5	Uniform(0,1); Uniform(E-14, E)
Spline Y-Positions	5	Uniform(0,1); Uniform(0, popN)
Attack Rate Noise Scalars	Number of Age Groups	Truncated-Normal(1, 0.05) Bounds: 0.5, 1.5
Mean of Onset from Infection to Seroconversion	1	Truncated-Normal(18.3, 0.1) Bounds: 16, 21
Mean of Onset from Infection to Death	1	Truncated-Normal(19.8, 0.1) Bounds: 18, 20
Coefficient of Variation of Onset from Infection to Death	1	Beta(2550, 450)
Weibull Shape Pattern for Seroreversion	1	Truncated-Normal(3.67, 0.5) Bounds: 2, 5
Weibull Scale Pattern for Seroreversionn	1	Truncated-Normal(130.4, 0.1) Bounds: 127, 133

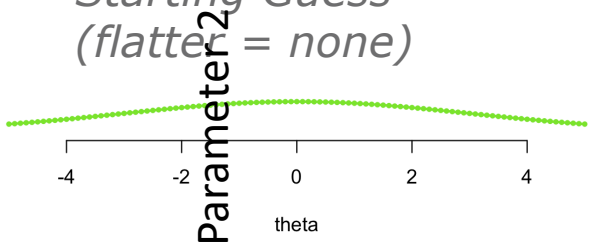
Sensitivity and Specificity based on Serovalidation Numbers
Sens: Beta(T+ (+) 0.5, D+ (-) T+ (+) 0.5)
Spec: Beta(T- (+) 0.5, D- (-) T- (+) 0.5)

- Simple Model
- Few Assumptions
  - “Uninformative” Priors
- Norelates (i.e. onset to outcome distribution changes)

MCMC (one slide)

Prior

Starting Guess
(flatter = none)



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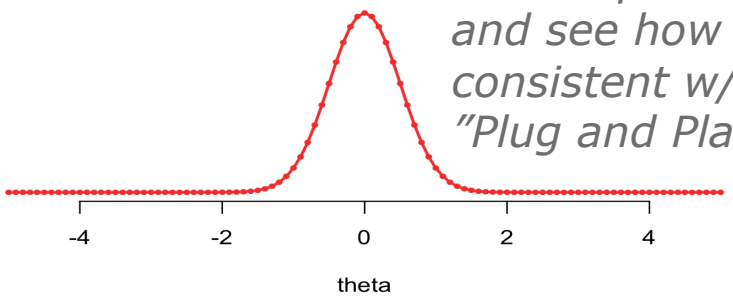

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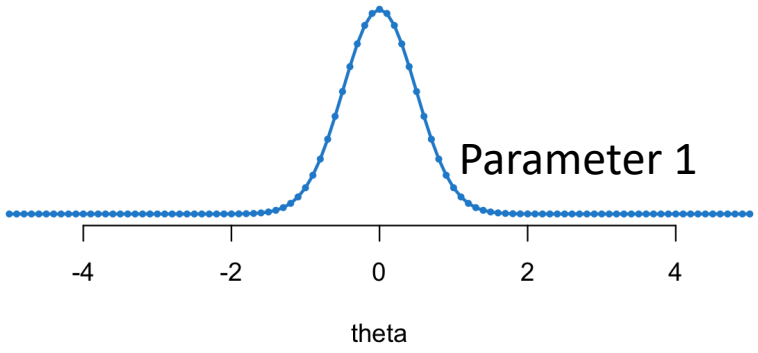

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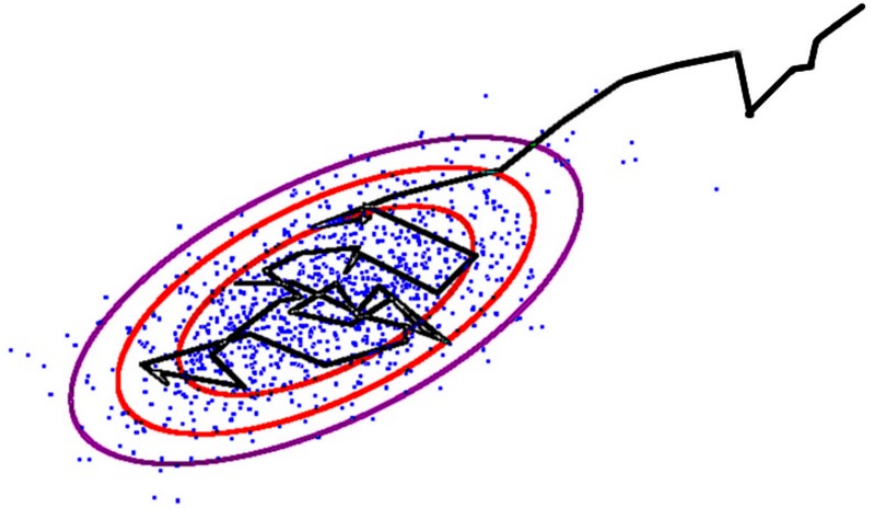

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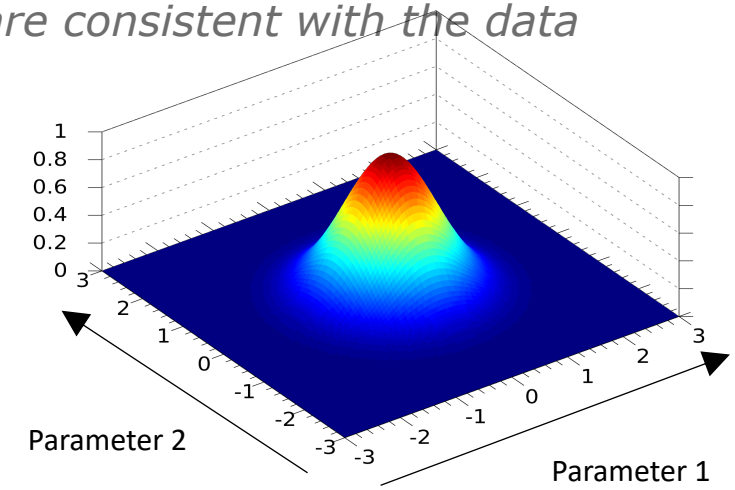
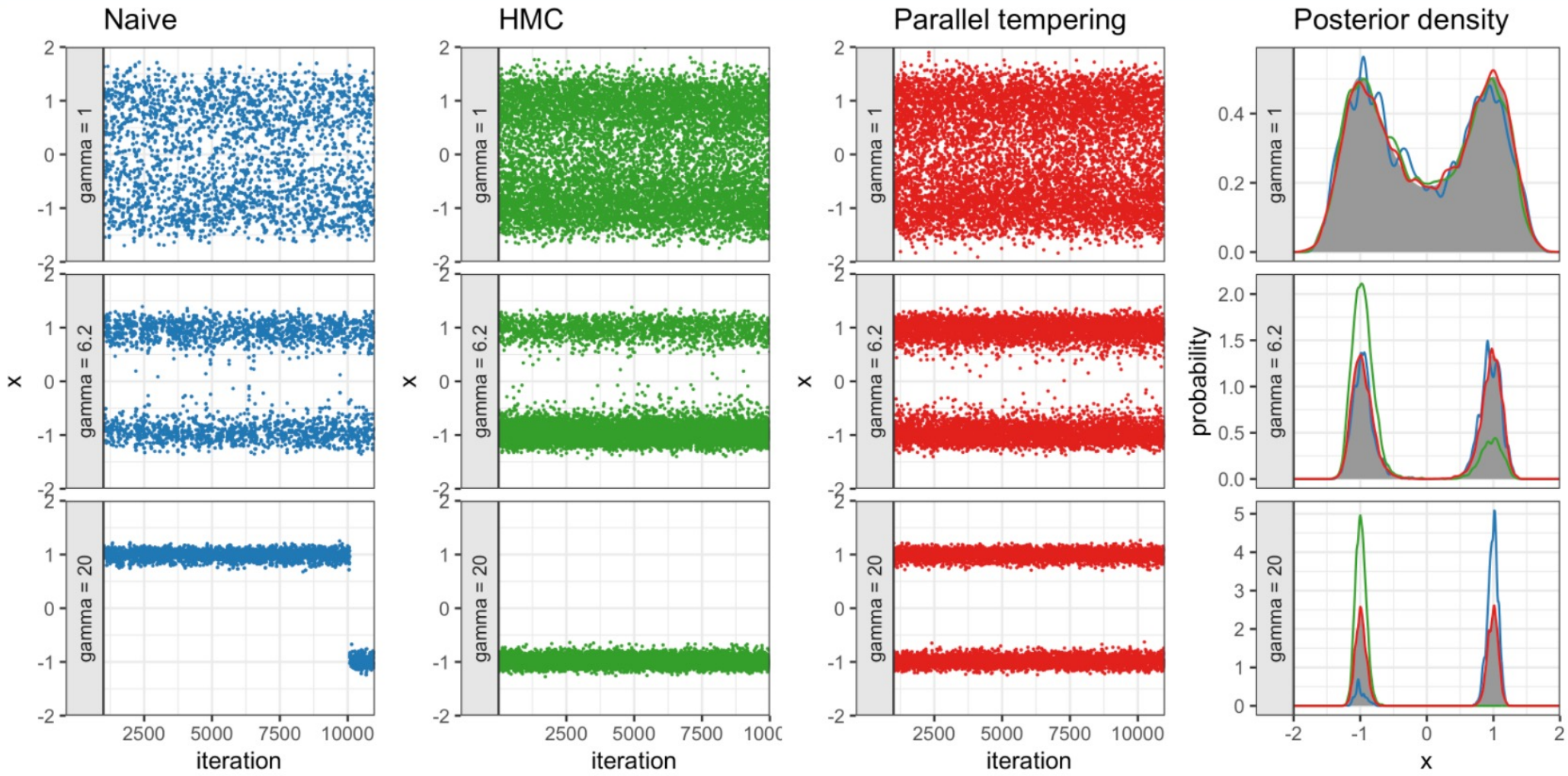


MCMCMC: Cheaper Lunch

- Simple Model
  - Many peaks of similar height (i.e. many “almost right” sets)
- Many parameters
  - Curse of dimensionality
- Inefficient sampling…Can’t brute force our way out in time.
- Who you gonna call?

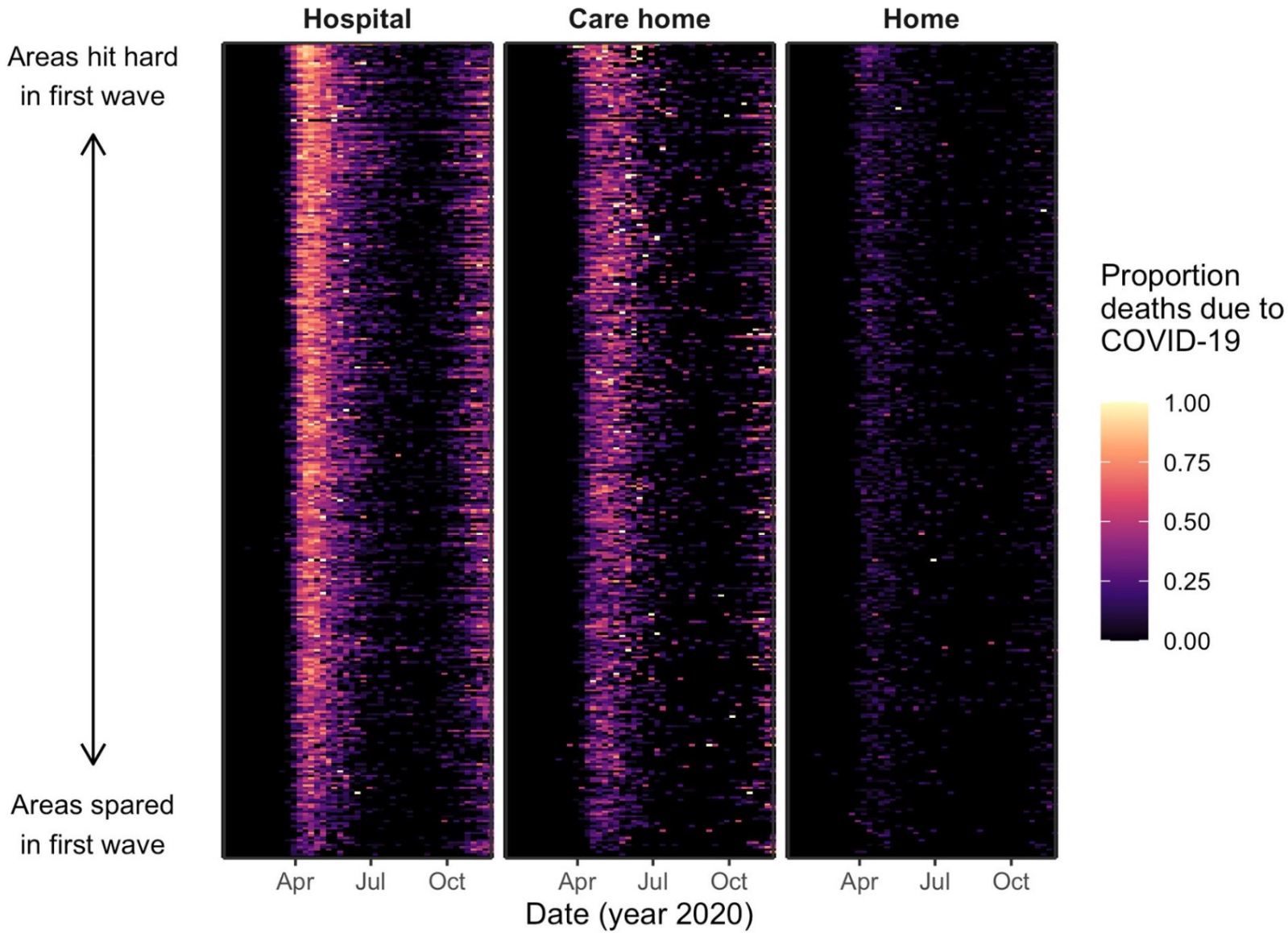
MCMCMC: Cheaper Lunch



<u>Takeaway</u>: Better algorithms → better sampling → better exploration of parameter space (thereby allowing us to have fewer assumptions at start)

First vs Second Wave Parts

Has the second wave affected the same or different parts of the UK?



Data from ONS (https://tinyurl.com/y7vefxce). England and Wales only
code available at https://github.com/bobverity/COVID_datavis

Real-Time-Modeling UK

Lilith Whittles, Marc Baguelin, Rich Fitzjohn, Edward Knock, John Lees and Bob Verity

UK RTM: Report 41