Epidemiology, modelling and COVID-19

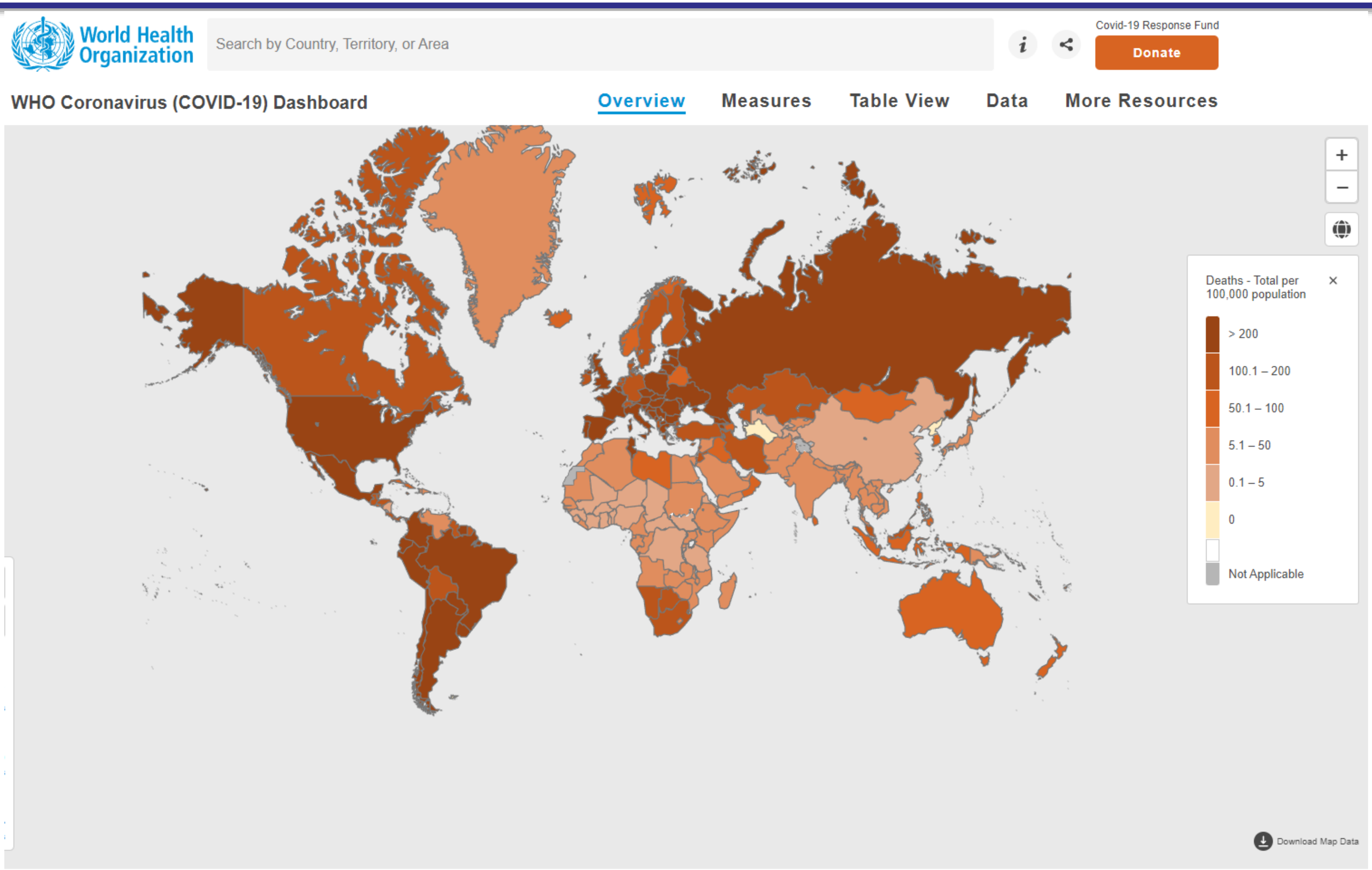
Neil Ferguson

WHO Collaborating Centre for Infectious Disease Modelling
MRC Centre for Global Infectious Disease Analysis
Jameel Institute

Imperial College London

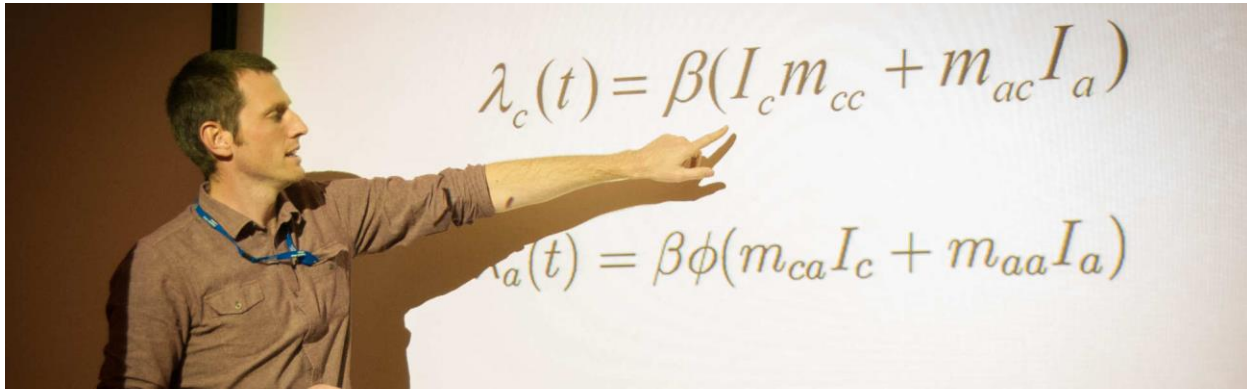
Topics

- Modelling
- Early pandemic
- Policy and science
- Vaccines & variants
- Reflections



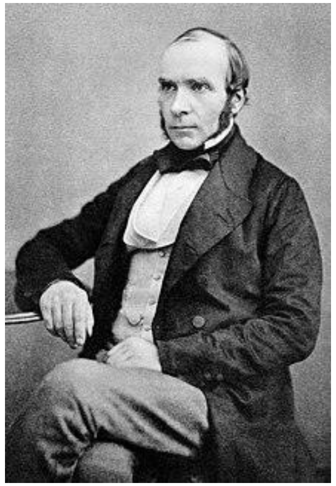
Globally, as of **6:24pm CEST, 21 October 2022**, there have been **623,893,894 confirmed cases** of COVID-19, including **6,553,936 deaths**, reported to WHO. As of **19 October 2022**, a total of **12,814,704,622 vaccine doses** have been administered.

Analysis and Modelling



Epidemiology

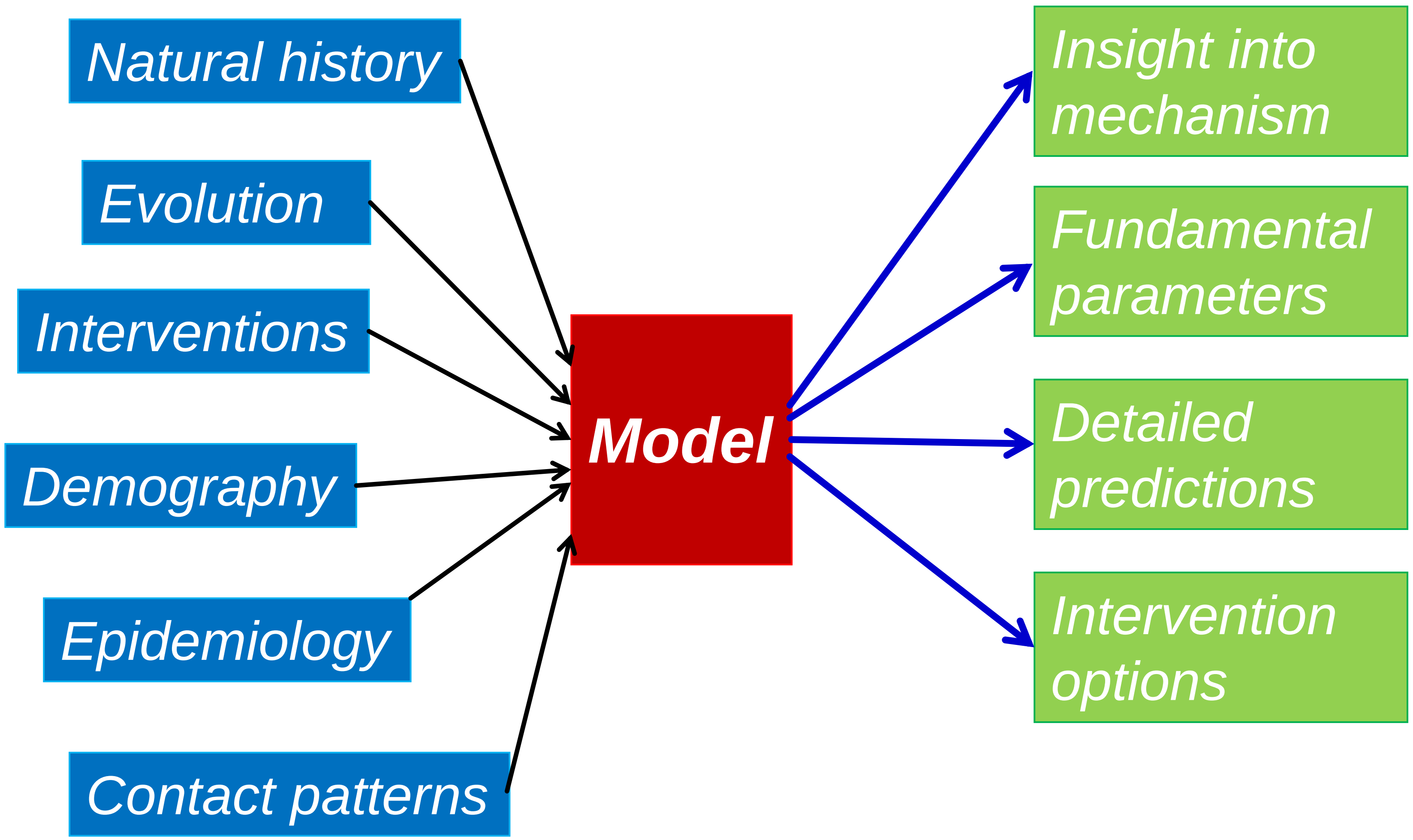
- *The study of the incidence, distribution and control of disease in a population*
- Strongly quantitative (statistical)
- Focus on rigorous data collection and analysis
- Most studies are *observational*, so need to account for biases
- Different challenges for chronic vs infectious diseases
  - Chronic diseases result from long-term exposures
  - Infectious disease spread from person to person
- Now a very broad subject, making use of many other disciplines: modern statistics, genetics, mathematical modelling, machine learning/AI,…



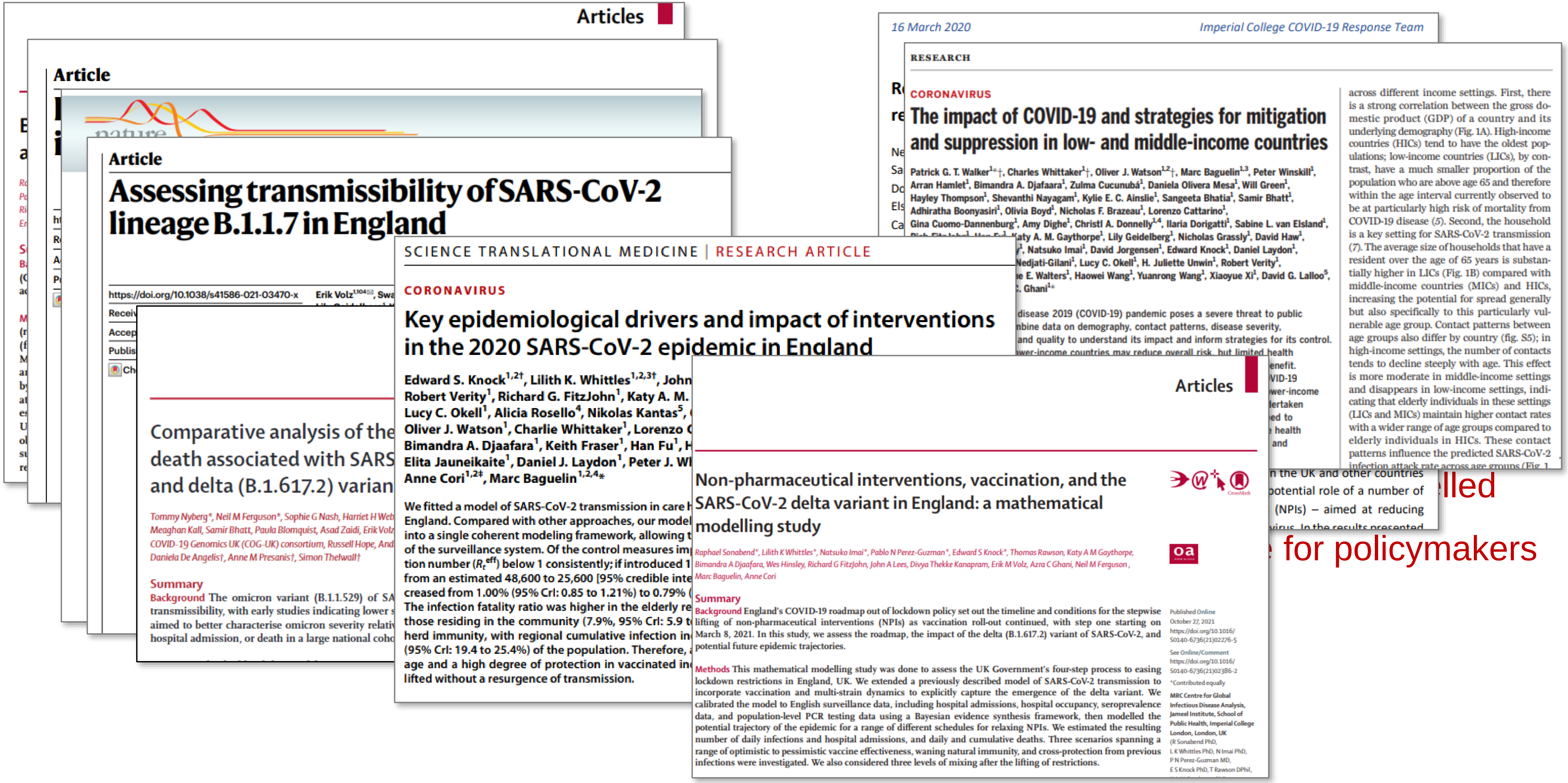
Outbreak analytics

- Analysis:
  - ➢ Incubation period, generation time
  - ➢ Severity
  - ➢ Transmissibility
  - ➢ Risk assessment
  - ➢ Assessment of interventions
- Dynamic modelling:
  - ➢ Intervention options (counterfactuals)
  - ➢ Forecasting

Knowledge synthesis

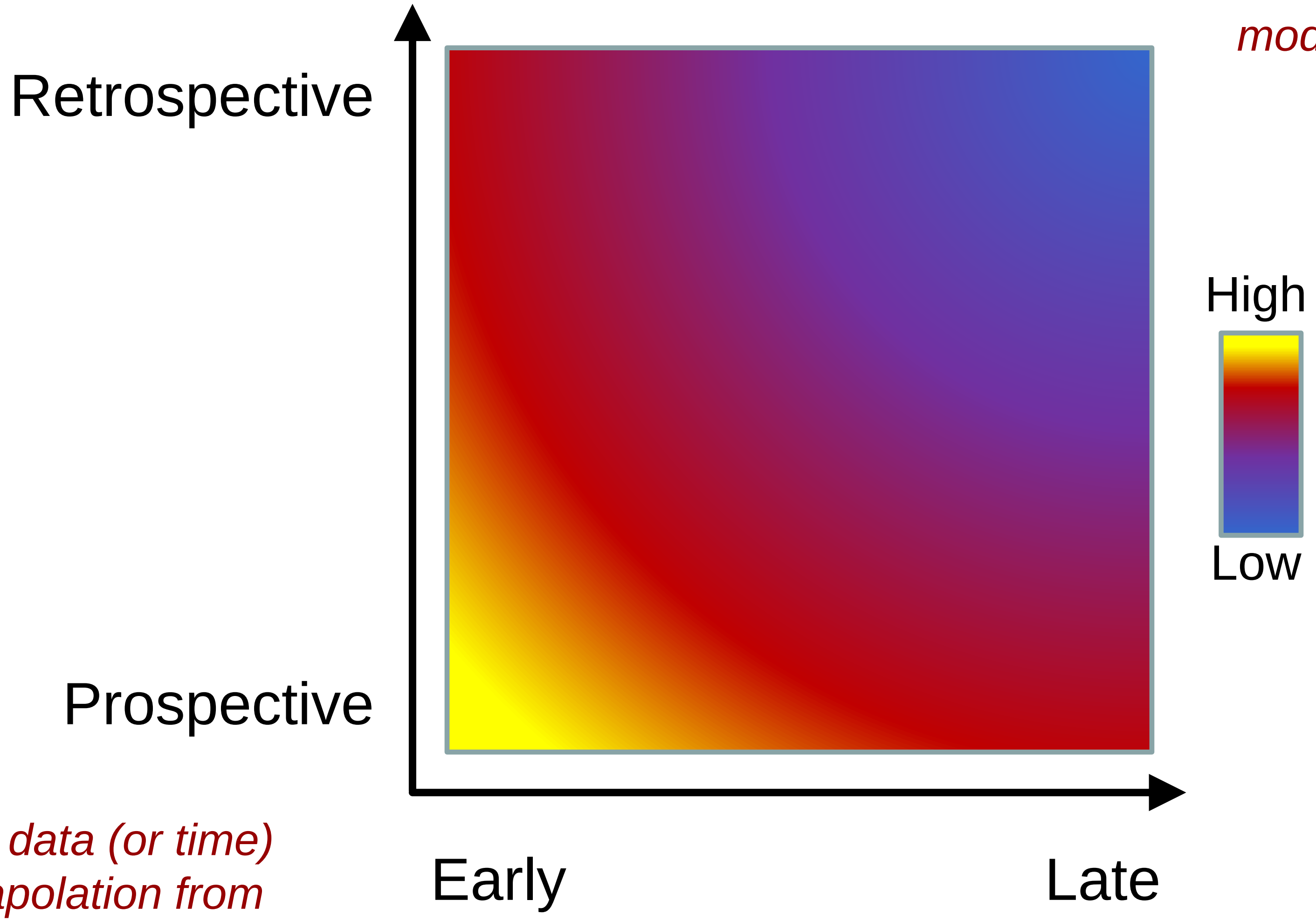


Types of modelling



Model uncertainty during a pandemic

- *Lots of data*
- *Well-established models/analytical tools*



- *Little data (or time)*
- *Extrapolation from other diseases*

Multiple models

Analytical

EpiEstim

github.com/mrc-ide/EpiEstim

epidemia

github.com/ImperialCollegeLondon/epidemia

Compartmental

SIRCOVID

github.com/mrc-ide/sircovid

squire

mrc-ide.github.io/squire/

odin

github.com/mrc-ide/odin

Individual-based

CovidSim

github.com/mrc-ide/covid-sim

safir2

github.com/mrc-ide/safir2

individual

github.com/mrc-ide/individual

Early findings which drove policy

ADAM ROGERS SCIENCE 01.31.2020 03:40 PM

Coronavirus Research Is Moving at Top Speed—With a Catch

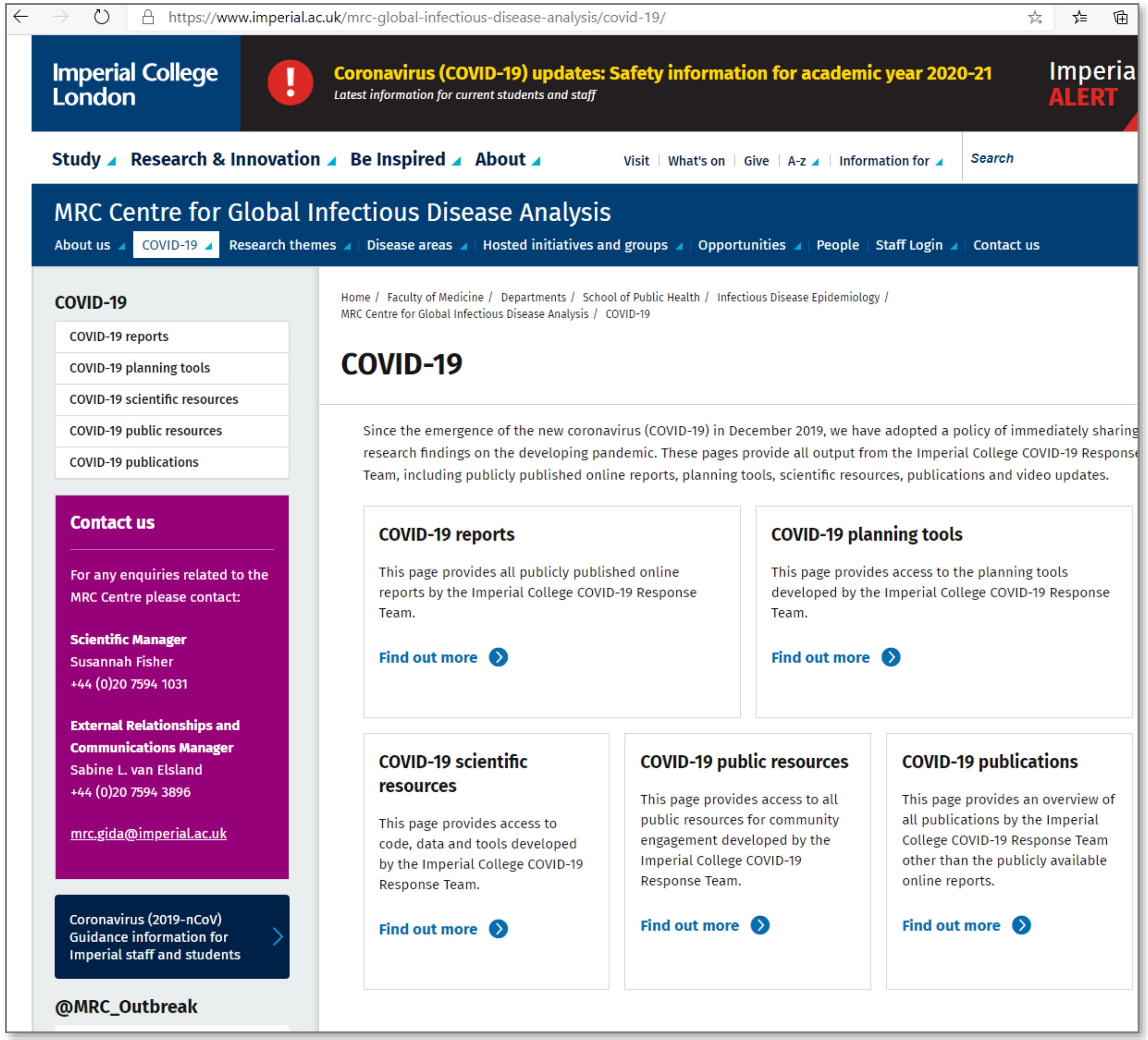
Scientists are posting their papers on the China outbreak as fast as they can write them, skipping traditional journals.

PHOTOGRAPH: REUTERS

https://www.wired.com/story/coronavirus-research-preprint-servers/

Science in a pandemic

- Limited data
- High uncertainty
- Research needs to be fast to be useful
- Multiple views better than one
- Aiming for consensus while understanding differences



Early questions

- What is the true scale of the epidemic?
- How fast is it spreading?
- How much of a threat does it pose?
- What can we do?

Size of the outbreak in Wuhan

- 16 January 2020
  - 41 cases reported in Wuhan
  - 2 deaths

- 3 international cases
  - 2 Thailand
  - 1 Japan

- 1 in 600 chance a case would have flown from Wuhan

Olivia Siong
@OliviaSiongCNA

JUST IN: China is reporting a second death in the pneumonia outbreak in Wuhan, which has since been linked to a new coronavirus

Japan and Thailand Confirm New Cases of Chinese Coronavirus

The two new patients will add to fears that the virus will spread further outside China's borders.

A seafood wholesale market in Wuhan, China, now shut down, where some people appear to have contracted the new coronavirus. Noel Celis/Agence France-Presse — Getty Images

Thailand finds second case of new Chinese virus, says no outbreak

AFP

The latest patient is from China's central city of Wuhan, which has reported 41 cases of pneumonia potentially linked to the new type of virus, with two deaths.

Published **17 JANUARY, 2020** UPDATED 17 JANUARY, 2020

Size of the outbreak in Wuhan

Results as of 17 January 2020

Report 1, shorturl.at/rsNO4

Table 1: Estimated case numbers based on the baseline assumptions and alternative scenarios explored.

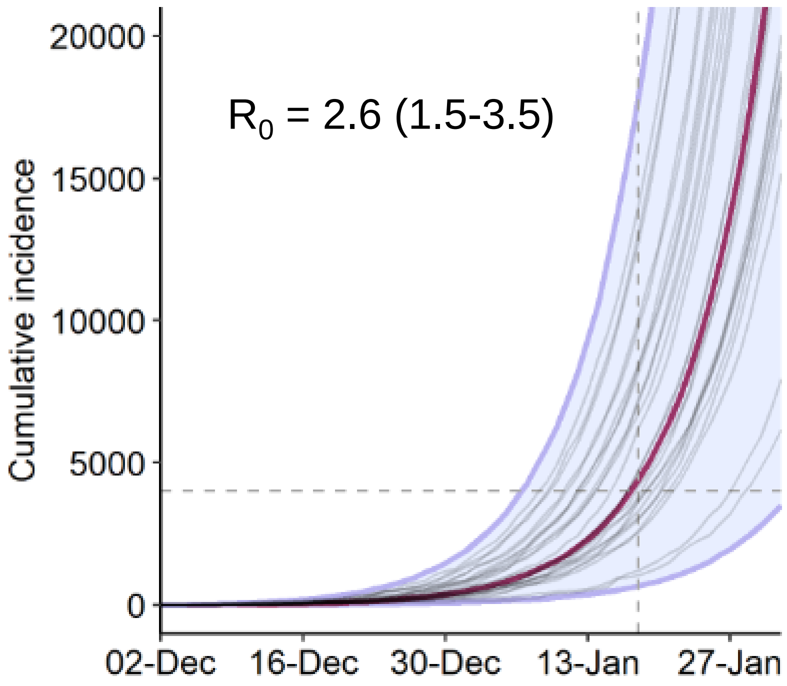
	Baseline	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Exported number of confirmed cases*	3	3	3	2	4
Daily international passengers travelling out of Wuhan International airport[1]	3,301	3,301	3,301	3,301	3,301
Effective catchment population of Wuhan airport	19 million	11 million	19 million	19 million	19 million
Detection window (days)	10 days	10 days	8 days	10 days	10 days
Estimated Total number of cases (95% CI)	1,723 (427 – 4,471)	996 (246 – 2,586)	2,155 (535 – 5,590)	1149 (190 – 3,549)	2,298 (712 – 5,341)

*reported number of confirmed cases detected internationally. [1]calculated from the 3 month totals reported by [11] corrected for the travel surge during Chinese New Year (see Summary).

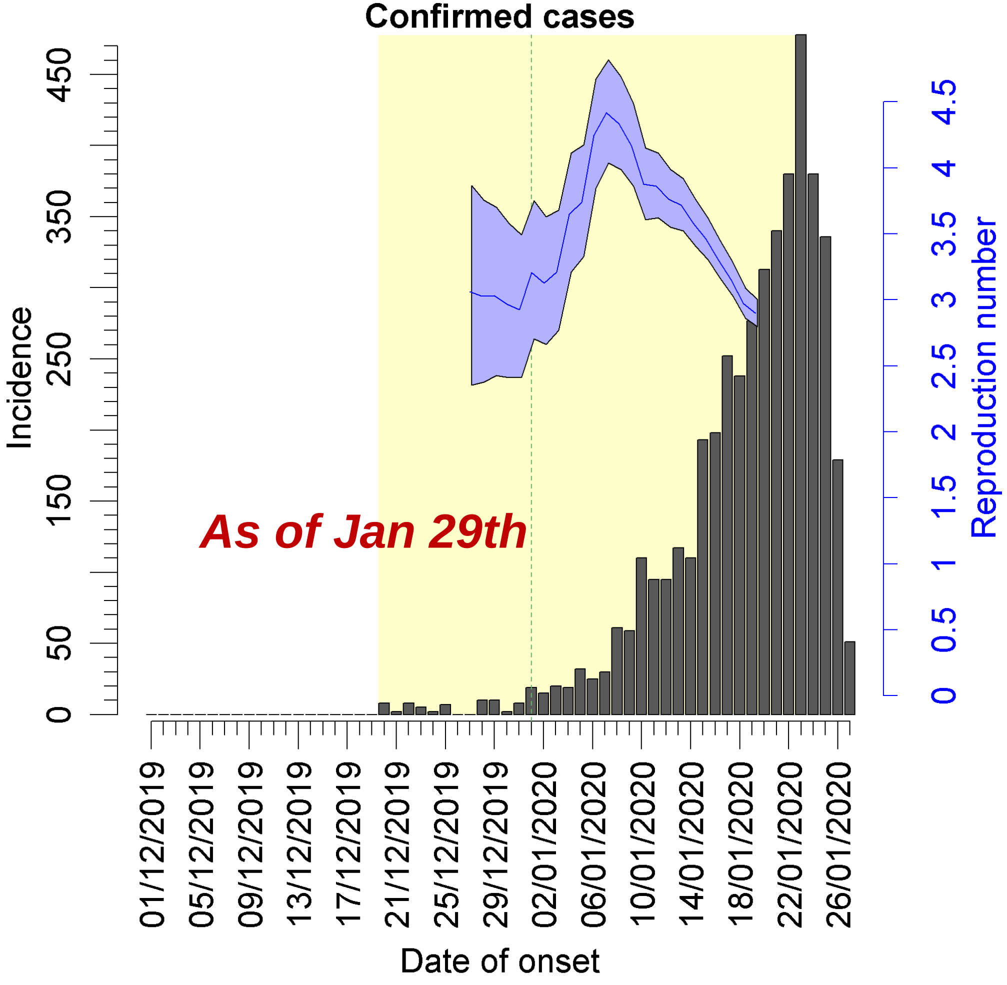
By 3 Feb, estimated 110,000 (49,000-266,000) cumulative symptomatic cases (compared with 6,400 reported cases)

Transmissibility

- 25th January estimate of from v limited data on the early Wuhan epidemic
- Later confirmed by detailed cases data from Wuhan



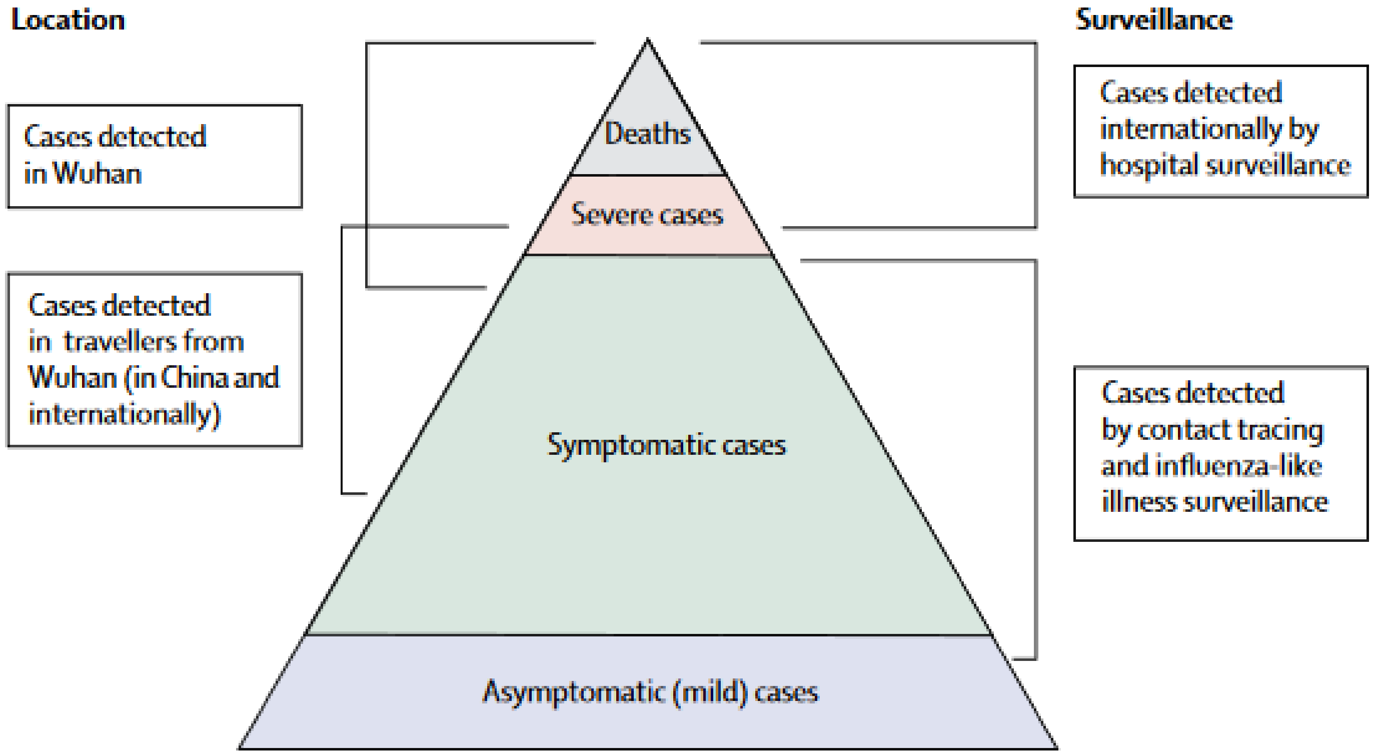
Report 3, shorturl.at/bxPQU



Severity

- IFR (Infection Fatality Ratio) = proportion who die from infection
- Difficult to estimate
  - Delays to death
  - Easier to detect severe cases
  - Hard to estimate number infected
- Early infection prevalence estimates were crucial

Spectrum of COVID-19 cases



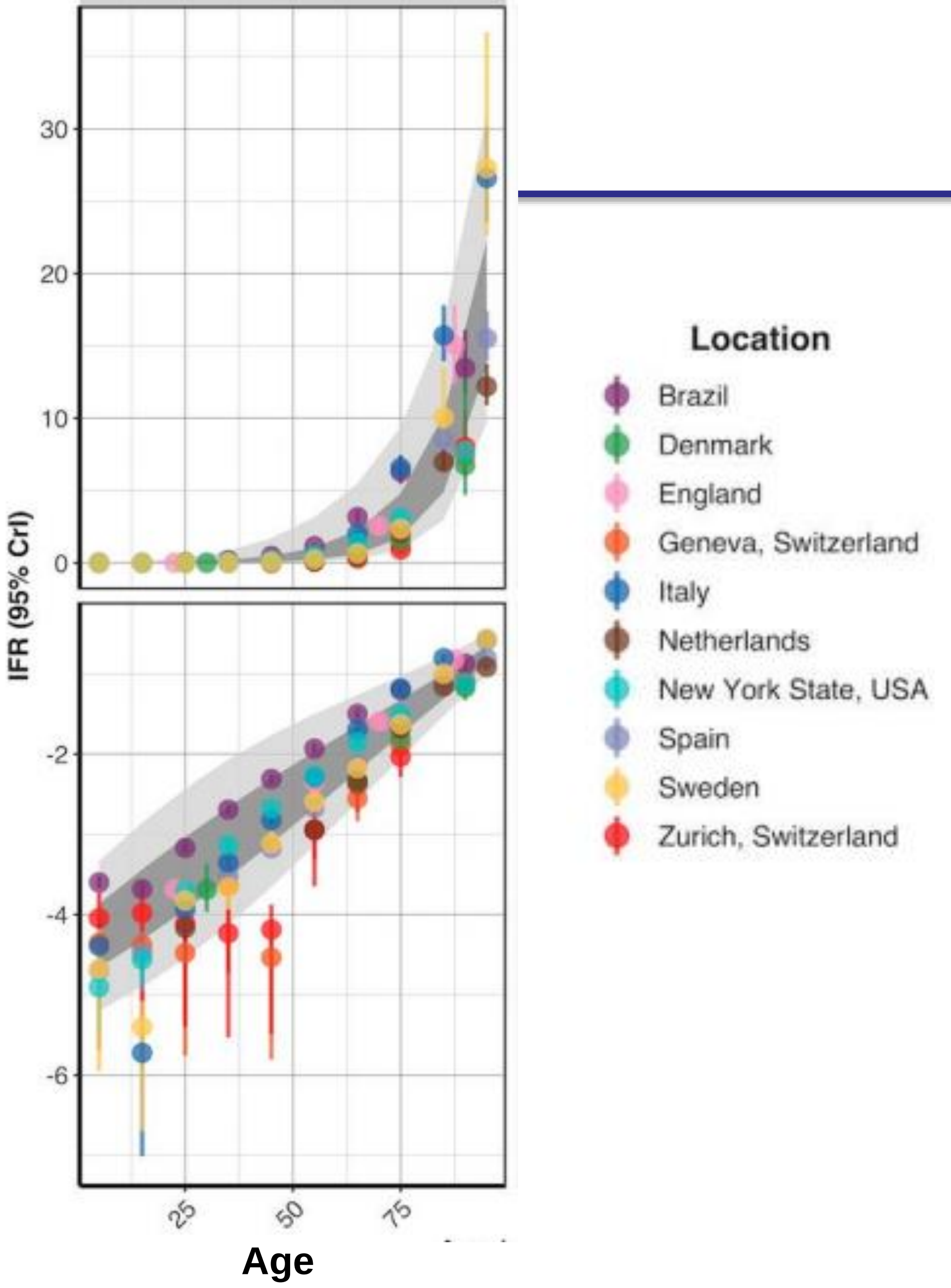
Report 4, shorturl.at/oxQ03

Severity

Early (Feb 2020) estimates for China

- 0.7% IFR = 0.9% in UK
- Exponentially increasing with age
- 3x more need hospital

Later estimate using European data – 0.8-1.2% in UK



Verity et al. 2020 (Lancet ID)

Brazeau et al. 2020 - https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-34-ifr/

Intervention modelling for COVID-19

- No drugs or vaccines initially
- Only social-distancing, case-isolation etc.
- Some data on effectiveness for flu (1918)
- Economically costly
- Key strategic question:
  - ➢ follow China and supress transmission?
  - ➢ or "mitigate" only?
- Decision driven by predicted (overwhelming) level of healthcare demand

Report 9 https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-9-impact-of-npis-on-covid-19/

Davies et al, 2020, Lancet Public Health

Walker et al, Science 2020


16 March 2020 Imperial College COVID-19 Response Team

Report 9: Impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand

Neil M Ferguson, Daniel Laydon, Gemma Nedjati-Gilani, Natsuko Imai, Kylie Ainslie, Marc Baguelin, Sangeeta Bhatia, Adhiratha Boonyasiri, Zulma Cucunubá, Gina Cuomo-Dannenburg, Amy Dighe, Ilaria Dorigatti, Han Fu, ...

Articles

Effects of non-pharmaceutical interventions on COVID-19 cases, deaths, and demand for hospital services in the UK: a modelling study

Nicholas G Davies, Adam J Kucharski*, Rosalind M Eggo*, Amy Gimma, W John Edmunds, on behalf of the Centre for the Mathematical Modelling of Infectious Diseases COVID-19 working group†

Lancet Public Health 2020
Published Online June 2, 2020
https://doi.org/10.1016/S2468-2667(20)30133-X

RESEARCH

CORONAVIRUS

The impact of COVID-19 and strategies for mitigation and suppression in low- and middle-income countries

Patrick G. T. Walker[1]*†, Charles Whittaker[1]†, Oliver J. Watson[1,2]†, Marc Baguelin[1,3], Peter Winskill[1], Arran Hamlet[1], Bimandra A. Djafaara[1], Zulma Cucunubá[1], Daniela Olivera Mesa[1], Will Green[1], Hayley Thompson[1], Shevanthi Nayagam[1], Kylie E. C. Ainslie[1], Sangeeta Bhatia[1], Samir Bhatt[1], Adhiratha Boonyasiri[1], Olivia Boyd[1], Nicholas F. Brazeau[1], Lorenzo Cattarino[1], Gina Cuomo-Dannenburg[1], Amy Dighe[1], Christl A. Donnelly[1,4], Ilaria Dorigatti[1], Sabine L. van Elsland[1], Rich FitzJohn[1], Han Fu[1], Katy A. M. Gaythorpe[1], Lily Geidelberg[1], Nicholas Grassly[1], David Haw[1], Sarah Hayes[1], Wes Hinsley[1], Natsuko Imai[1], David Jorgensen[1], Edward Knock[1], Daniel Laydon[1], Swapnil Mishra[1], Gemma Nedjati-Gilani[1], Lucy C. Okell[1], H. Juliette Unwin[1], Robert Verity[1], Michaela Vollmer[1], Caroline E. Walters[1], Haowei Wang[1], Yuanrong Wang[1], Xiaoyue Xi[1], David G. Lalloo[5], Neil M. Ferguson[1]*, Azra C. Ghani[1]*

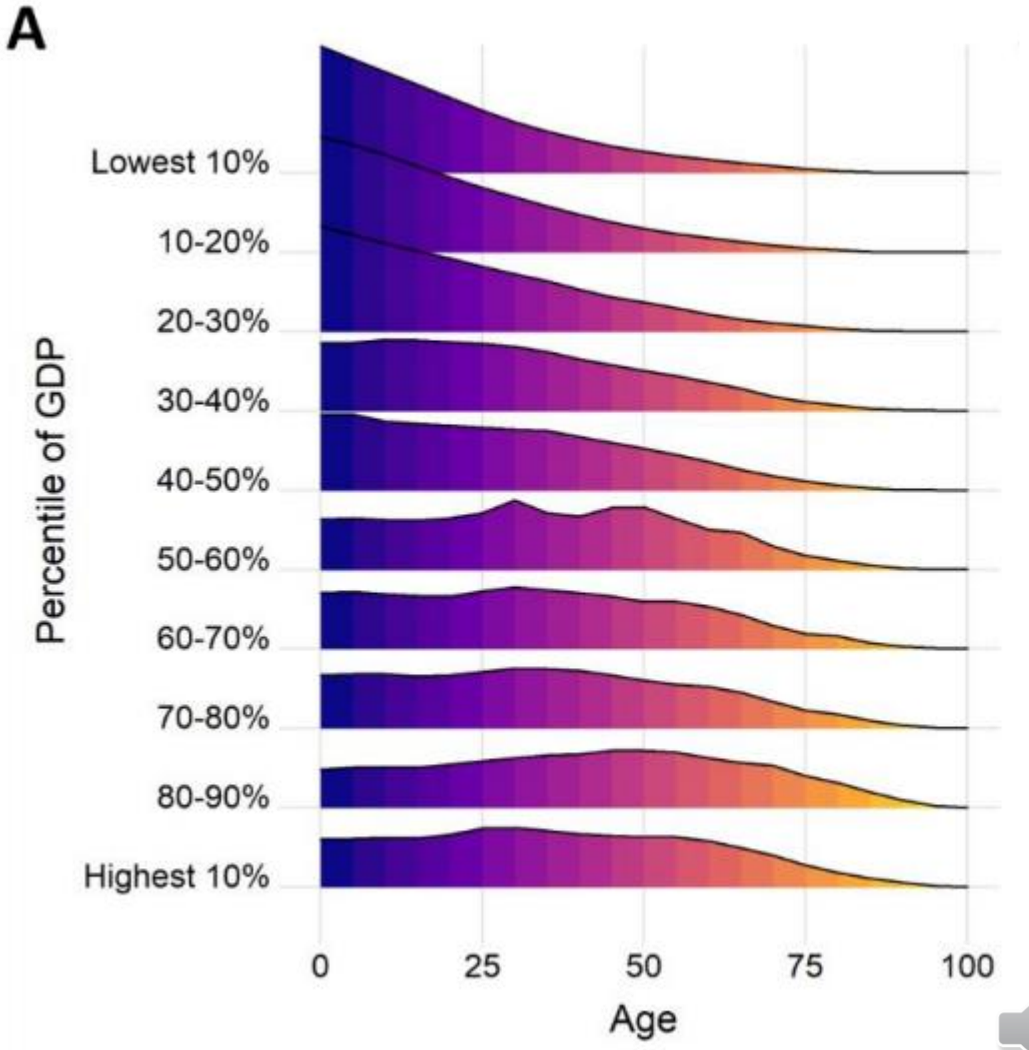
The ongoing coronavirus disease 2019 (COVID-19) pandemic poses a severe threat to public health worldwide. We combine data on demography, contact patterns, disease severity, and health care capacity and quality to understand its impact and inform strategies for its control. Younger populations in lower-income countries may reduce overall risk, but limited health system capacity coupled with closer intergenerational contact largely negates this benefit. Mitigation strategies that slow but do not interrupt transmission will still lead to COVID-19 epidemics rapidly overwhelming health systems, with substantial excess deaths in lower-income countries resulting from the poorer health care available. Of countries that have undertaken suppression to date, lower-income countries have acted earlier. However, this will need to be maintained or triggered more frequently in these settings to keep below available health capacity, with associated detrimental consequences for the wider health, well-being, and economies of these countries.

across different income settings. First, there is a strong correlation between the gross domestic product (GDP) of a country and its underlying demography (Fig. 1A). High-income countries (HICs) tend to have the oldest populations; low-income countries (LICs), by contrast, have a much smaller proportion of the population who are above age 65 and therefore within the age interval currently observed to be at particularly high risk of mortality from COVID-19 disease (5). Second, the household is a key setting for SARS-CoV-2 transmission (7). The average size of households that have a resident over the age of 65 years is substantially higher in LICs (Fig. 1B) compared with middle-income countries (MICs) and HICs, increasing the potential for spread generally but also specifically to this particularly vulnerable age group. Contact patterns between age groups also differ by country (fig. S5); in high-income settings, the number of contacts tends to decline steeply with age. This effect is more moderate in middle-income settings and disappears in low-income settings, indicating that elderly individuals in these settings (LICs and MICs) maintain higher contact rates with a wider range of age groups compared to elderly individuals in HICs. These contact patterns influence the predicted SARS-CoV-2 infection attack rate across age groups (Fig. 1

DOI: https://doi.org/10.25561/77482 Page 1 of 20

Early global projections

- In March 2020, projected pandemic could cause 40m deaths and 7bn infections globally, in the extreme counterfactual of no interventions
- And that this could be halved to 20m deaths by adopting “mitigation” measures (short of suppression)
- Suppression measures could reduce this further, but would need to be sustained until vaccination could be rolled out
- Highlighted the importance of demography – low income countries have younger populations, would experience much lower total per capita mortality

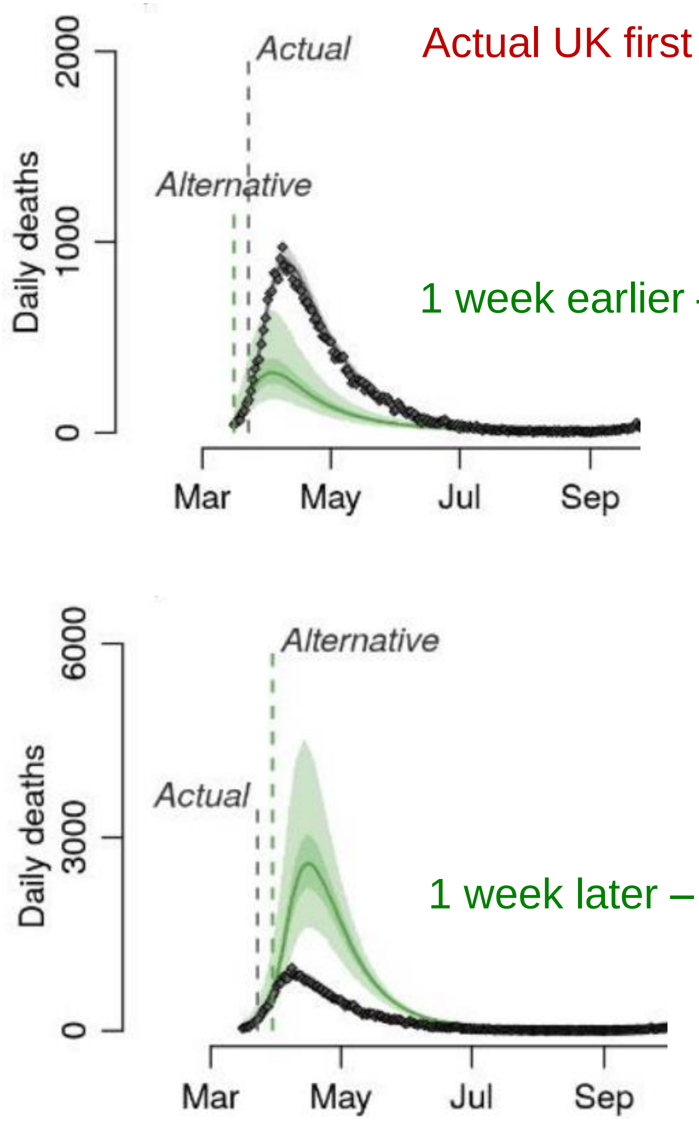


Walker et al, Report 12, https://doi.org/10.25561/77735

Walker et al, Science 2020

Timing of suppression

- Acting early always beneficial
- If infections are doubling every 4 days, then:
  - A 4-day delay in implementing controls can lead to a 2x more cases
  - An 8-day delay to 4x more cases
  - …



Actual UK first wave deaths = 37k

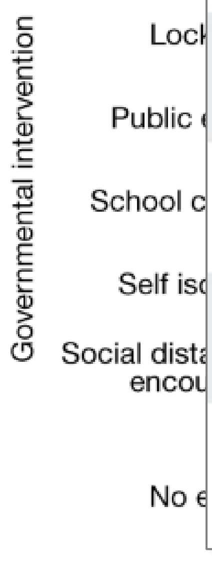
1 week earlier – 15k deaths

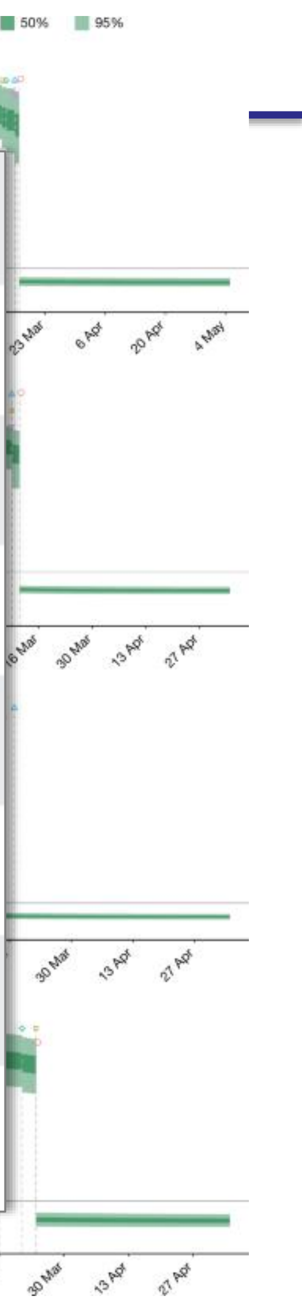
1 week later – 100k deaths

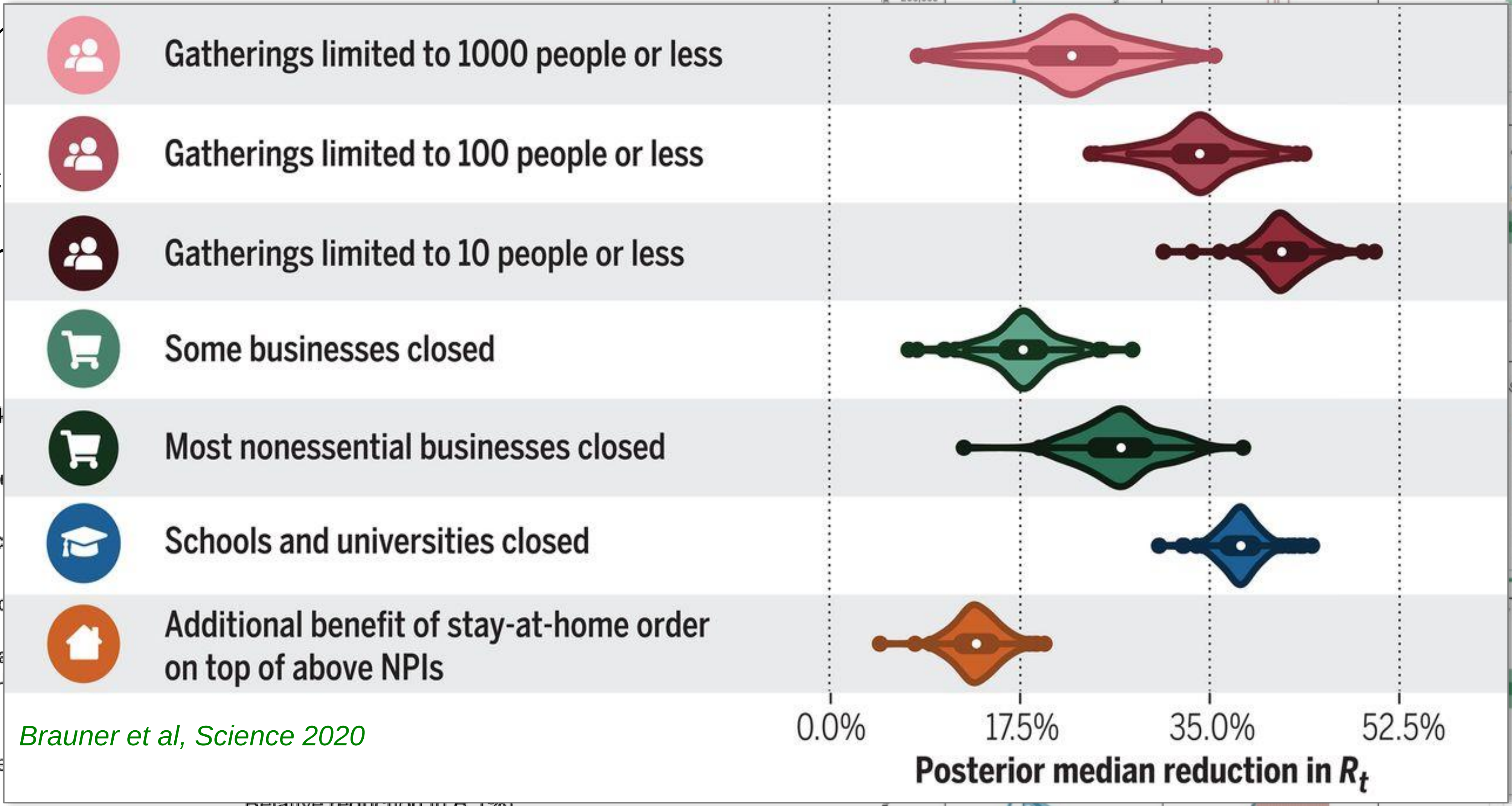
Knock et al. Science Translational Medicine, 2021

Inferring impact of NPIs

- Sign
  pan
- Foc
- Mar





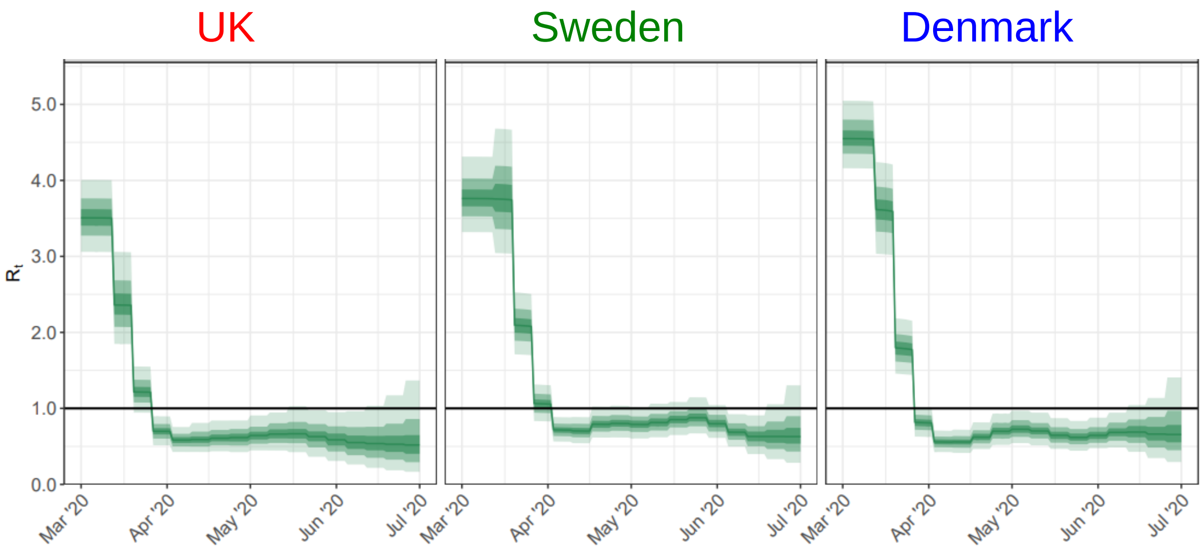


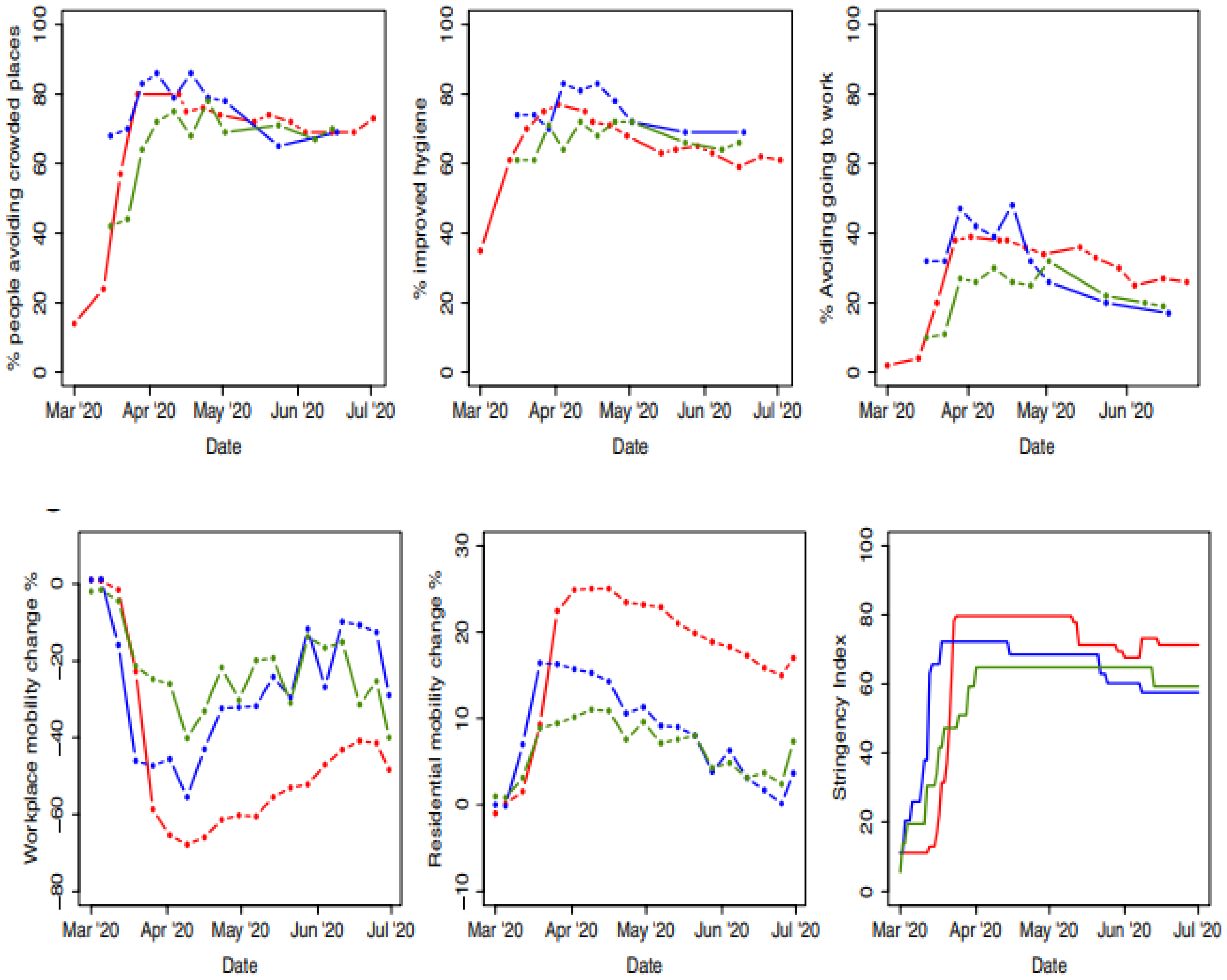
Brauner et al, Science 2020

Flaxman et al, Nature 2020

NPIs and behaviour

- High correlations between self-reported behaviour, mobility data, intervention stringency and impact on transmission
- But significant country differences in the precise relationships





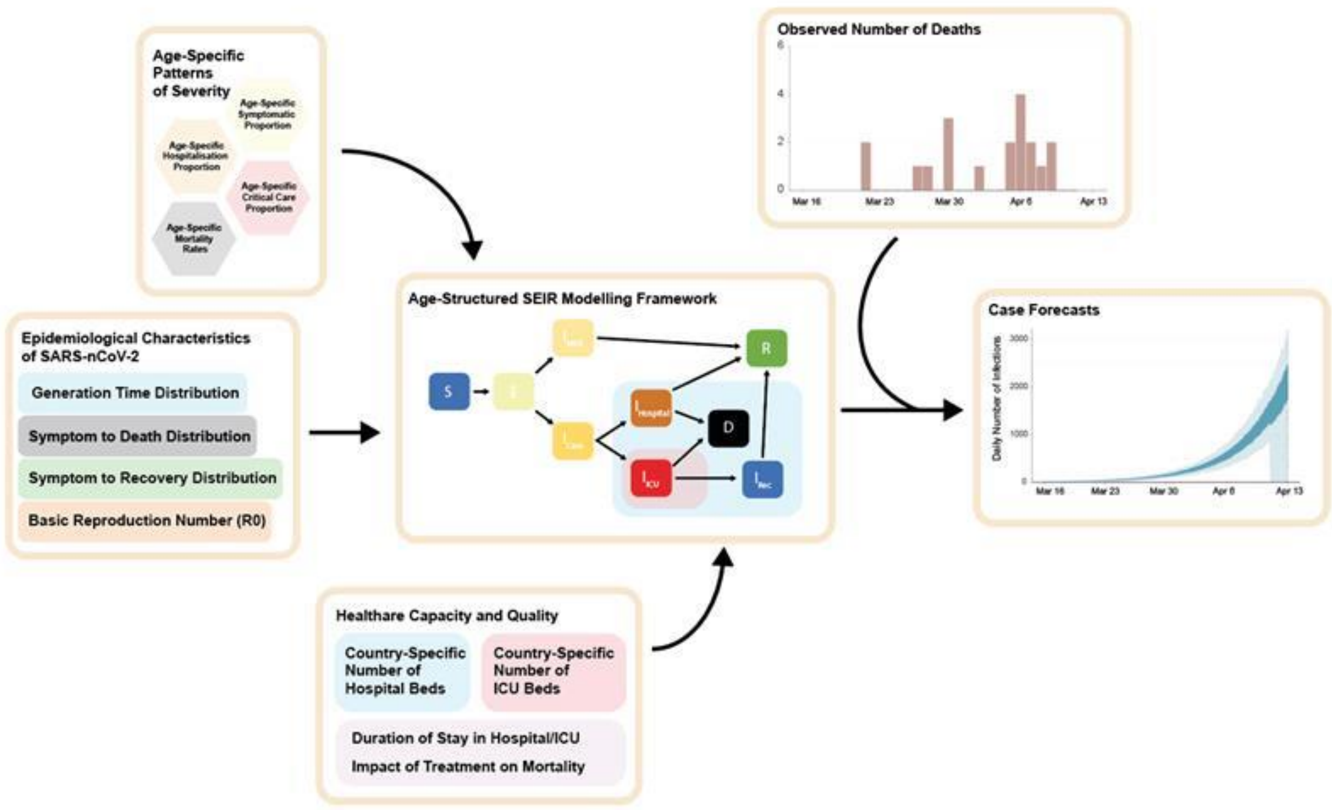
Mishra et al, Scientific reports 2021

Non-UK work

MRC Centre for Global Infectious Disease Analysis

Imperial College London

- *Squire*: estimate transmission (R) and make short-term forecasts using mortality data
- Information to support resource planning: https://mrc-ide.github.io/global-lmic-reports/
- In-depth work with 11+ countries through existing research or public health partnerships:
    - ➢ Brazil, Colombia, Panama, Malawi, Zimbabwe, Senegal, Nigeria, Sierra Leone, India, Indonesia, Italy, US,…
- Scenario Analysis Tool for user-generated simulations: https://www.covidsim.org/



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

Some of our work with Brazilian colleagues

ARTICLES
https://doi.org/10.1038/s41562-020-0928-4
nature human behaviour
Check for updates

Epidemiological and clinical characteristics of the COVID-19 epidemic in Brazil

William Marciel de Souza[1,29], Lewis Fletcher Buss[2,29], Darlan da Silva Candido[2,3,29], Jean-Paul Carrera[3,4,29], Sabrina Li[5,29], Alexander E. Zarebski[3], Rafael Henrique Moraes Pereira[6], Carlos A. Prete Jr[7], Andreza Aruska de Souza-Santos[8], Kris V. Parag[9], Maria Carolina T. D. Belotti[7], Maria F. Vincenti-Gonzalez[10], Janey Messina[5,11], Flavia Cristina da Silva Sales[2], Pamela dos Santos Andrade[2], Vítor Heloiz Nascimento[7], Fabio Ghilardi[2], Leandro Abade[3], Bernardo Gutierrez[3,12], Moritz U. G. Kraemer[3,13,14], Carlos K. V. Braga[6], Renato Santana Aguiar[15], Neal Alexander[16], Philippe Mayaud[17], Oliver J. Brady[15,18], Izabel Marcilio[19], Nelson Gouveia[20], Guangdi Li[21], Adriana Tami[10], Silvano Barbosa de Oliv… Walquiria Aparecida Fe… Eduardo Marques Maca… Oliver G. Pybus[3], Chie… Nuno Rodrigues Faria…

The first case of COVID-19 w… graphic and clinical findings f… cases, including 29,314 deat… regions of Brazil. The R_0 valu… but overlapping credible inte… higher per-capita income an… with unknown aetiology were… but at very low levels. These f… help to guide subsequent me…

RESEARCH
CORONAVIRUS

Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil

Nuno R. Faria[1,2,3,4]*†, Thomas A. Mellan[1,2]†, Charles Whittaker[1,2]†, Ingra M. Claro[3,5]†, Darlan da S. Candido[3,4]†, Swapnil Mishra[1,2]†, Myuki A. E. Crispim[6,7], Flavia C. S. Sales[3,5], Iwona Hawryluk[1,2], John T. McCrone[8], Ruben J. G. Hulswit[9], Lucas A. M. Franco[3,5], Mariana S. Ramundo[3,5], Jaqueline G. de Jesus[3,5], Pamela S. Andrade[10], Thais M. Coletti[3,5], Giulia M. Ferreira[11], Camila A. M. Silva[3,5], Erika R. Manuli[3,5], Rafael H. M. Pereira[12], Pedro S. Peixoto[13], Moritz U. G. Kraemer[4], Nelson Gaburo Jr.[14], Cecilia da C. Camilo[14], Henrique Hoeltgebaum[15], William M. Souza[16], Esmenia C. Rocha[3,5], Leandro M. de Souza[3,5], Mariana C. de Pinho[3,5], Leonardo J. T. Araujo[17], Frederico S. V. Malta[18], Aline B. de Lima[18], Joice do P. Silva[18], Danielle A. G. Zauli[18], Alessandro C. de S. Ferreira[18], Ricardo P. Schnekenberg[19], Daniel J. Laydon[1,2], Patrick G. T. Walker[1,2], Hannah M. Schlüter[15], Ana L. P. dos Santos[20], Maria S. Vidal[20], Valentina S. Del Caro[20], Rosinaldo M. F. Filho[20], Helem M. dos Santos[20], Renato S. Aguiar[21], José L. Proença-Modena[22], Bruce Nelson[23], James A. Hay[24,25], Mélodie Monod[15], Xenia Miscou… Helen Coupland[1,2], Raphael Sonabend[1,2], Michaela Vollmer[1,2], Axel Gandy[15], Carlos A. Prete Jr.… Vitor H. Nascimento[26], Marc A. Suchard[27], Thomas A. Bowden[9], Sergei L. K. Pond[28], Chieh-Hsi… Oliver Ratmann[15], Neil M. Ferguson[1,2], Christopher Dye[4], Nick J. Loman[30], Philippe Lemey[31], Andrew Rambaut[8], Nelson A. Fraiji[6,32], Maria do P. S. S. Carvalho[6,33], Oliver G. Pybus[4,34]‡, Seth Flaxman[15]‡, Samir Bhatt[1,2,35]*‡, Ester C. Sabino[3,5]*‡

Cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Manaus, B… resurged in late 2020 despite previously high levels of infection. Genome sequencing of viruses s…

transmission and mortality there during late 2020 and early 2021 (5), which has placed substantial pressure on the city's health care system.

Here, we show that the second wave of infection in Manaus was associated with the emergence and rapid spread of a new SARS-CoV-2 lineage of concern, named lineage P.1. The lineage carries a distinctive constellation of mutations (table S1), including several that have been previously determined to be of virological importance (6–10) and that are located in the spike protein receptor binding domain (RBD), the region of the virus involved in recognition of the angiotensin-converting enzyme-2 (ACE2) cell surface receptor (11). Using genomic data, structure-based mapping of mutations of interest onto the spike protein, and…

RESEARCH
CORONAVIRUS

Three-quarters attack rate of SARS-CoV-2 in the Brazilian Amazon during a largely unmitigated epidemic

Lewis F. Buss[1]*, Carlos A. Prete Jr.[2]*, Claudia M. M. Abrahim[3]*, Alfredo Mendrone Jr.[4,5]*, Tassila Salomon[6,7]*, Cesar de Almeida-Neto[4,5], Rafael F. O. França[8], Maria C. Belotti[2], Maria P. S. S. Carvalho[3], Allyson G. Costa[3], Myuki A. E. Crispim[3], Suzete C. Ferreira[4,5], Nelson A. Fraiji[3], Susie Gurzenda[9], Charles Whittaker[10], Leonardo T. Kamaura[11], Pedro L. Takecian[11], Pedro da Silva Peixoto[11], Marcio K. Oikawa[12], Anna S. Nishiya[4,5], Vanderson Rocha[4,5], Nanci A. Salles[4], Andreza Aruska de Souza Santos[13], Martirene A. da Silva[3], Brian Custer[14,15], Kris V. Parag[16], Manoel Barral-Netto[17], Moritz U. G. Kraemer[18], Rafael H. M. Pereira[19], Oliver G. Pybus[18], Michael P. Busch[14,15], Márcia C. Castro[9], Christopher Dye[18], Vítor H. Nascimento[2], Nuno R. Faria[1,16,18]†, Ester C. Sabino[1]†

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread rapidly in Manaus, the capital of Amazonas state in northern Brazil. The attack rate there is an estimate of the final size of the largely unmitigated epidemic that occurred in Manaus. We use a convenience sample of blood donors to show that by June 2020, 1 month after the epidemic peak in Manaus, 44% of the population had detectable immunoglobulin G (IgG) antibodies. Correcting for cases without a detectable antibody response and for antibody waning, we estimate a 66% attack rate in June, rising to 76% in October. This is higher than in São Paulo, in southeastern Brazil, where the estimated attack rate in October was 29%. These results confirm that when poorly controlled, COVID-19 can infect a large proportion of the population, causing high mortality.

ARTICLES
https://doi.org/10.1038/s41591-022-01807-1
nature medicine
Check for updates
OPEN

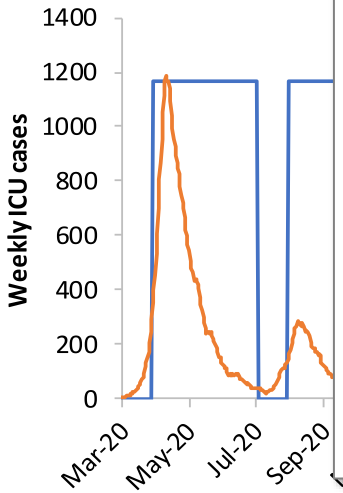
Spatial and temporal fluctuations in COVID-19 fatality rates in Brazilian hospitals

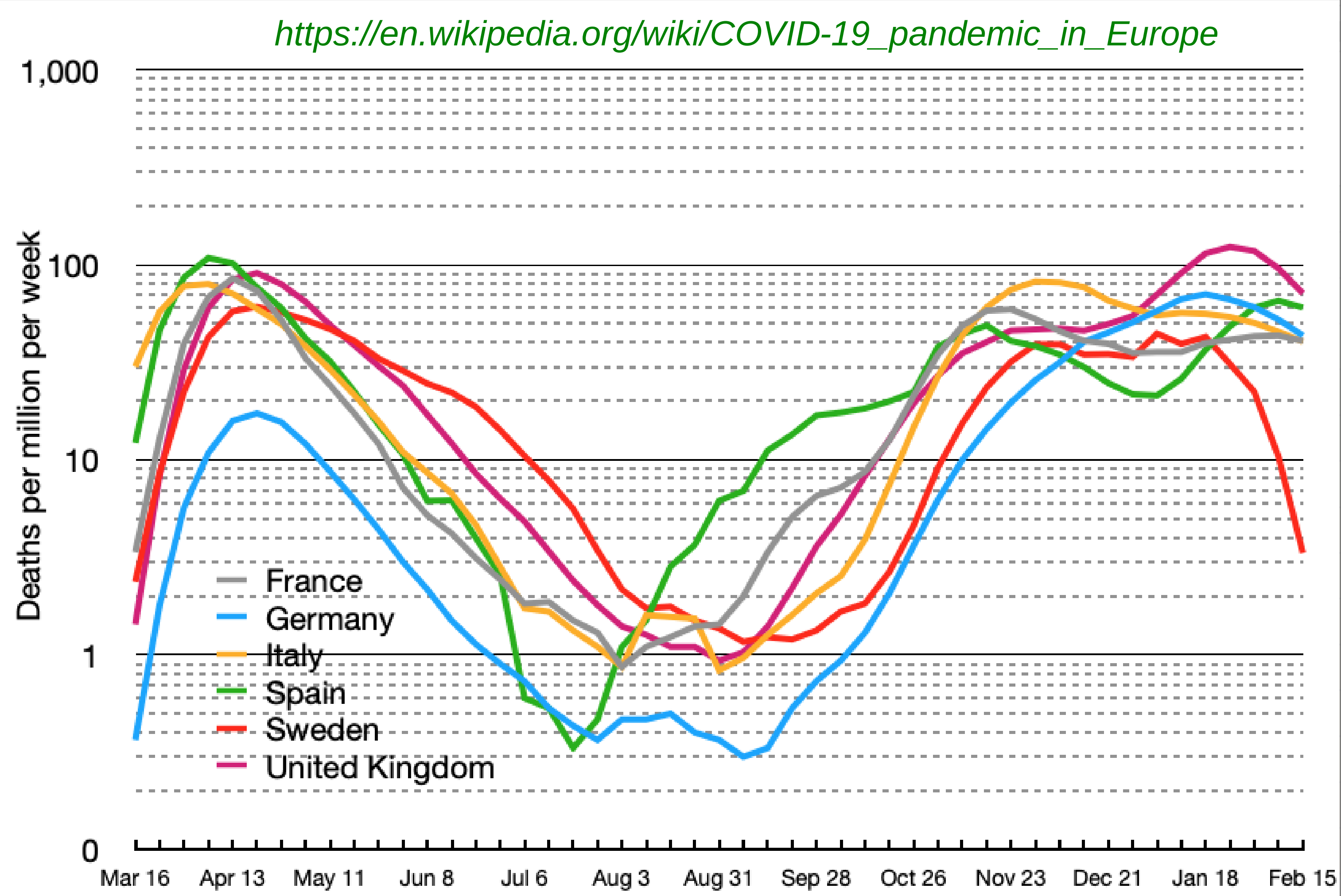
Andrea Brizzi[1,23], Charles Whittaker[2,23], Luciana M. S. Servo[3,23], Iwona Hawryluk[2,23], Carlos A. Prete Jr[4,23], William M. de Souza[5,23], Renato S. Aguiar[6,7], Leonardo J. T. Araujo[8], Leonardo S. Bastos[9], Alexandra Blenkinsop[1], Lewis F. Buss[2,10], Darlan Candido[11], Marcia C. Castro[12], Silvia F. Costa[10], Julio Croda[13], Andreza Aruska de Souza Santos[14], Christopher Dye[11], Seth Flaxman[15], Paula L. C. Fonseca[6], Victor E. V. Geddes[6], Bernardo Gutierrez[11], Philippe Lemey[16], Anna S. Levin[10], Thomas Mellan[2], Diego M. Bonfim[6], Xenia Miscouridou[1], Swapnil Mishra[2,17], Mélodie Monod[1], Filipe R. R. Moreira[18], Bruce Nelson[19], Rafael H. M. Pereira[3], Otavio Ranzani[20], Ricardo P. Schnekenberg[21], Elizaveta Semenova[1], Raphael Sonabend[2], Renan P. Souza[6], Xiaoyue Xi[1], Ester C. Sabino[10]✉, Nuno R. Faria[2,10,11,22]✉, Samir Bhatt[2,17]✉ and Oliver Ratmann[1,23]✉

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Gamma variant of concern has spread rapidly across Brazil since late 2020, causing substantial infection and death waves. Here we used individual-level patient records after hospitalization with suspected or confirmed coronavirus disease 2019 (COVID-19) between 20 January 2020 and 26 July 2021 to document temporary, sweeping shocks in hospital fatality rates that followed the spread of Gamma across 14 state capitals, during which typically more than half of hospitalized patients aged 70 years and older died. We show that such extensive shocks in COVID-19 in-hospital fatality rates also existed before the detection of Gamma. Using a Bayesian fatality rate model, we found that the geographic and temporal fluctuations in Brazil's COVID-19 in-hospital fatality rates were primarily associated with geographic inequities and shortages in healthcare capacity. We estimate that approximately half of the COVID-19 deaths in hospitals in the 14 cities could have been avoided without pre-pandemic geographic inequities and without pandemic healthcare pressure. Our results suggest that investments in healthcare resources, healthcare optimization and pandemic preparedness are critical to minimize population-wide mortality and morbidity caused by highly transmissible and deadly pathogens such as SARS-CoV-2, especially in low- and middle-income countries.

Multiple lockdowns predicted to be needed

- Aim – to keep
- On/off trigger l
  usage



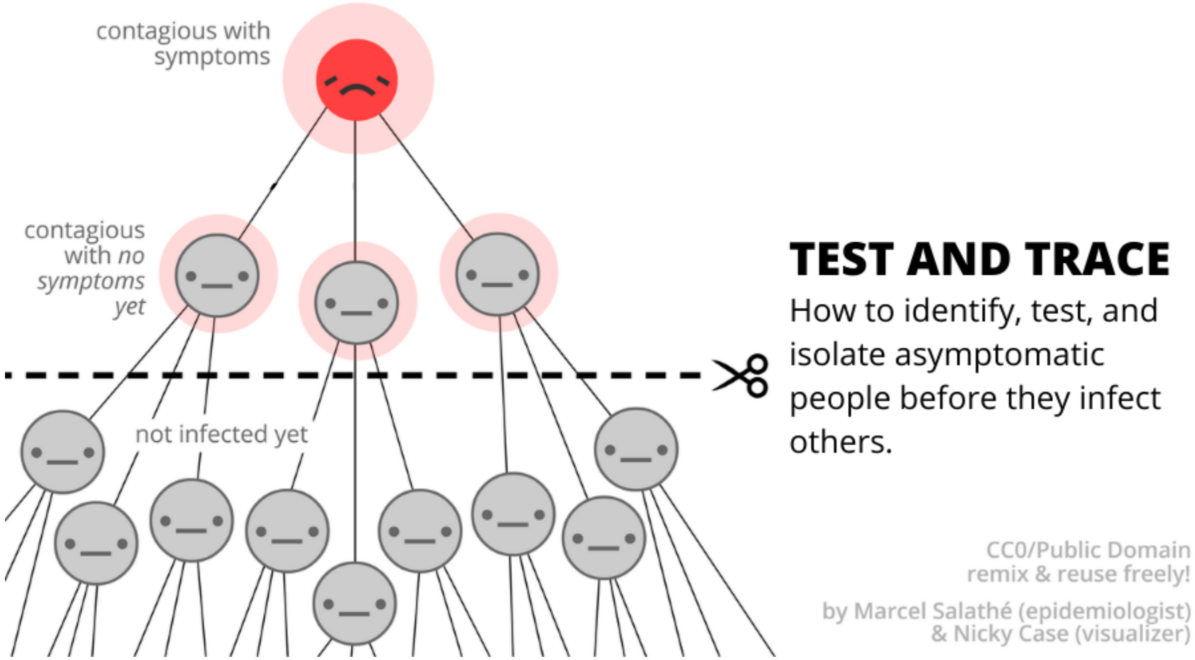


otal deaths	
C_CI_SD	PC_CI_HQ_SD
12,000	8,700
15,000	10,000
14,000	11,000
19,000	13,000
20,000	15,000
21,000	16,000
30,000	24,000
36,000	27,000
40,000	30,000
43,000	34,000
48,000	37,000
52,000	39,000
53,000	39,000
61,000	46,000
65,000	51,000

Ferguson et al. Imperial College Report 9
Walker et al, Science 2020

Alternative to suppression: test and trace

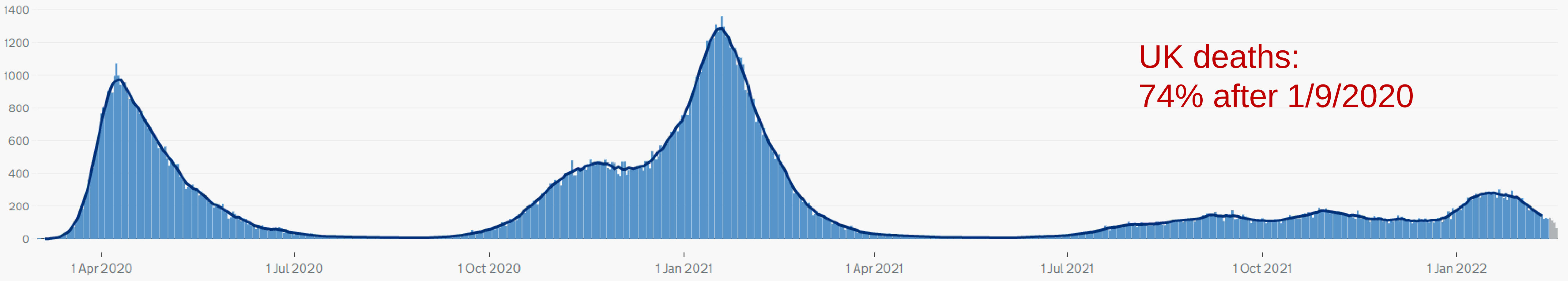
- Difficult due to pre-symptomatic/asymptomatic transmission
- Prompt case isolation: 25-30% reduction in R
- + household quarantine: 35-40%
- + intensive contact tracing: 55-65%
- *e.g.* S. Korea, Vietnam – but requires very intensive tracing, cluster detection
- UK and other European countries achieved much less (perhaps 35%)
- Insufficient to keep R<1 in autumn



Kucharski et al., Lancet ID 2020

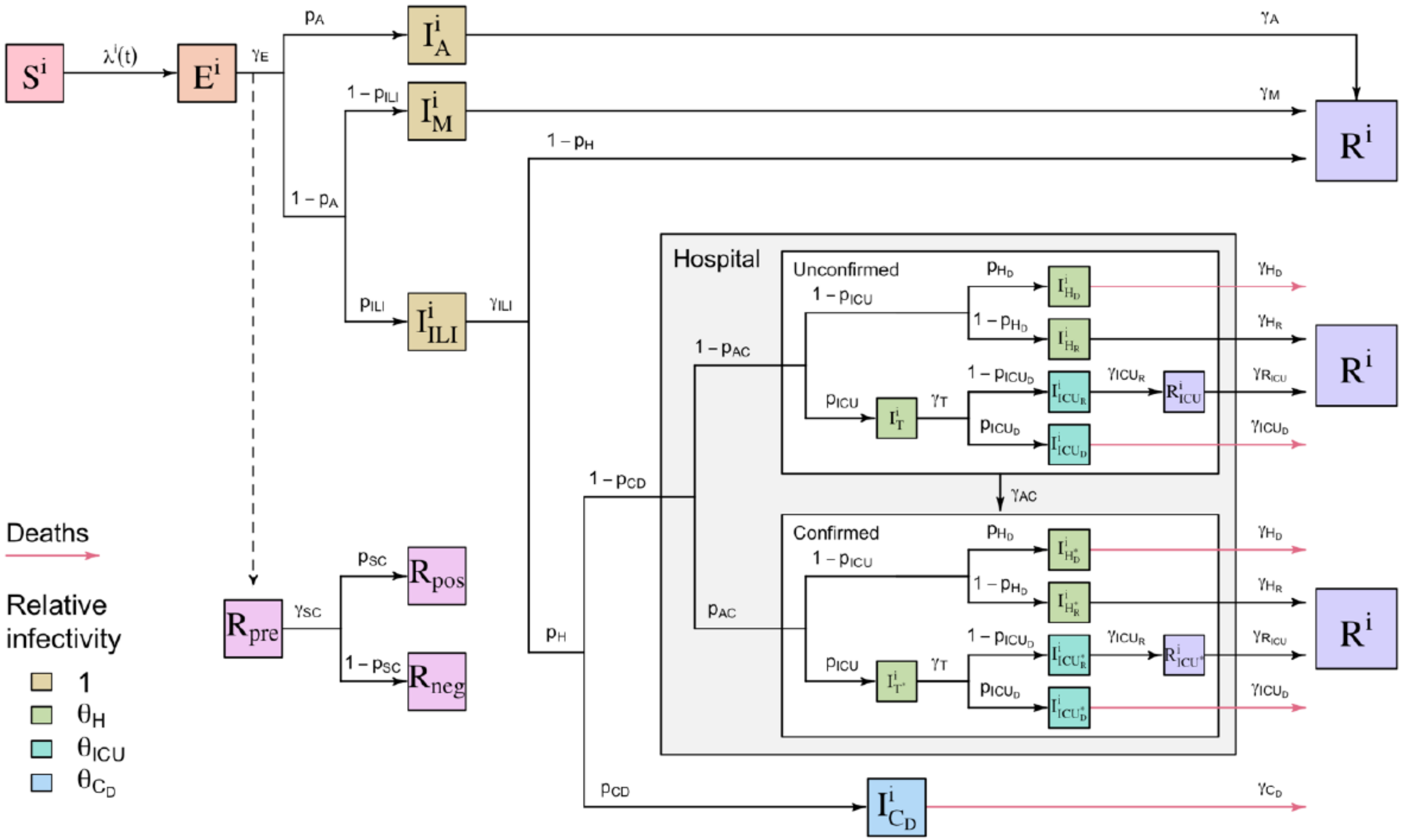
The second (UK) wave

- Countries across Europe slow to act, despite clear science
- Economic and social impacts of controls more apparent
- Noise in the popular discourse, more scepticism
- Hope that test-and-trace would suffice
- Governments adopted incremental and localised approach
- Resulted in “levelling up” of most regions to high infection levels
- Countries which acted earlier (e.g. Denmark) saw many fewer deaths



Real-time modelling to inform policy

- Complex mathematical transmission model
- Fitted to multiple data streams
- Run each week during pandemic:
  - ➢ Estimate R
  - ➢ Medium-term projections
  - ➢ Evaluate potential policy options

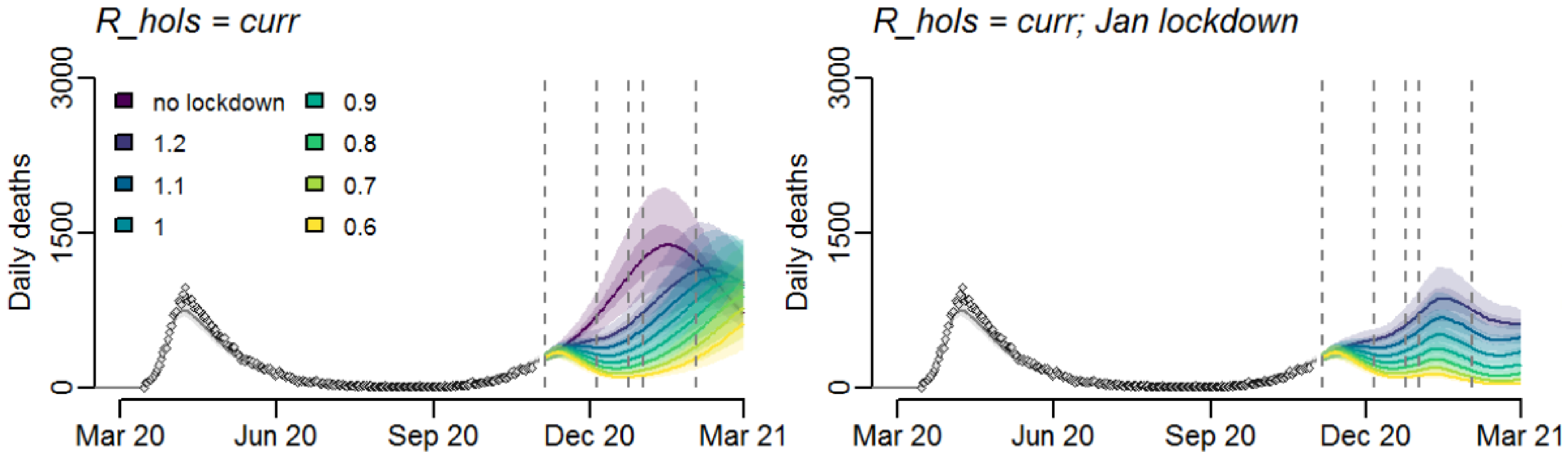


Knock et al. Science Translational Medicine, 2021

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

October 2020: example of counterfactual modelling

- For SAGE
- Evaluating need for November and January lockdowns
- (and Christmas relaxation of rules)

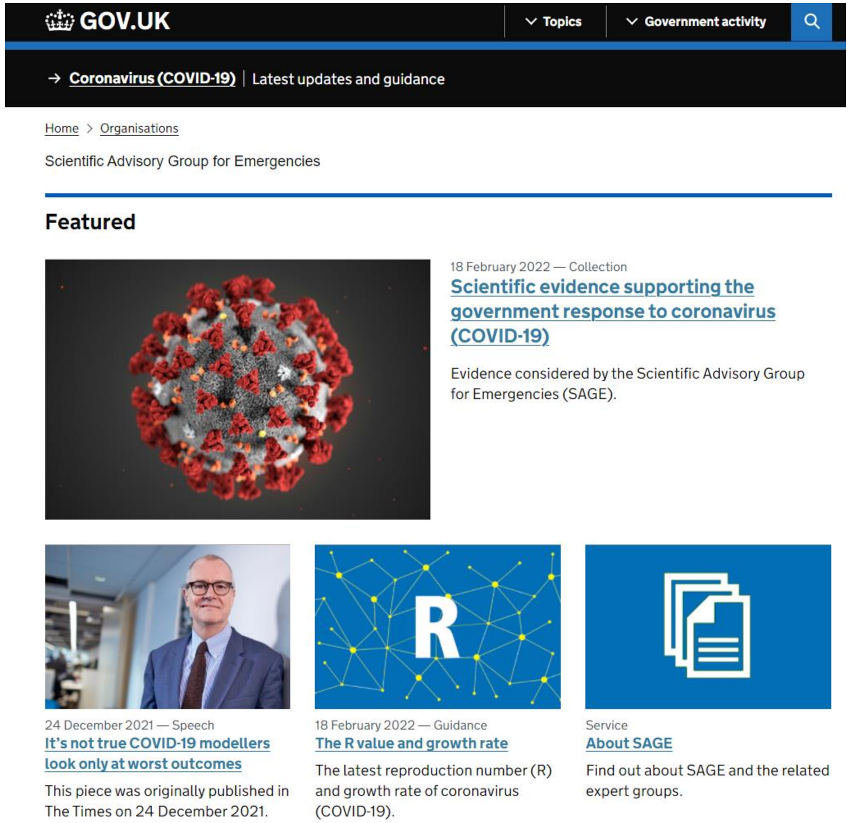


Knock et al., Sci Trans Med, 2021
https://github.com/mrc-ide/sircovid

Science, policy and politics

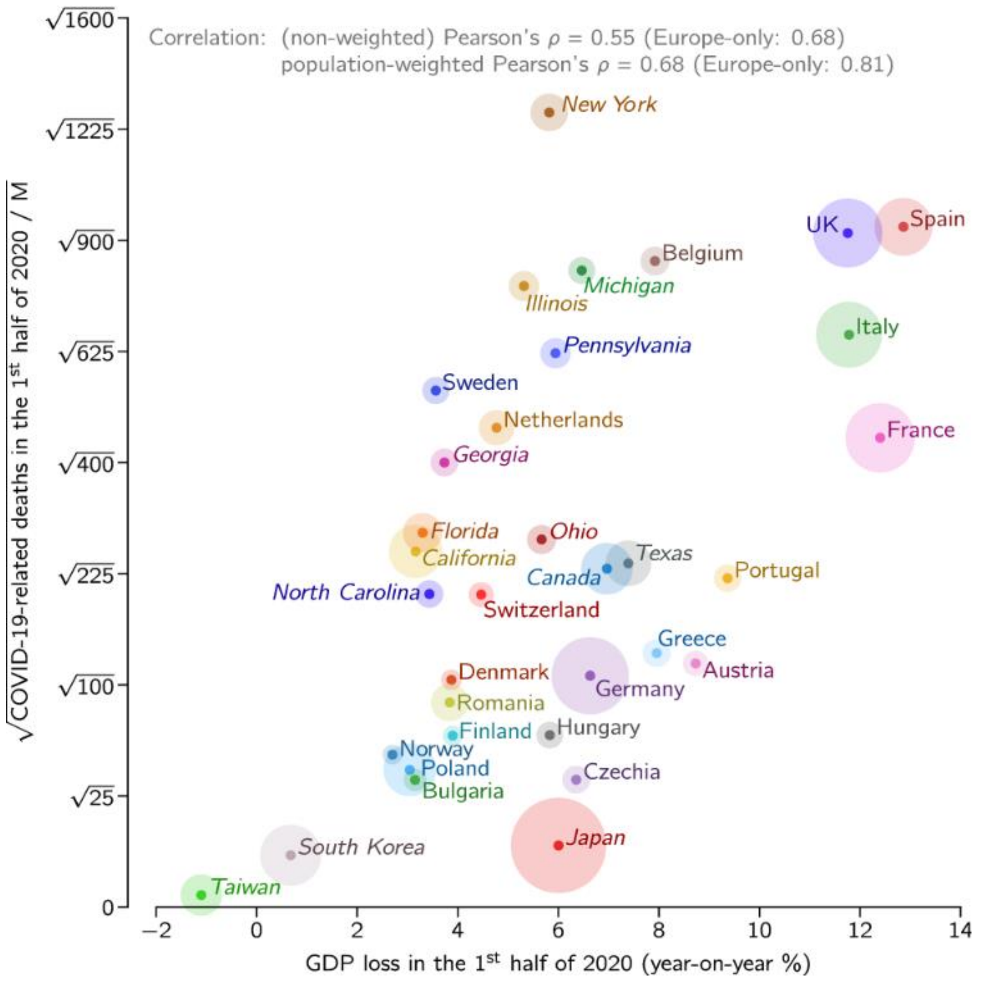
UK approach

- Generally, academic scientists do not give advice direct to ministers
- Advice through committees – SAGE, NERVTAG, SPI-M, ….
- CSA and CMO responsible for communicating consensus (and uncertainty) to politicians
- Intent: advise on the likely impacts of different policy options, but don't say what policy *should* be
- Multiple academic groups examine each question
- Checks and balances enhance authority, reduce agility



Issues

- Fine line between advising on policy options and recommending particular policies
- SAGE walked either side of that line at different times
- Too much initial focus on the “reasonable worst case”, rather than planning for a range of scenarios
- Strategic objectives lacking – e.g. “what policy will minimise economic impact while preventing health service being overwhelmed”



Kochańczyk, M., Lipniacki, T. Sci Rep 11, 2425 (2021). https://doi.org/10.1038/s41598-021-81869-2

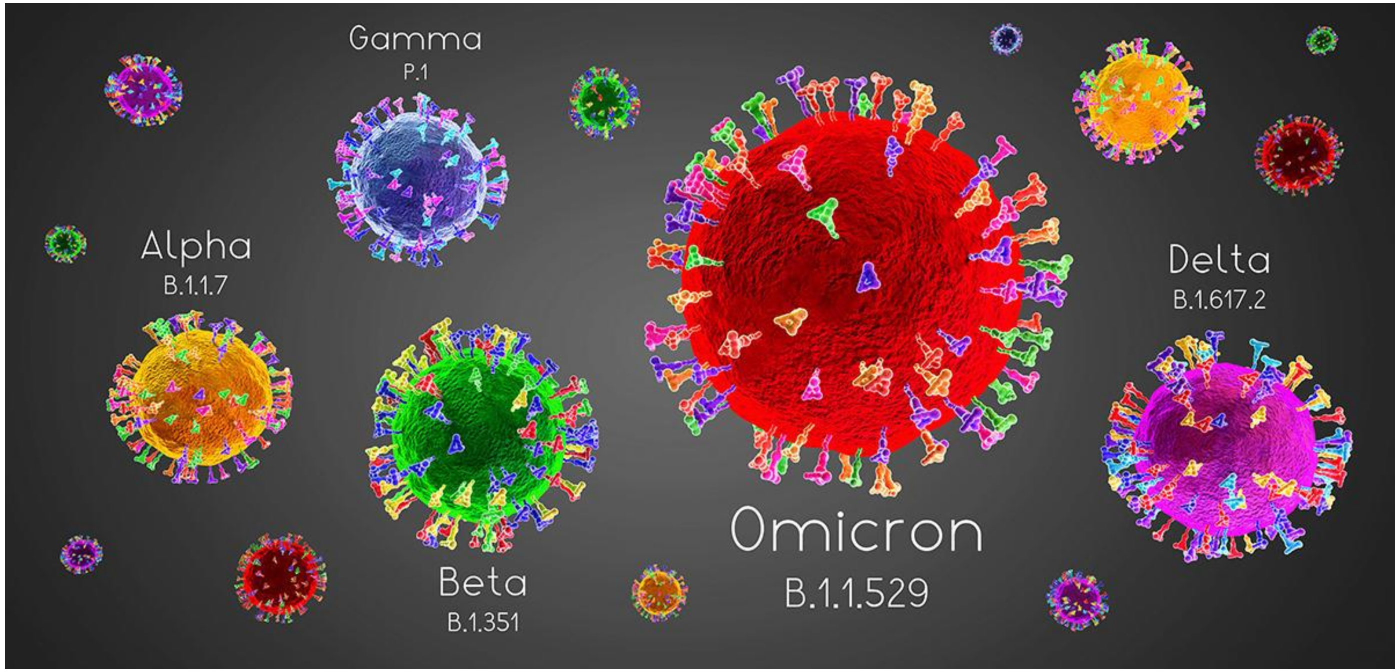
Diversity of scientific views

- Inevitable when data is noisy, not always consistent
- Uncertainties remained – plenty of areas for debate
- Unhelpful and inaccurate to portray diversity as dichotomous (two ‘camps’)
- Infectious disease researchers working on COVID more credible than scientists with no background in the area
- False balance was a problem in Summer/Autumn 2020 – encouraged lockdown scepticism, delayed action

Ideologically-motivated criticism

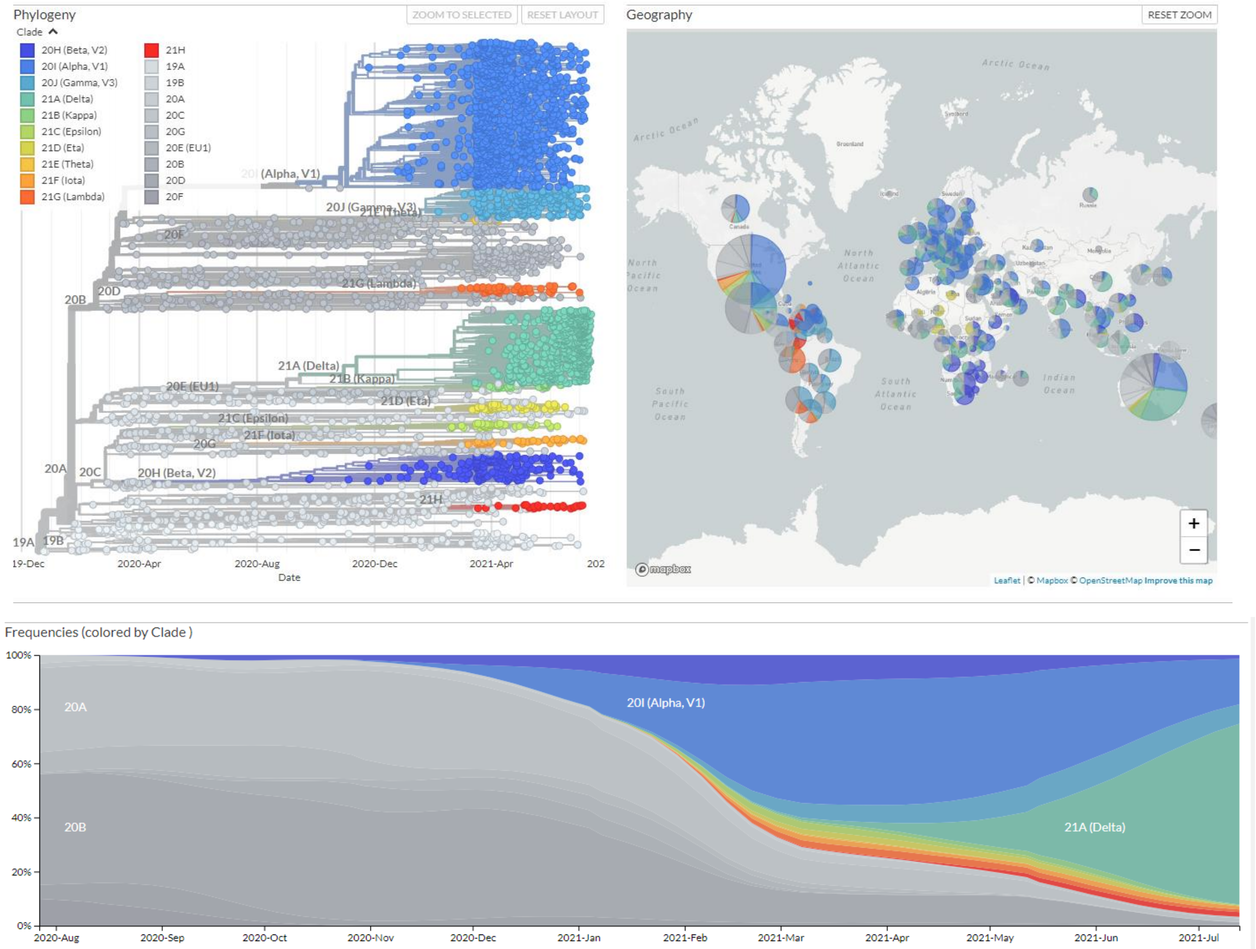
- Scientists received a torrent of abuse
- Attacks on science & scientists have been primarily ideologically driven:
  - ➢ Downplaying risk, cherry-picking, misinformation, conspiracies
  - ➢ Various groups: lockdown sceptics, antivaxers, COVID-sceptics, …
  - ➢ Reject evidence incompatible with world view, rely on rhetoric, want someone to blame
- Not just UK – and worse in current populist, polarised, "post-truth", social media age

2021: Variants and Vaccines



Modelling got more difficult

- Prediction always hard – though only a small part of what we do:
  - ➢ Predicting impact of policies in advance
  - ➢ And population behaviour change
- But easier to model spread of new virus in population with no immunity
- Things got more complicated:
  - ➢ Naturally-acquired immunity
  - ➢ New variants
  - ➢ Vaccination



https://nextstrain.org/ncov/gisaid/global

Characterising variants

CellPress OPEN ACCESS — Cell

Article

Evaluating the Effects of SARS-CoV-2 Spike Mutation D614G on Transmissibility and Pathogenicity

Erik Volz,[1,13,*] Verity Hill,[2] John T. McCrone,[2] Anna Price,[3] David Jorgensen,[1] Áine O'Toole,[2] Joel So…
Robert Johnson,[1] Ben Jackson,[2] Fabricia F. Nascimento,[1] Sara M. Rey,[4] Samuel M. Nicholls,[5] Rach…
Ana da Silva Filipe,[6] James Shepherd,[6] David J. Pascall,[7] Rajiv Shah,[6] Natasha Jesudason,[6] Kathy L…
Nicole Pacchiarini,[4] Matthew Bull,[4] Lily Geidelberg,[1] Igor Siveroni,[1] COG-UK Consortium,[8] Ian Good…
Nicholas J. Loman,[5] Oliver G. Pybus,[10,11] David L. Robertson,[6] Emma C. Thomson,[6] Andrew Ramba…
and Thomas R. Connor[3,4,12,*]
[1]MRC Centre for Global Infectious Disease Analysis, School of Public Health, Imperial College London, London, UK
[2]Institute of Evolutionary Biology, University of Edinburgh, Edinburgh, UK
[3]School of Biosciences, Cardiff University, Cardiff, UK
[4]Pathogen Genomics Unit, Public Health Wales NHS Trust, Cardiff, UK

Article

Assessing transmissibility of SARS-C… lineage B.1.1.7 in England

https://doi.org/10.1038/s41586-021-03470-x
Received: 31 December 2020
Accepted: 18 March 2021
Published online: 25 March 2021
Check for updates

Erik Volz[1,104], Swapnil Mishra[1,104], Meera Chand[2,104], Jeffrey C. B… Lily Geidelberg[1], Wes R. Hinsley[1], Daniel J. Laydon[1], Gavin Dabre… Robert Amato[3], Manon Ragonnet-Cronin[1], Ian Harrison[2], Ben Ja… Olivia Boyd[1], Nicholas J. Loman[2,5], John T. McCrone[6], Sónia Gon… Richard Myers[2], Verity Hill[6], David K. Jackson[3], Katy Gaythorpe… John Sillitoe[3], Dominic P. Kwiatkowski[3], The COVID-19 Genomics UK (COG-UK) consortium*, Seth Flaxman[8], Oliver Ratmann[8], Samir Bhatt[1,7], Susan Hopkins[2], Axel Gandy[8,104] Andrew Rambaut[6,104] & Neil M. Ferguson[1,104]

The SARS-CoV-2 lineage B.1.1.7, designated variant of concern (VOC) 202012/01 by Public Health England[1], was first identified in the UK in late summer to early autumn 2020[2]. Whole-genome SARS-CoV-2 sequence data collected from community-based diagnostic testing for COVID-19 show an extremely rapid expansion of the B.1.1.7 lineage during autumn 2020, suggesting that it has a selective advantage. Here we show that changes in VOC frequency inferred from genetic data correspond closely to changes inferred by *S* gene target failures (SGTF) in community-based diagnostic PCR testing. Analysis of trends in SGTF and non-SGTF case numbers in local areas across England shows that B.1.1.7 has higher transmissibility than non-VOC lineages, even if it has a different latent period or generation time. The SGTF data indicate a transient shift in the age composition of reported cases, with cases of B.1.1.7 including a larger share of under 20-year-olds than non-VOC cases. We estimated time-varying reproduction numbers for B.1.1.7 and co-circulating lineages using SGTF and genomic data. The best-supported models did not indicate a substantial difference in VOC transmissibility among different age groups, but all analyses agreed that B.1.1.7 has a substantial transmission advantage over other lineages, with a 50% to 100% higher reproduction number.

RESEARCH

CORONAVIRUS

Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil

Nuno R. Faria[1,2,3,4*†], Thomas A. Mellan[1,2†], Charles Whittaker[1,2†], Ingra M. Claro[3,5†], Darlan da S. Candido[3,4†], Swapnil Mishra[1,2†], Myuki A. E. Crispim[6,7], Flavia C. S. Sales[3,5], Iwona Hawryluk[1,2], John T. McCrone[8], Ruben J. G. Hulswit[9], Lucas A. M. Franco[3,5], Mariana S. Ramundo[3,5], Jaqueline G. de Jesus[3,5], Pamela S. Andrade[10], Thais M. Coletti[3,5], Giulia M. Ferreira[11], Camila A. M. Silva[3,5], Erika R. Manuli[3,5], Rafael H. M. Pereira[12], Pedro S. Peixoto… Moritz U. G. Kraemer[4], Nelson Gaburo Jr.[14], Cecilia da C. Camilo[14], Henrique Hoeltgebaum[15], William M. Souza[16], Esmenia C. Rocha[3,5], Leandro M. de Souza[3,5], Mariana C. de Pinho[3,5], Leonardo J. T. Araujo[17], Frederico S. V. Malta[18], Aline B. de Lima[18], Joice do P. Silva[18], Danielle A. G. Zauli[18], Alessandro C. de S. Ferreira[18], Ricardo P. Schnekenberg[19], Daniel J. Laydon[1,2], Patrick G. T. Walker[1,2], Hannah M. Schlüter[15], Ana L. P. dos Santos[20], Maria S. Vidal[20], Valentina S. Del Caro[20], Rosinaldo M. F. Filho[20], Helem M. dos Santos[20], Renato S. Aguiar[21], José L. Proença-Modena[22], Bruce Nelson[23], James A. Hay[24,25], Mélodie Monod[15], Xenia Miscouridou… Helen Coupland[1,2], R… Vitor H. Nascimento… Oliver Ratmann[15], N… Andrew Rambaut[8], N… Seth Flaxman[15‡], Sa…

Cases of severe acut… resurged in late 2020…

Articles

Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study

Tommy Nyberg, Neil M Ferguson*, Sophie G Nash, Harriet H Webster, Seth Flaxman, Nick Andrews, Wes Hinsley, Jamie Lopez Bernal, Meaghan Kall, Samir Bhatt, Paula Blomquist, Asad Zaidi, Erik Volz, Nurin Abdul Aziz, Katie Harman, Sebastian Funk, Sam Abbott, COVID-19 Genomics UK (COG-UK) consortium, Russell Hope, Andre Charlett, Meera Chand, Azra C Ghani, Shaun R Seaman, Gavin Dabrera, Daniela De Angelis†, Anne M Presanis†, Simon Thelwall†*

Summary

Background The omicron variant (B.1.1.529) of SARS-CoV-2 has demonstrated partial vaccine escape and high transmissibility, with early studies indicating lower severity of infection than that of the delta variant (B.1.617.2). We aimed to better characterise omicron severity relative to delta by assessing the relative risk of hospital attendance, hospital admission, or death in a large national cohort.

Lancet 2022; 399: 1303–12
Published Online March 16, 2022
https://doi.org/10.1016/S0140-6736(22)00462-7

Non-pharmaceutical interventions, vaccination, and the SARS-CoV-2 delta variant in England: a mathematical modelling study

Raphael Sonabend, Lilith K Whittles*, Natsuko Imai*, Pablo N Perez-Guzman*, Edward S Knock*, Thomas Rawson, Katy A M Gaythorpe, Bimandra A Djaafara, Wes Hinsley, Richard G FitzJohn, John A Lees, Divya Thekke Kanapram, Erik M Volz, Azra C Ghani, Neil M Ferguson, Marc Baguelin, Anne Cori*

Summary

Background England's COVID-19 roadmap out of lockdown policy set out the timeline and conditions for the stepwise lifting of non-pharmaceutical interventions (NPIs) as vaccination roll-out continued, with step one starting on March 8, 2021. In this study, we assess the roadmap, the impact of the delta (B.1.617.2) variant of SARS-CoV-2, and potential future epidemic trajectories.

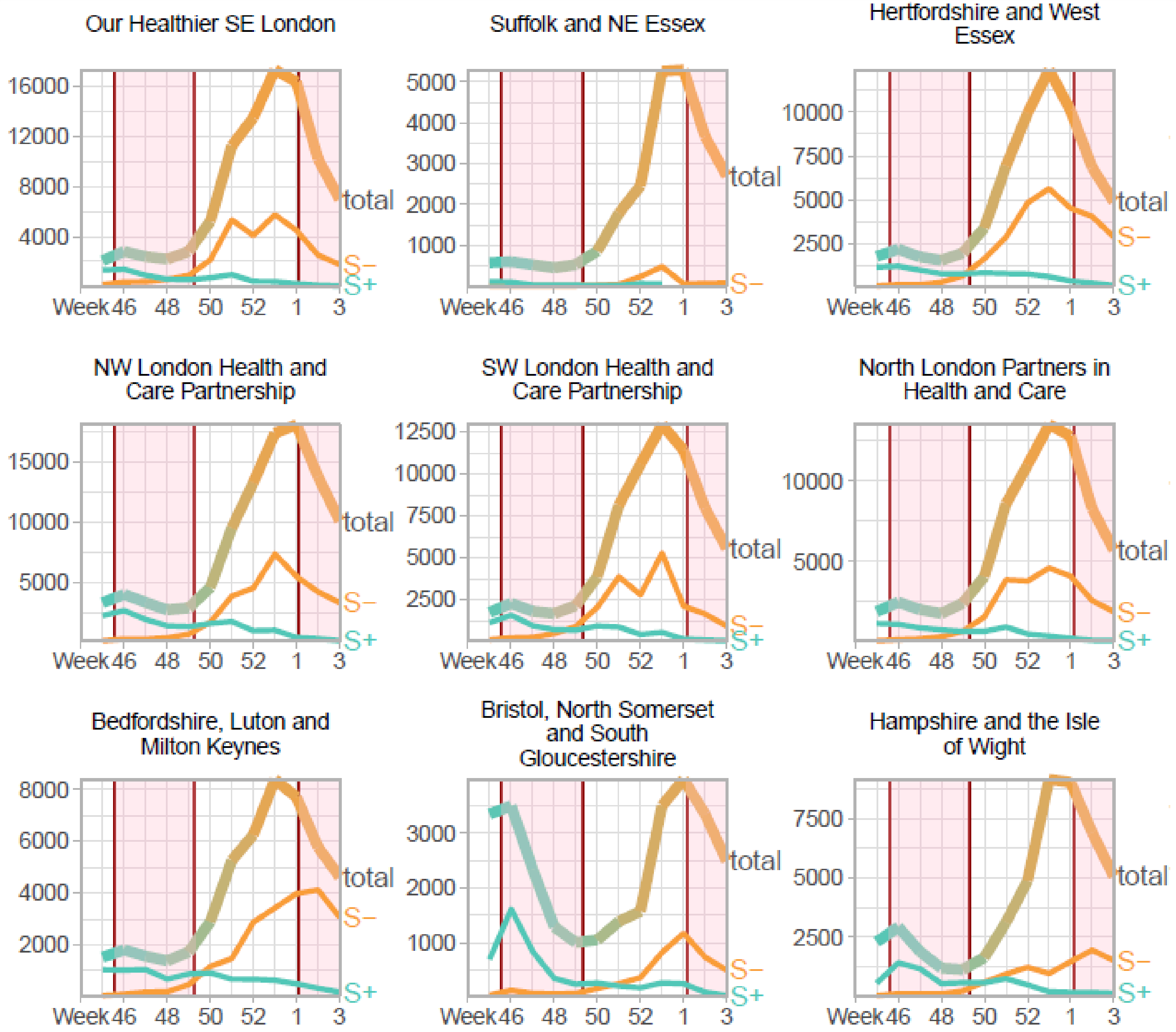
Methods This mathematical modelling study was done to assess the UK Government's four-step process to easing lockdown restrictions in England, UK. We extended a previously described model of SARS-CoV-2 transmission to incorporate vaccination and multi-strain dynamics to explicitly capture the emergence of the delta variant. We calibrated the model to English surveillance data, including hospital admissions, hospital occupancy, seroprevalence data, and population-level PCR testing data using a Bayesian evidence synthesis framework, then modelled the potential trajectory of the epidemic for a range of different schedules for relaxing NPIs. We estimated the resulting number of daily infections and hospital admissions, and daily and cumulative deaths. Three scenarios spanning a range of optimistic to pessimistic vaccine effectiveness, waning natural immunity, and cross-protection from previous infections were investigated. We also considered three levels of mixing after the lifting of restrictions.

Lancet 2021; 398: 1825–35
Published Online October 27, 2021
https://doi.org/10.1016/S0140-6736(21)02276-5
See Comment page 1781
*Contributed equally

MRC Centre for Global Infectious Disease Analysis, Jameel Institute, School of Public Health, Imperial College London, London, UK (R Sonabend PhD, L K Whittles PhD, N Imai PhD, P N Perez-Guzman MD, E S Knock PhD, T Rawson DPhil,

Alpha variant (B.1.1.7)

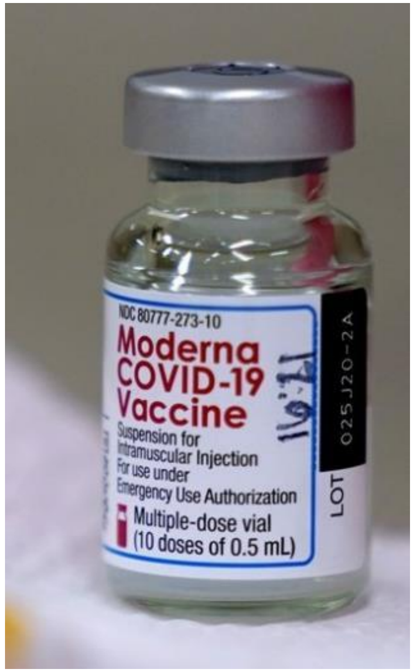
- The first of many variants of concern
- Originated Aug-Sept 2020 in UK
- Spread accelerated Nov-Dec, even during 2nd England lockdown
- Rapidly dominated in UK, then EU
- Higher transmissibility (50-80%) and severity



Volz et al., Nature 2021

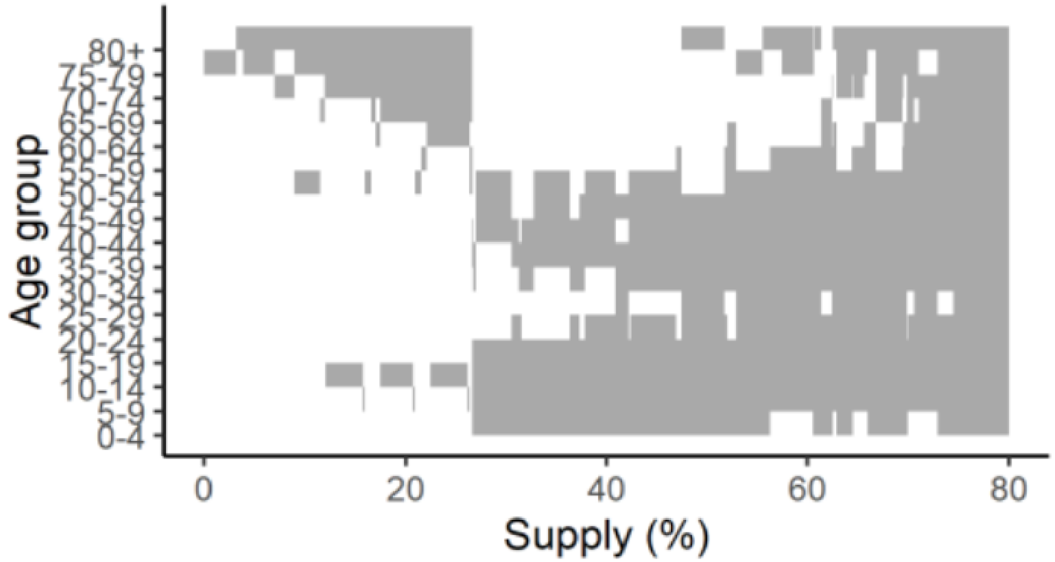
The solution: vaccines

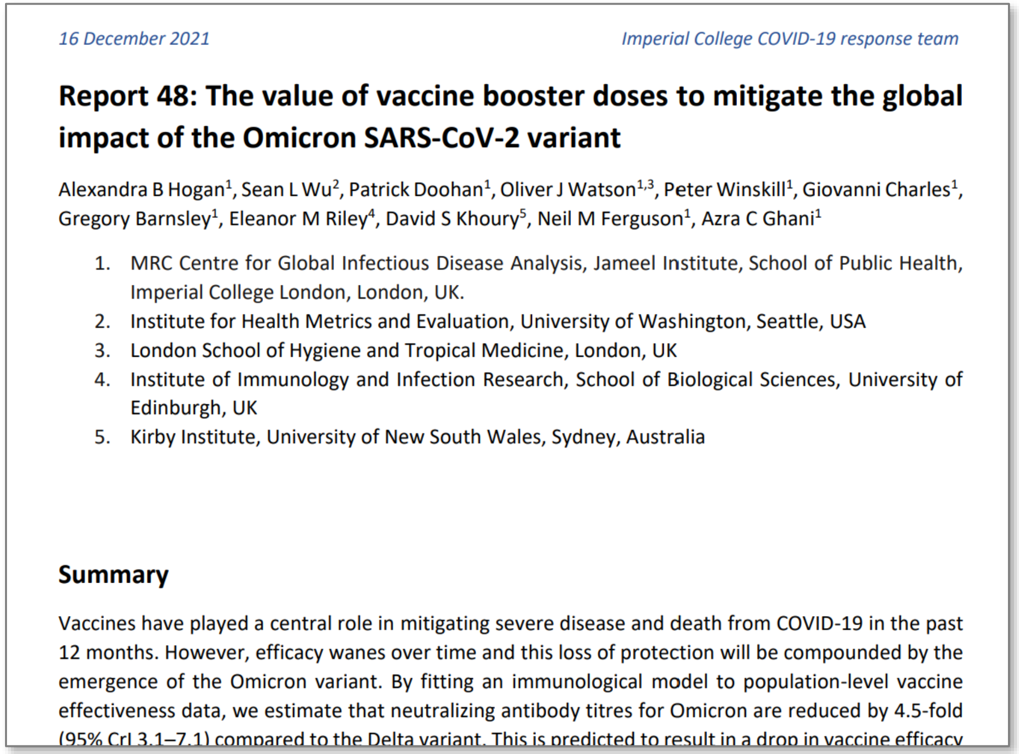
- Now 90%+ coverage in high-risk (65+) age groups in most European countries



Global vaccination modelling

- Modelling alternative strategies
- This and a lot of later work informed decisions by WHO, Gavi, CEPI, countries





16 December 2021 *Imperial College COVID-19 response team*

Report 48: The value of vaccine booster doses to mitigate the global impact of the Omicron SARS-CoV-2 variant

Alexandra B Hogan[1], Sean L Wu[2], Patrick Doohan[1], Oliver J Watson[1,3], Peter Winskill[1], Giovanni Charles[1], Gregory Barnsley[1], Eleanor M Riley[4], David S Khoury[5], Neil M Ferguson[1], Azra C Ghani[1]

1. MRC Centre for Global Infectious Disease Analysis, Jameel Institute, School of Public Health, Imperial College London, London, UK.
2. Institute for Health Metrics and Evaluation, University of Washington, Seattle, USA
3. London School of Hygiene and Tropical Medicine, London, UK
4. Institute of Immunology and Infection Research, School of Biological Sciences, University of Edinburgh, UK
5. Kirby Institute, University of New South Wales, Sydney, Australia

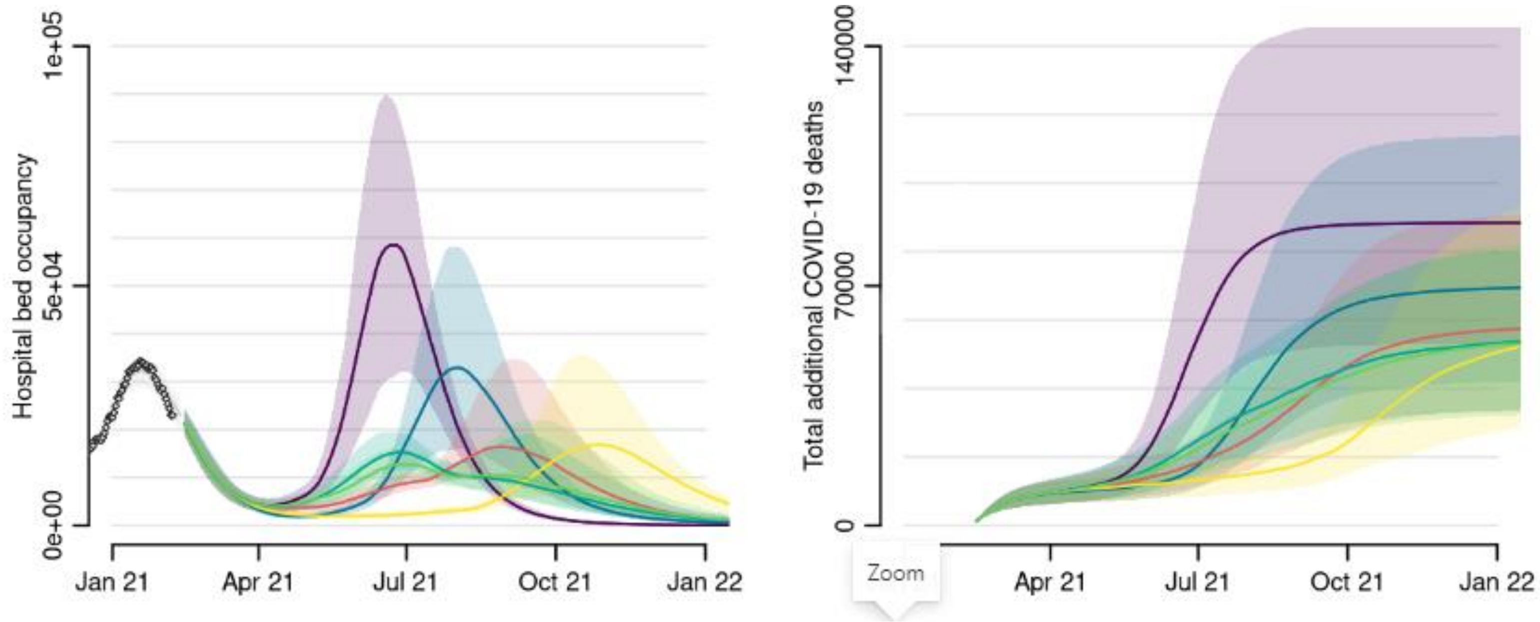
Summary

Vaccines have played a central role in mitigating severe disease and death from COVID-19 in the past 12 months. However, efficacy wanes over time and this loss of protection will be compounded by the emergence of the Omicron variant. By fitting an immunological model to population-level vaccine effectiveness data, we estimate that neutralizing antibody titres for Omicron are reduced by 4.5-fold (95% CrI 3.1–7.1) compared to the Delta variant. This is predicted to result in a drop in vaccine efficacy

Hogan et al, Report 33 and Vaccine, 2021

Modelling the UK roadmap out of lockdown in 2021

- Simulate impact of vaccine rollout
- Input data on vaccine effectiveness and variants
- Simulated possible lockdown “exit strategies”
- Aim: balance increasing immunity with higher contact rates
- Relaxing too quickly risked large third wave
- So UK adopted incremental, staggered relaxation

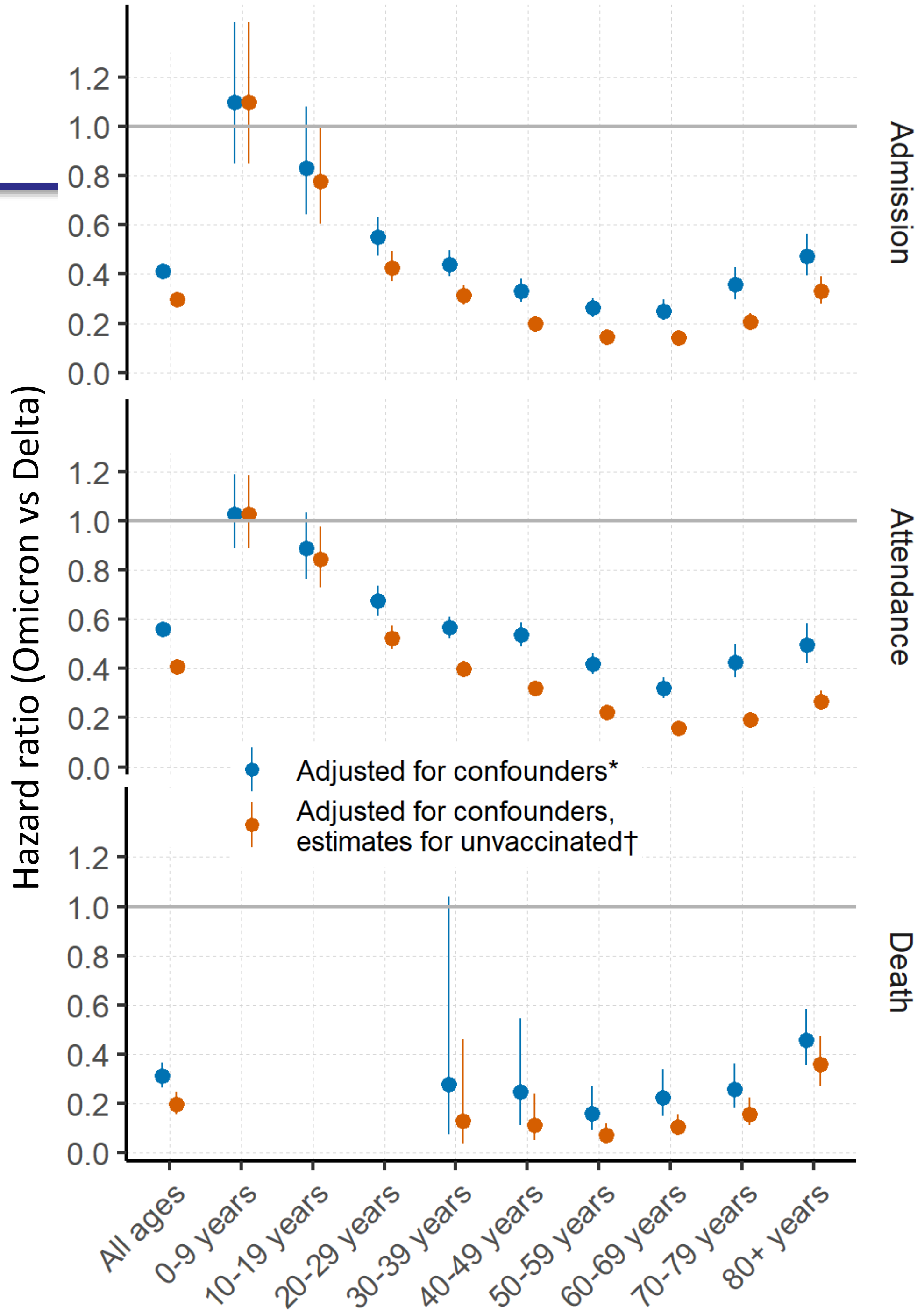


Sonabend et al. Lancet, 2021

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/963440/S1129__Unlocking__Roadmap_Scenarios_for_England_.pdf

The Omicron era

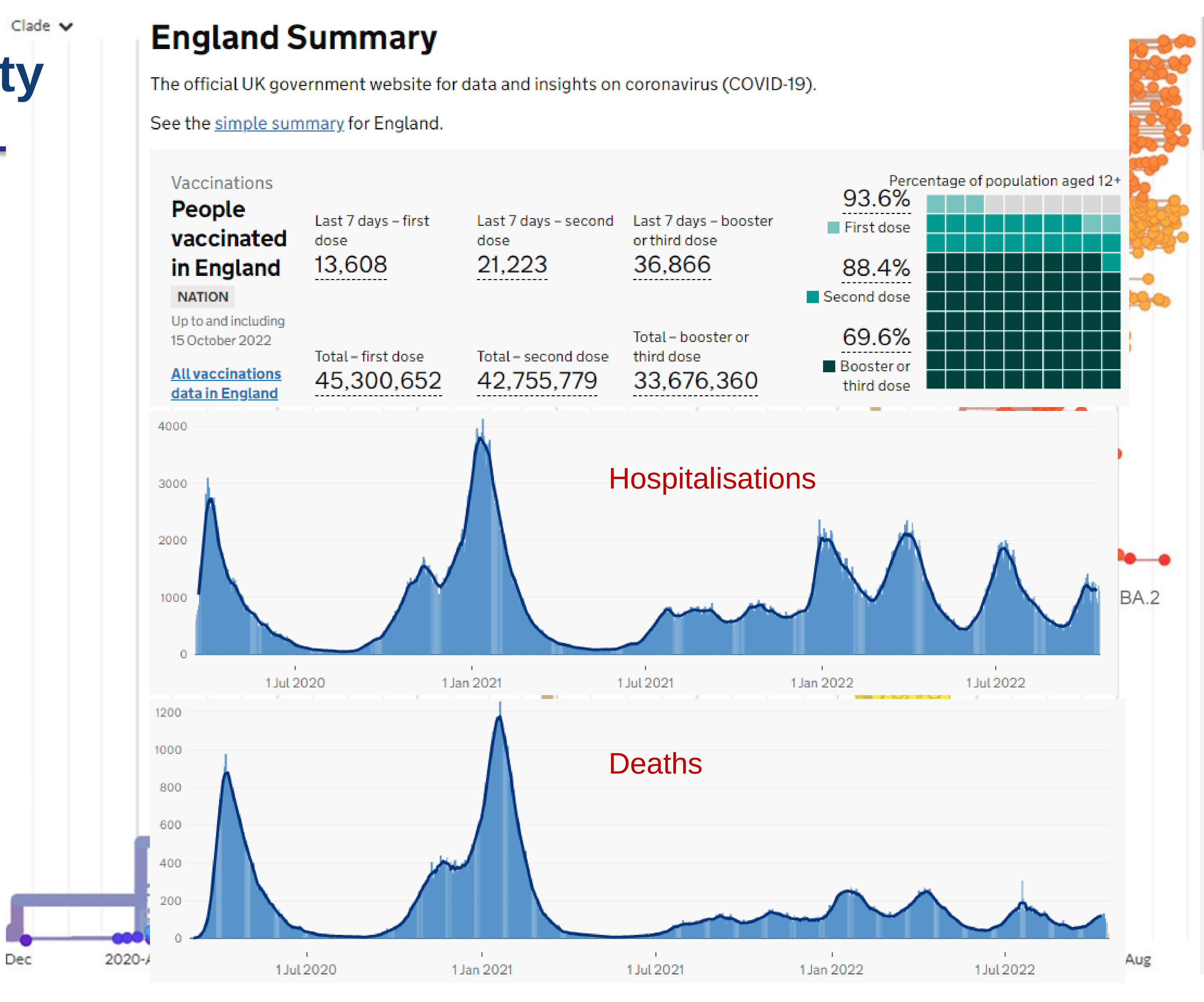
- Seeded into UK from southern Africa, Nov 2021
- Most rapid growth of any variant – immune escape
- First assessments of severity – 21-22 December
- Massive data linkage exercise + survival analysis
- Indicated much lower severity than Delta
  - ➢ 60% lower for hospitalisation, 70% for death
- Reduction varied substantially by age



Ferguson et al., Report 50, Imperial College
Nyberg, Ferguson et al. Lancet, 2022

Transition to endemicity

- 2022-23: Waves of antigenically diversifying Omicron variants
- Significant healthcare burden (mitigated by additional boosters)
- High immunity across world
- >1% infected all year in 2022 (in UK) – so high mutation rate
- When infection incidence drops, so does mutation rate – may now be happening
- But long-term trajectory remains uncertain



Contribution to clinical studies

- REACT infection survey (Elliott, Ward, Riley, …)
- Personal interest in viral kinetics
  - ➢ Transmission in households (Lalvani,…)
  - ➢ Human challenge (Chiu, Barclay,…)

Articles

Community transmission and viral load kinetics of the SARS-CoV-2 delta (B.1.617.2) variant in vaccinated and unvaccinated individuals in the UK: a prospective, longitudinal, cohort study

Anika Singanayagam*, Seran Hakki*, Jake Dunning*, Kieran J Madon, Michael A Crone, Aleksandra Koycheva, Nieves Derqui-Fernandez, Jack L Barnett, Michael G Whitfield, Robert Varro, Andre Charlett, Rhia Kundu, Joe Fenn, Jessica Cutajar, Valerie Quinn, Emily Conibear, Wendy Barclay, Paul S Freemont, Graham P Taylor, Shazaad Ahmad, Maria Zambon, Neil M Ferguson†, Ajit Lalvani†, on behalf of the ATACCC Study Investigators‡

Lancet Infect Dis 2022; 22: 183–95
Published Online October 28, 2021
https://doi.org/10.1016/S1473-3099(21)00648-4
This online publication has been corrected. The corrected version first appeared at thelancet.com/infection on

Summary

Background The SARS-CoV-2 delta (B.1.617.2) variant is highly transmissible and spreading globally, including in populations with high vaccination rates. We aimed to investigate transmission and viral load kinetics in vaccinated and unvaccinated individuals with mild delta variant infection in the community.

Methods Between Sept 13, 2020, and Sept 15, 2021, 602 community contacts (identified via the UK contract-tracing system) of 471 UK COVID-19 index cases were recruited to the Assessment of Transmission and Contagiousness of COVID-19 in Contacts cohort study and contributed 8145 upper respiratory tract samples from daily sampling for up to 20 days. Household and non-household exposed contacts aged 5 years or older were eligible for recruitment if they could provide informed consent and agree to self-swabbing of the upper respiratory tract. We analysed transmission

nature medicine
ARTICLES
https://doi.org/10.1038/s41591-022-01780-9

Check for updates

Safety, tolerability and viral kinetics during SARS-CoV-2 human challenge in young adults

Ben Killingley[1,16], Alex J. Mann[2,16], Mariya Kalinova[2], Alison Boyers[2], Niluka Goonawardane[3], Jie Zhou[3], Kate Lindsell[4], Samanjit S. Hare[5], Jonathan Brown[3], Rebecca Frise[3], Emma Smith[6], Claire Hopkins[7], Nicolas Noulin[2], Brandon Löndt[2], Tom Wilkinson[8], Stephen Harden[9], Helen McShane[10], Mark Baillet[11], Anthony Gilbert[4], Michael Jacobs[12], Christine Charman[4], Priya Mande[4], Jonathan S. Nguyen-Van-Tam[13], Malcolm G. Semple[14], Robert C. Read[8], Neil M. Ferguson[15], Peter J. Openshaw[6], Garth Rapeport[6], Wendy S. Barclay[3], Andrew P. Catchpole[2] and Christopher Chiu[3] ✉

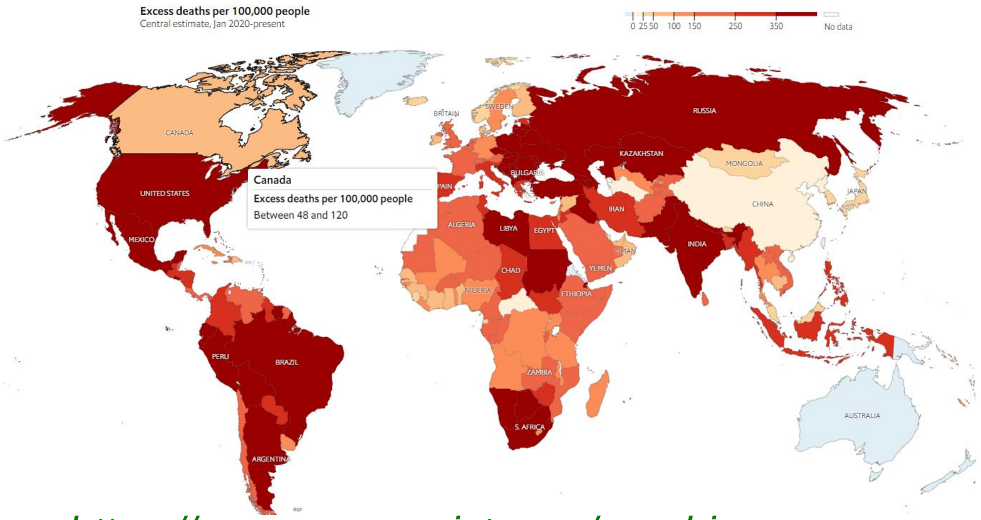
Since its emergence in 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused hundreds of millions of cases and continues to circulate globally. To establish a novel SARS-CoV-2 human challenge model that enables controlled investigation of pathogenesis, correlates of protection and efficacy testing of forthcoming interventions, 36 volunteers aged 18–29 years without evidence of previous infection or vaccination were inoculated with 10 $TCID_{50}$ of a wild-type virus (SARS-CoV-2/human/GBR/484861/2020) intranasally in an open-label, non-randomized study (ClinicalTrials.gov identifier NCT04865237; funder, UK Vaccine Taskforce). After inoculation, participants were housed in a high-containment quarantine unit, with 24-hour close medical monitoring and full access to higher-level clinical care. The study's primary objective was to identify an inoculum dose that induced well-tolerated infection in more than 50% of participants, with secondary objectives to assess virus and symp-

Reflections

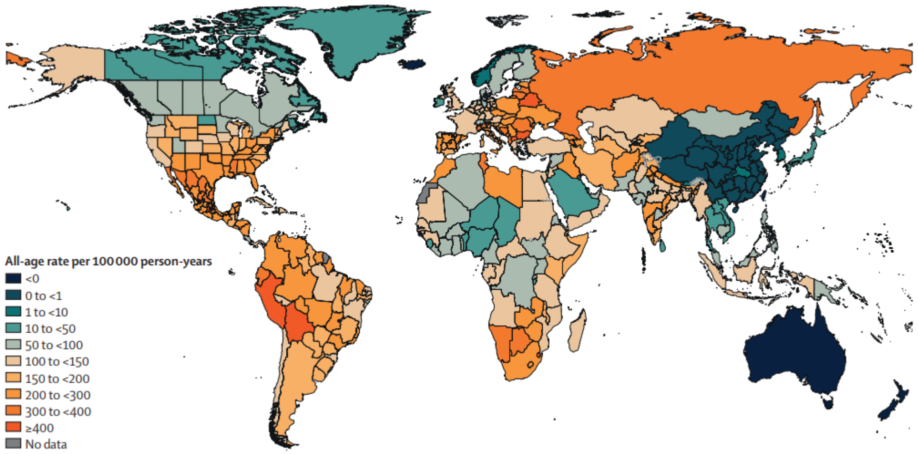
© FT/PA

Global mortality to date

- 6.5m reported COVID-19 deaths to date
- But *excess* deaths 3x higher
- Three sets of global estimates, none perfect:
  - The Economist – 20.1m (14.0m-24.4m) to 18/3/2022
  - IHME – 18.2m (17.1m-19.6m) to 31/12/2021
  - WHO – 14.9m (13.3m-16.6m) to 31/12/2021
- Same ballpark as our 20m from March 2020
- But reality didn't fully match Walker et al – new variants, vaccine roll-out, control measures a mix



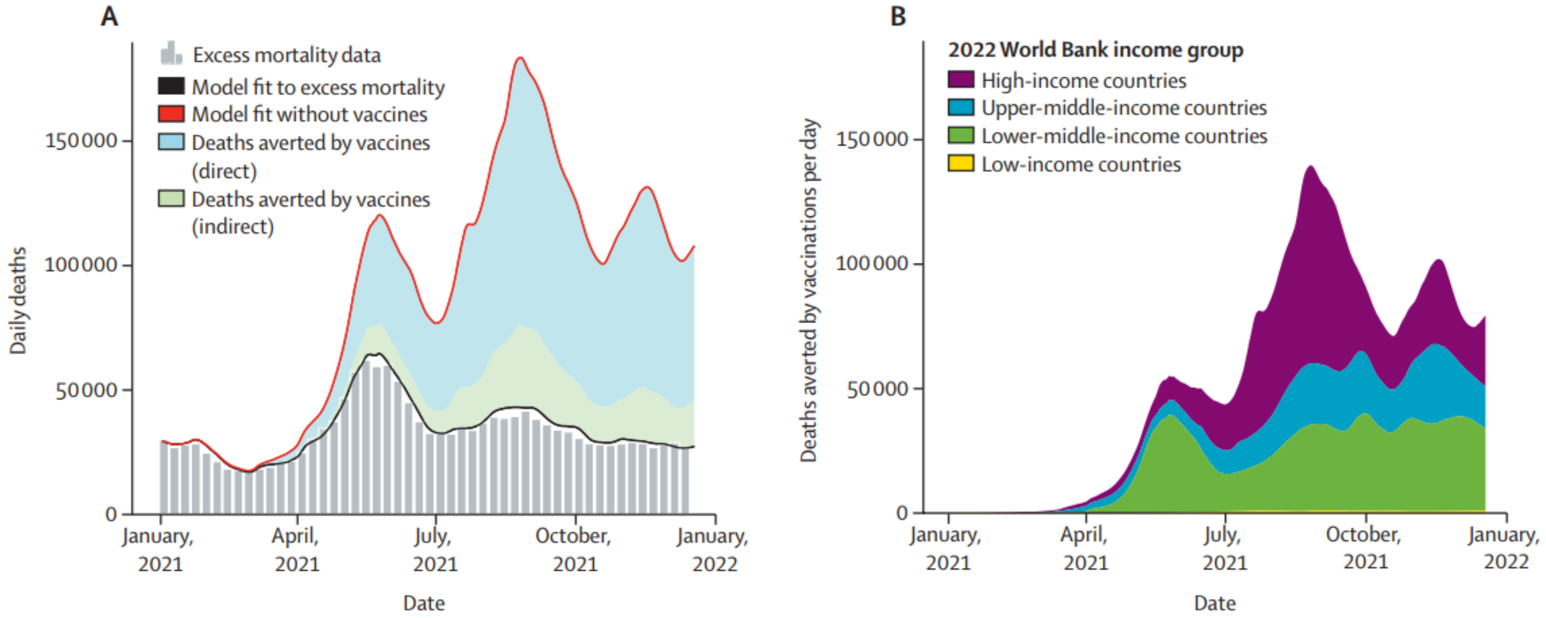
https://www.economist.com/graphic-detail/coronavirus-excess-deaths-estimates



Wang et al, Lancet 2022

Global impact of vaccines

- Estimated 20m deaths averted under simple counterfactual



	Total excess deaths	Estimated deaths averted by vaccinations		
		Total	Per 10 000 people	Per 10 000 vaccines
Worldwide	17 990 000 (17 610 000–18 530 000)	19 810 000 (19 130 000–20 380 000)	31·21 (30·14–32·1)	35·68 (34·47–36·71)
World Bank income group				
High-income countries	2 503 000 (2 412 000–2 609 000)	8 004 000 (7 644 000–8 438 000)	66·18 (63·20–69·77)	46·14 (44·07–48·64)
Upper-middle-income countries	4 717 000 (4 611 000–4 827 000)	4 230 000 (4 051 000–4 384 000)	36·97 (35·40–38·31)	33·71 (32·28–34·94)
Lower-middle-income countries	9 688 000 (9 329 000–10 170 000)	7 401 000 (6 841 000–7 655 000)	22·23 (20·55–23·00)	29·69 (27·44–30·71)
Low-income countries	1 087 000 (1 068 000–1 106 000)	180 300 (171 400–188 900)	2·711 (2·576–2·840)	26·23 (24·93–27·48)

Deaths averted are presented as medians with 95% credible intervals, with values also presented per 10 000 total population and per 10 000 vaccinations (first or second dose). Total deaths are all modelled deaths in the presence of vaccinations when fitted to excess mortality from the start of the pandemic up to Dec 8, 2021.

Table 2: **Estimated deaths averted in the first year of COVID-19 vaccinations worldwide based on fits to excess mortality**

Watson et al., Lancet ID, 2022

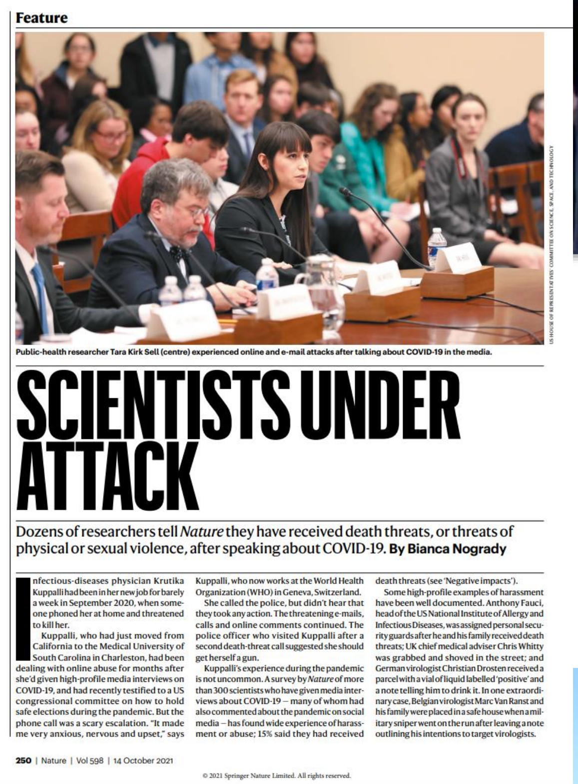
Lessons for future crisis management

- 2020 response rooted in the experience of earlier crises
- In UK, too much focus on single "reasonable worst case" scenarios – led to several problems in 2020
- Key issues: decision-making under uncertainty, time horizon for costs/benefits, trust in counterfactual modelling
- In future:
    - ➢ need to plan for a range of scenarios
    - ➢ generate policy playbooks for each
    - ➢ evaluate the costs of both inaction and action
    - ➢ use accumulating data to narrow down the set of compatible scenarios

PREPARING FOR EMERGENCIES

More general reflections

- COVID testing initially inadequate and misdirected
- Small differences in the timing of suppression led to large differences in deaths
- Science rapidly caught up in polarised politics
  – second wave predicted, but perhaps unavoidable
- Lack of international political coordination, but unprecedented scientific openness and collaboration
- UK punched above its weight in research, surveillance
- But mortality higher than other Northern European countries
- Analysis and modelling has played an important role



Feature

Public-health researcher Tara Kirk Sell (centre) experienced online and e-mail attacks after talking about COVID-19 in the media.

SCIENTISTS UNDER ATTACK

Dozens of researchers tell *Nature* they have received death threats, or threats of physical or sexual violence, after speaking about COVID-19. **By Bianca Nogrady**

Infectious-diseases physician Krutika Kuppalli had been in her new job for barely a week in September 2020, when someone phoned her at home and threatened to kill her.

Kuppalli, who had just moved from California to the Medical University of South Carolina in Charleston, had been dealing with online abuse for months after she'd given high-profile media interviews on COVID-19, and had recently testified to a US congressional committee on how to hold safe elections during the pandemic. But the phone call was a scary escalation. "It made me very anxious, nervous and upset," says Kuppalli, who now works at the World Health Organization (WHO) in Geneva, Switzerland.

She called the police, but didn't hear that they took any action. The threatening e-mails, calls and online comments continued. The police officer who visited Kuppalli after a second death-threat call suggested she should get herself a gun.

Kuppalli's experience during the pandemic is not uncommon. A survey by *Nature* of more than 300 scientists who have given media interviews about COVID-19 – many of whom had also commented about the pandemic on social media – has found wide experience of harassment or abuse; 15% said they had received death threats (see 'Negative impacts').

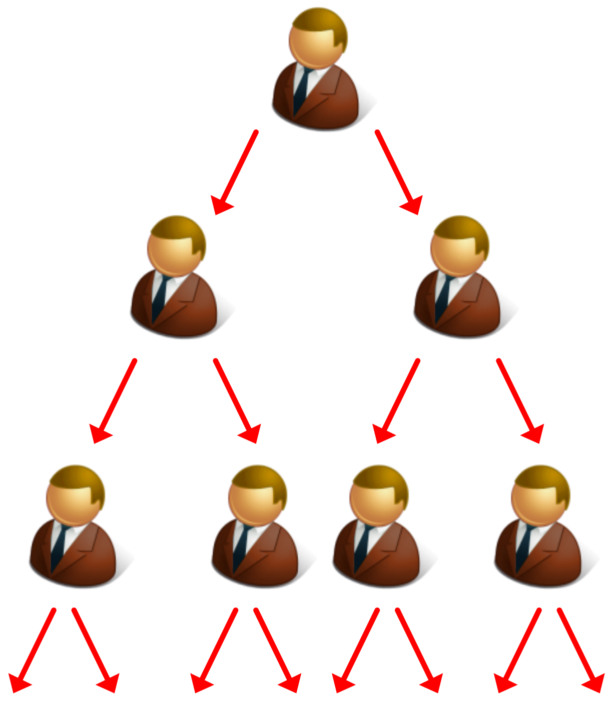
Some high-profile examples of harassment have been well documented. Anthony Fauci, head of the US National Institute of Allergy and Infectious Diseases, was assigned personal security guards after he and his family received death threats; UK chief medical adviser Chris Whitty was grabbed and shoved in the street; and German virologist Christian Drosten received a parcel with a vial of liquid labelled 'positive' and a note telling him to drink it. In one extraordinary case, Belgian virologist Marc Van Ranst and his family were placed in a safe house when a military sniper went on the run after leaving a note outlining his intentions to target virologists.

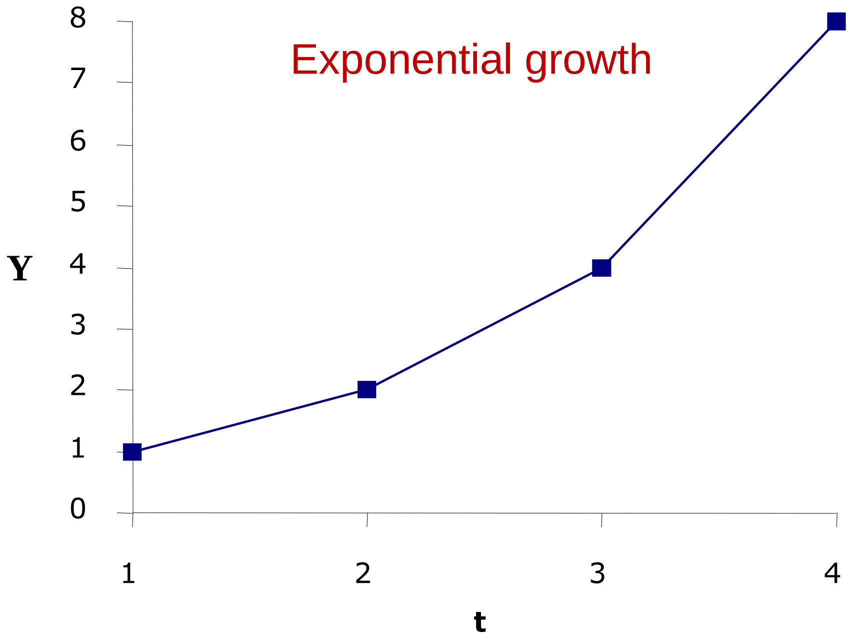
Acknowledgements

- Imperial COVID-19 response team (too many to list!)
- Including our Research Software Engineering Group
- Many collaborators from around the world
- Funding: MRC/NIHR/BMGF/DFID/ Community Jameel/Wellcome Trust

Transmissibility

Epidemic as chain reaction:



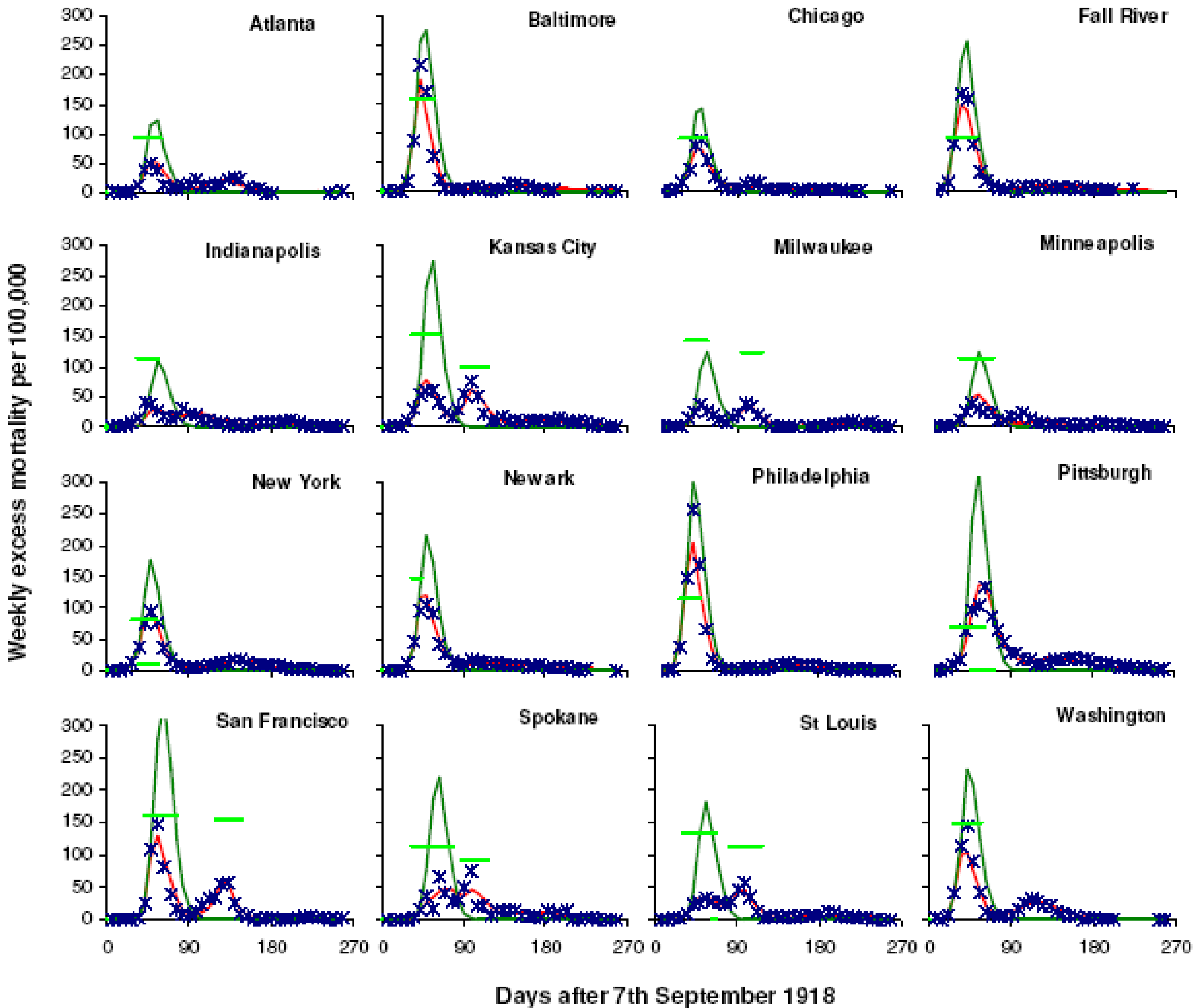


Governed by Reproduction Number **R**.

Need R_0 >1 for a large outbreak.

Interventions: 1918 in US cities

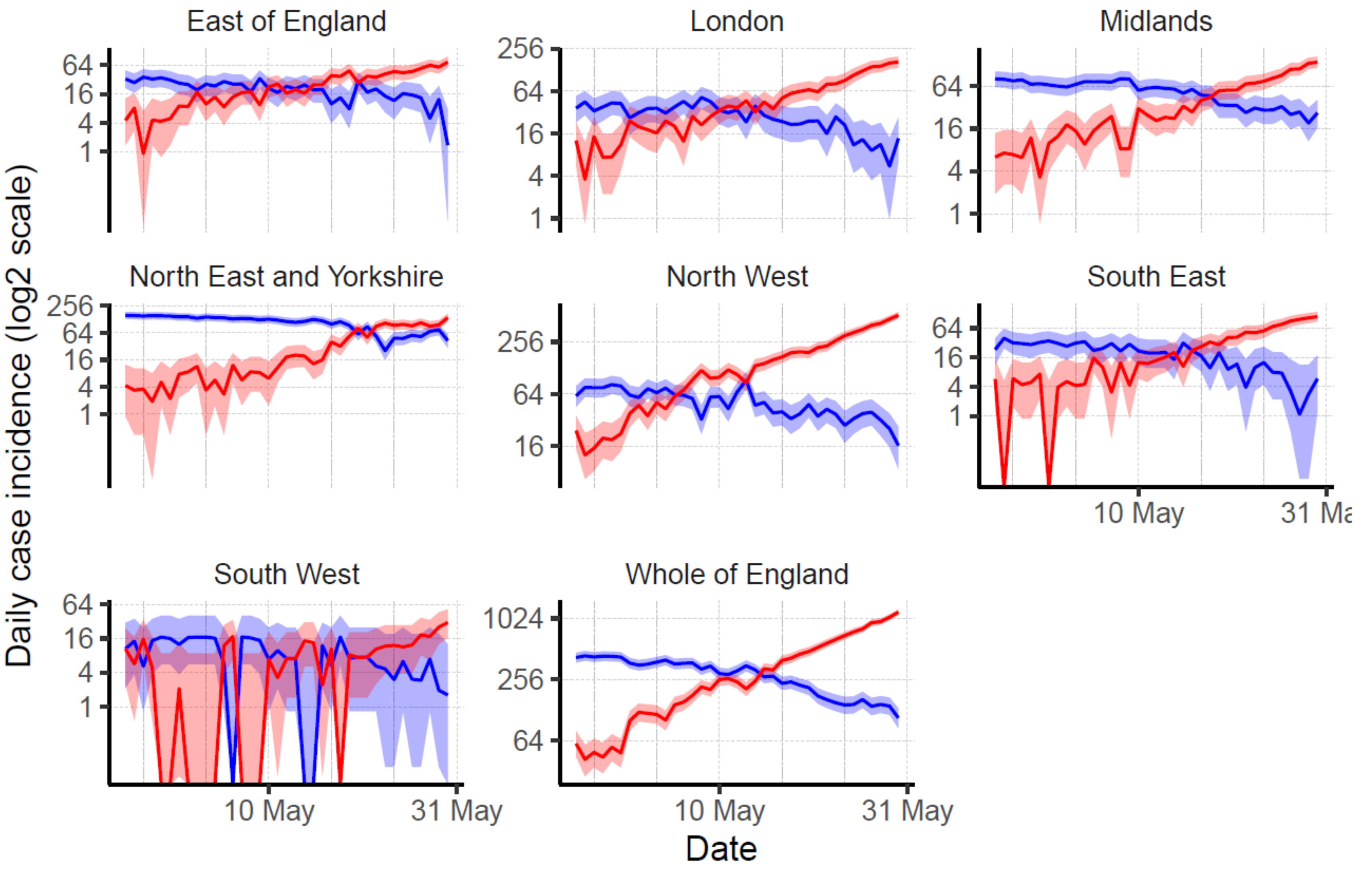
- Public health measures explain 1918 pattern well.
- Transmission cut by >50% in some cities.
- But measures often started too late, always lifted too early.
- Evidence of spontaneous behaviour change.



Bootsma and Ferguson, PNAS, 2007

April 2021: Delta (B.1.617.2) variant in UK

- Seeded into UK from India in April 2021
- Delta grew while Alpha was declining
- 40-80% more transmissible than Alpha



Ferguson et al., Report to SAGE, 2021, https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/993159/S1270_IMPERIAL_B.1.617.2.pdf

Comparing countries

- Countries should look outside their borders
- *e.g.* Netherlands: ~1/2 per-capita deaths of UK
- Denmark: ~1/2 of Netherlands
- Eastern Europe – 2nd and 3rd wave mortality much worse than Western Europe
- Final burden determined by timing of controls, vaccination coverage, demography, prevalence of comorbidities, health systems