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Center for Nonlinear Sciences
Georgia Institute of Technology

Dynamics of COVID-19: Near- and Long-Term Challenges

Joshua S. Weitz
School of Biological Sciences and School of Physics
Center for Microbial Dynamics and Infection
Quantitative Biosciences Program
Georgia Institute of Technology
Atlanta GA, USA

Technical References:
Shield Immunity: Weitz et al., medrxiv 10.1101/2020.04.01.20049767v1)
Asymptomatic transmission: Park, Cornforth, Dushoff & Weitz, Epidemics, in press (& medrxiv 2020.03.09.20033514v1)
R0 estimation: Park et al. (in review & available on medrxiv: 2020.01.30.20019877v3)
Generation intervals: Park et al., *Epidemics* 27:12 (2019)
Epidemics and behavior change: Eksin, Paarporn and Weitz *Epidemics* 27: 96-105 (2019)
Speed-strength and identifiability problems: Weitz & Dushoff, *Scientific Reports* 5: 8751 (2015)

Email: jsweitz@gatech.edu
Web: http://ecotheory.biology.gatech.edu

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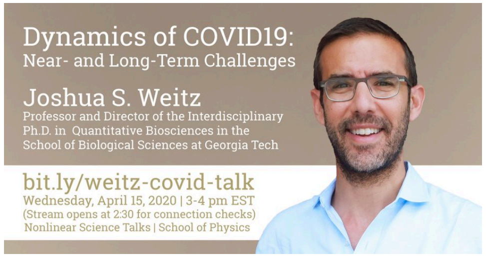
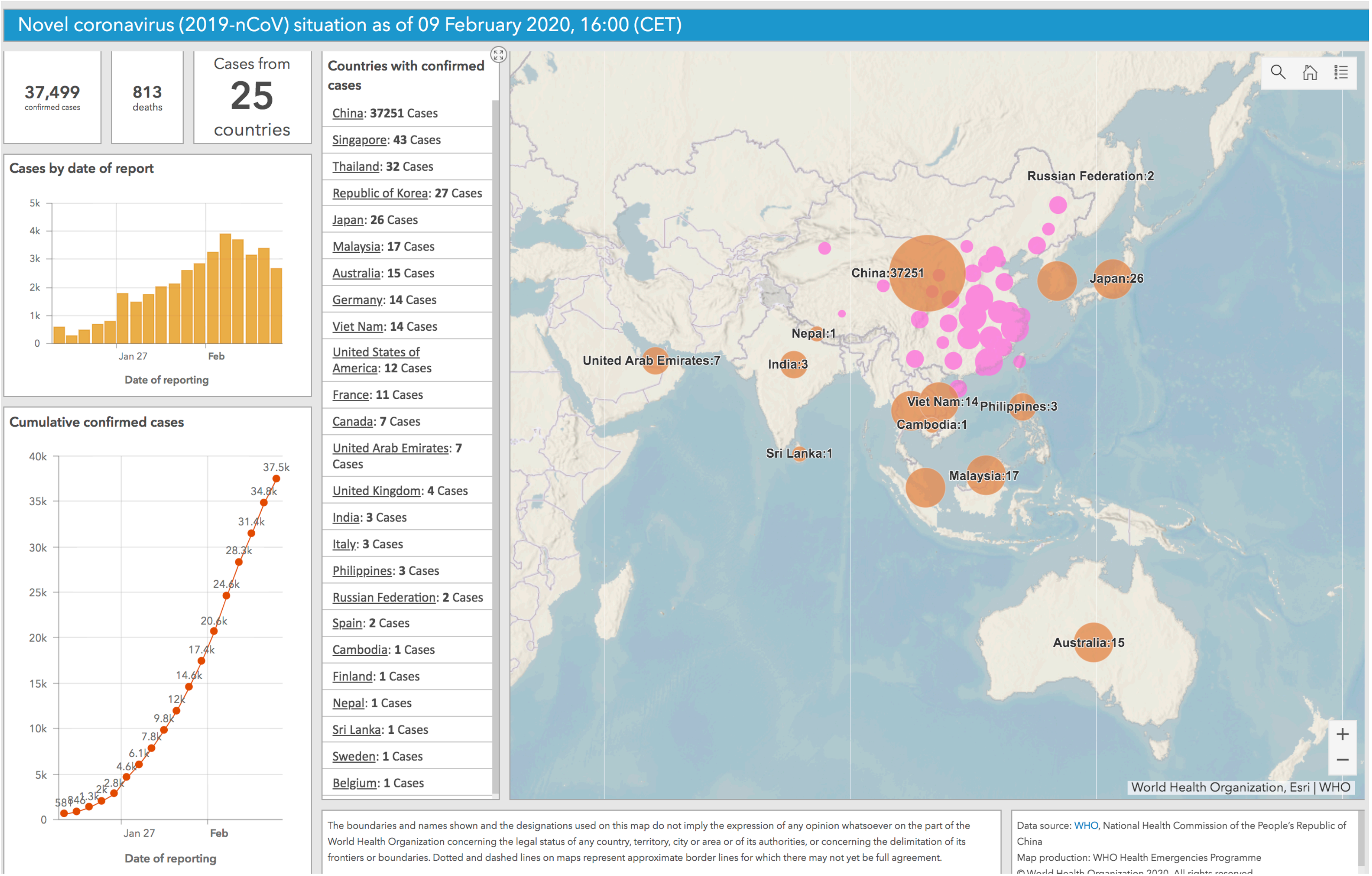
This work is the result of ongoing interdisciplinary collaborations:

Georgia Tech Team	Collaborators
Ashley Coenen	Clio Andris, GT
Dr. Stephen Beckett	Daniel Cornforth, GT
Dr. David Demory	Jonathan Dushoff, McMaster
Marian Dominguez-Mirazo	Ceyhun Eksin, Texas A&M
Dr. Joey Leung	Benjamin Lopman, Emory
Guanlin Li	Alicia Kraal, Emory
Andreea Magalie	Kristen Nelson, Emory
Daniel Muratore	Sang Woo Park, Princeton
Rogelio Rodriguez-Gonzalez	Yorai Wardi, GT
Dr. Adriana Sanz	
Shashwat Shivam	
Conan Zhao	

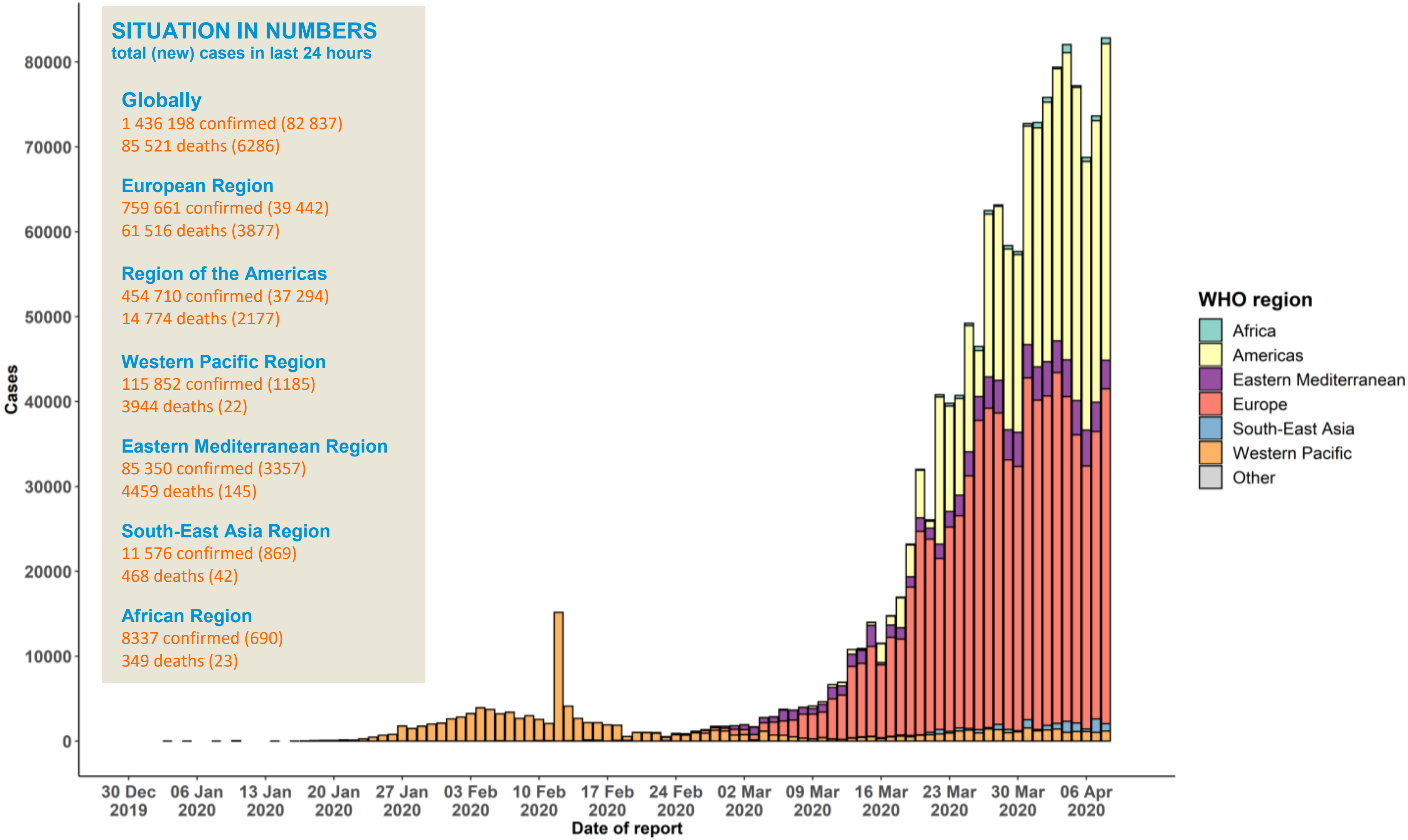


As advertised

Current status

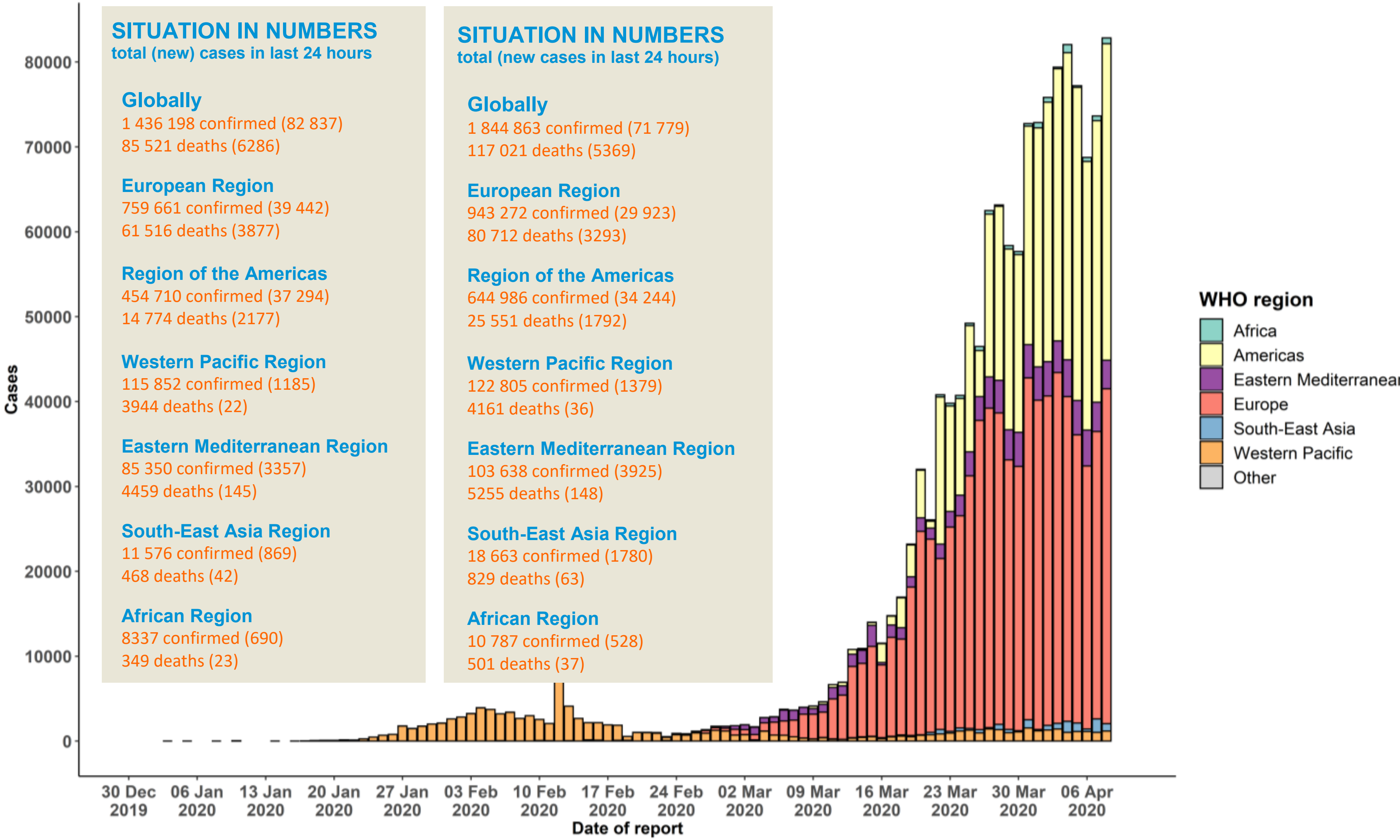


World Health Organization Situation Report
Source: WHO, Feb 9, 2020



World Health Organization Situation Report
Source: WHO, April 9, 2020 – 2 months later

April 14, 400K new cases
and 30K new deaths in 5 days



World Health Organization Situation Report
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Today's Talk

Part 1 – Dynamical Foundations of Epidemics
strength, speed, and size

Part 2 – Dynamics and Control
how we got to where we are now

Part 3 – Long-term strategies
how we might get out, in the absence of pharmaceutical interventions

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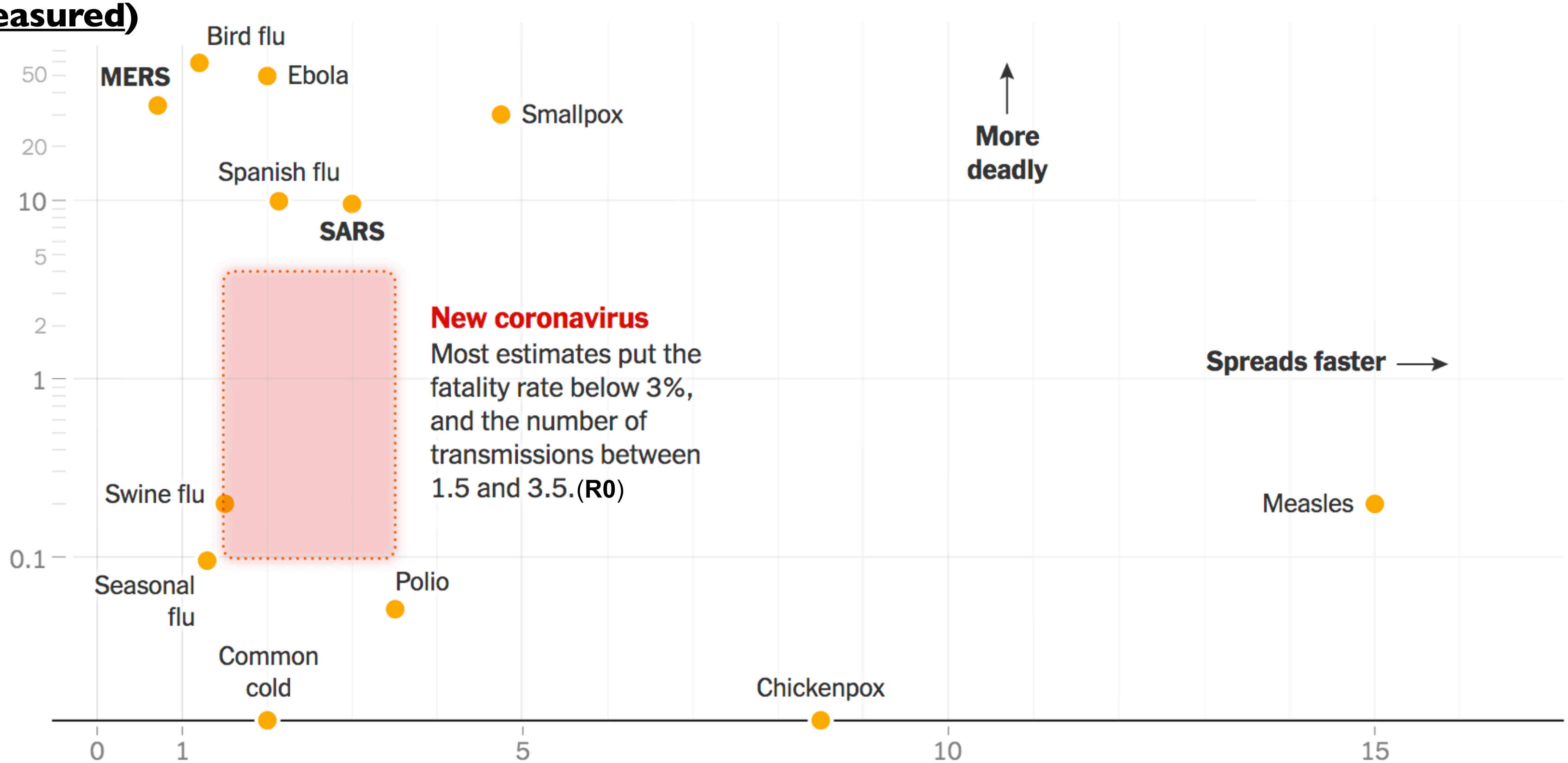
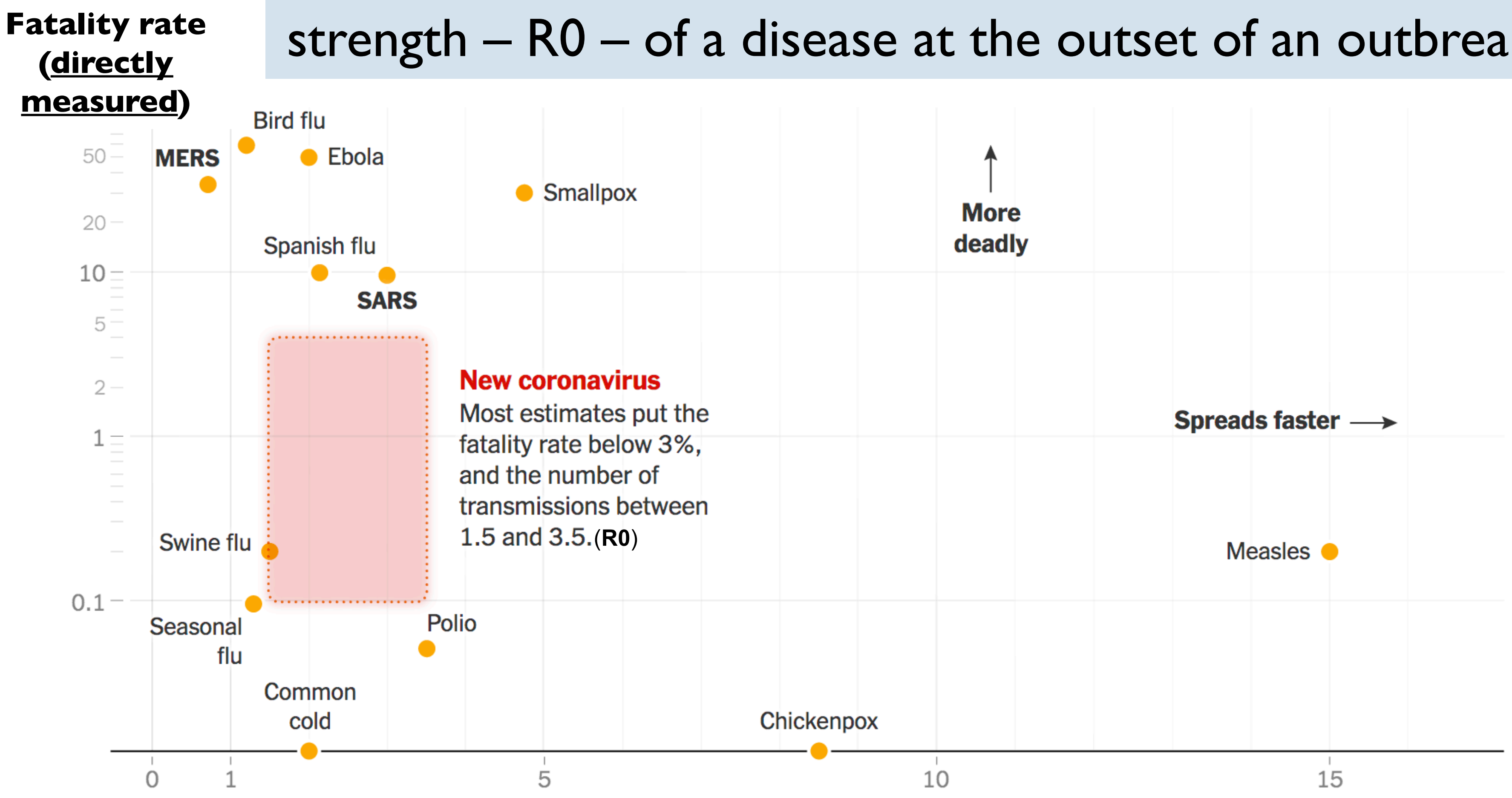
Fatality rate (<u>directly measured</u>)



Basic reproductive number, "R0"
Equal to the average number of new infections per sick person
<u>Indirectly measured</u>

Source: NY Times, Feb 7, 2020

Early Question Motivating Work:
How certain should we be about estimates of the strength – R0 – of a disease at the outset of an outbreak?



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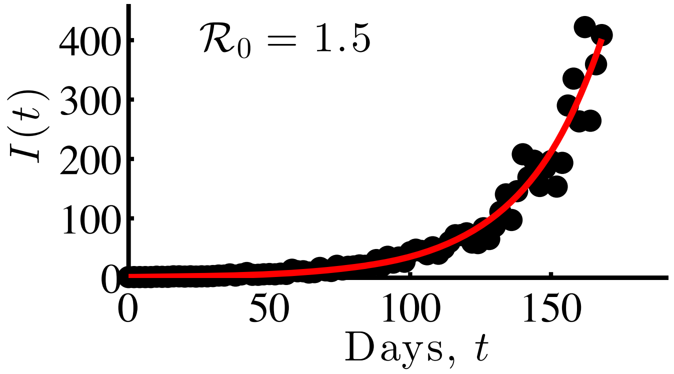
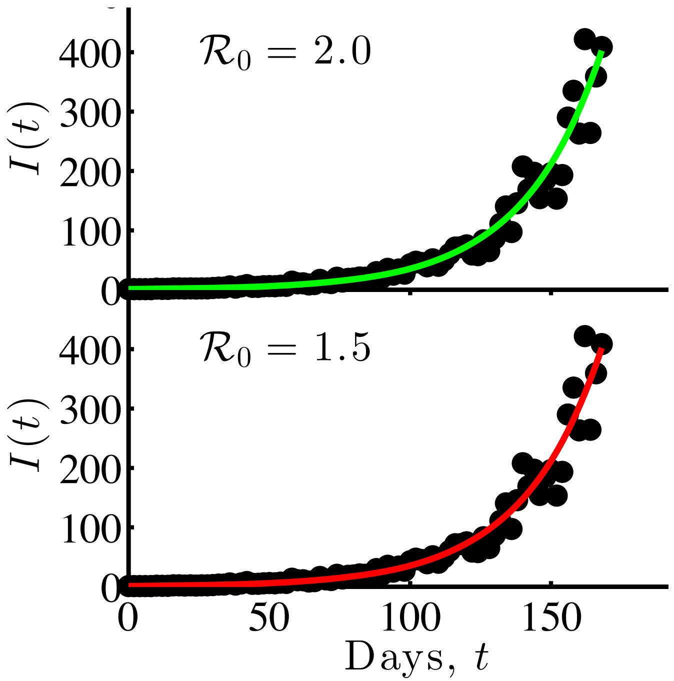
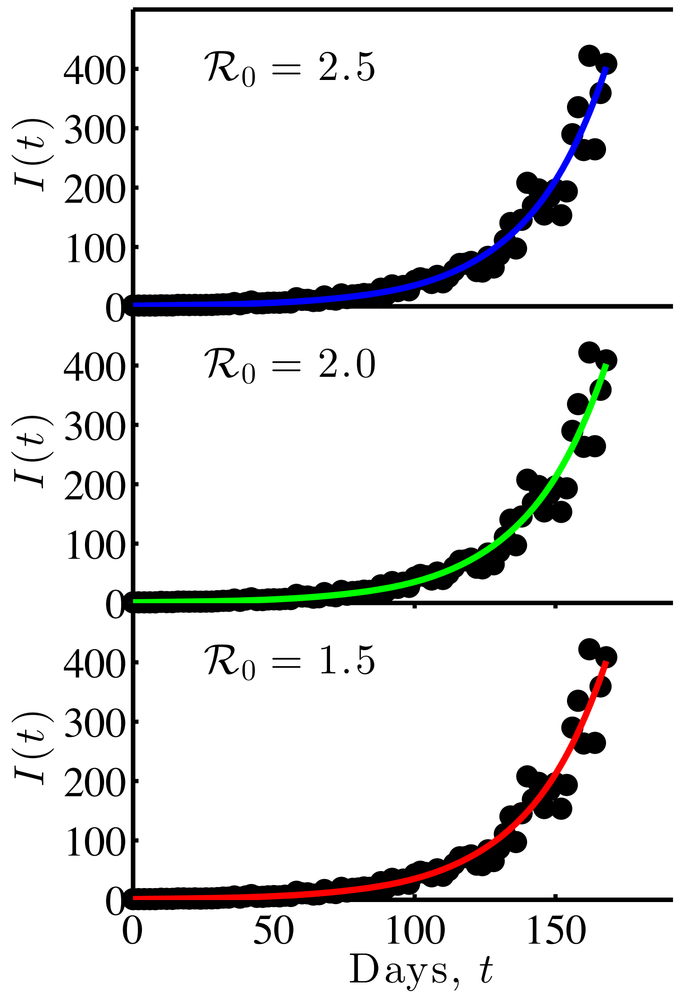


$\mathcal{R}_0 = 1.5$
400
300
200
100
0
$I(t)$
0
50
100
150
Days, t



$\mathcal{R}_0 = 2.0$
$\mathcal{R}_0 = 1.5$
$I(t)$
$I(t)$
400
300
200
100
0
400
300
200
100
0
0
50
100
150
Days, t



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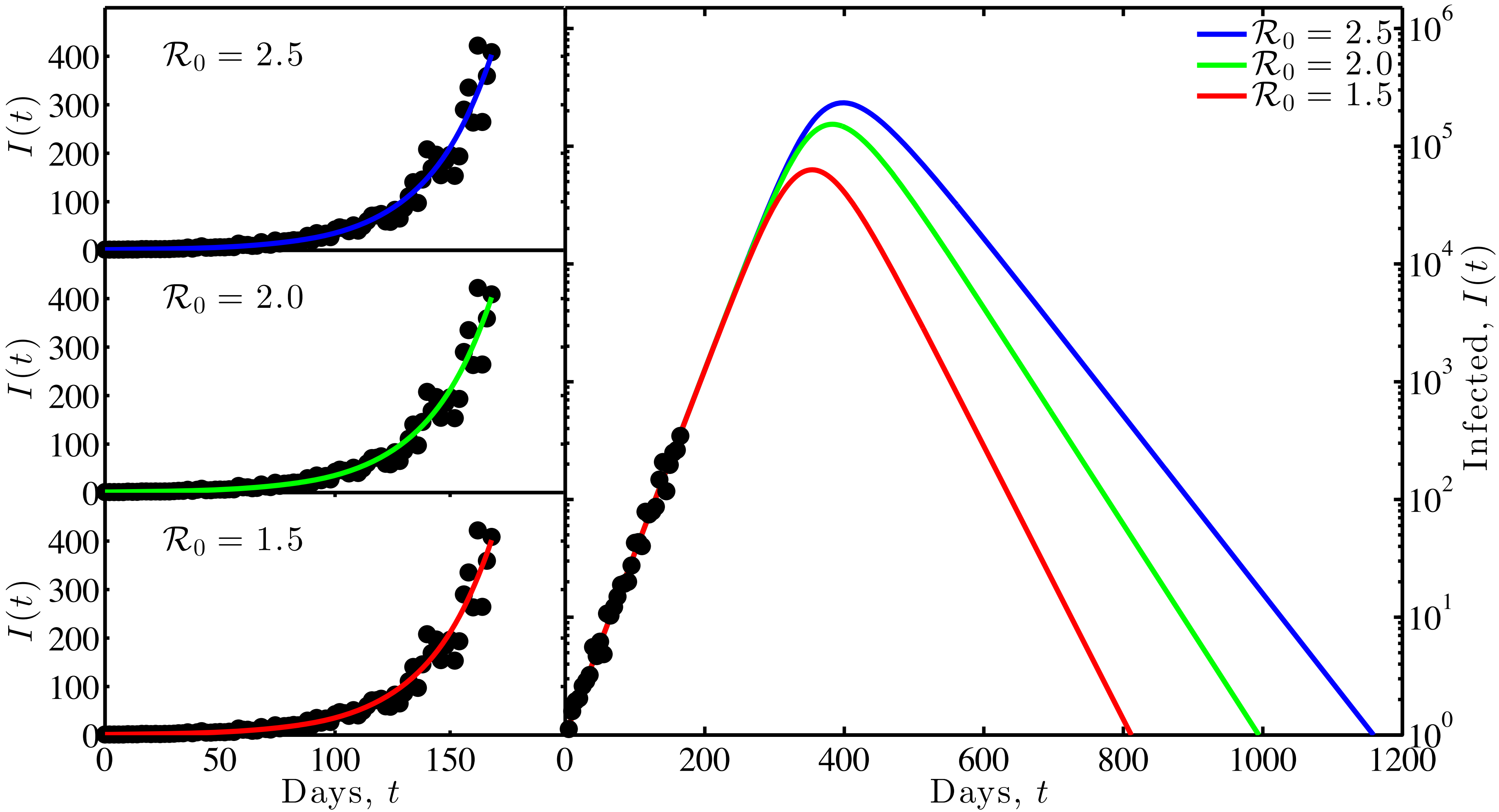
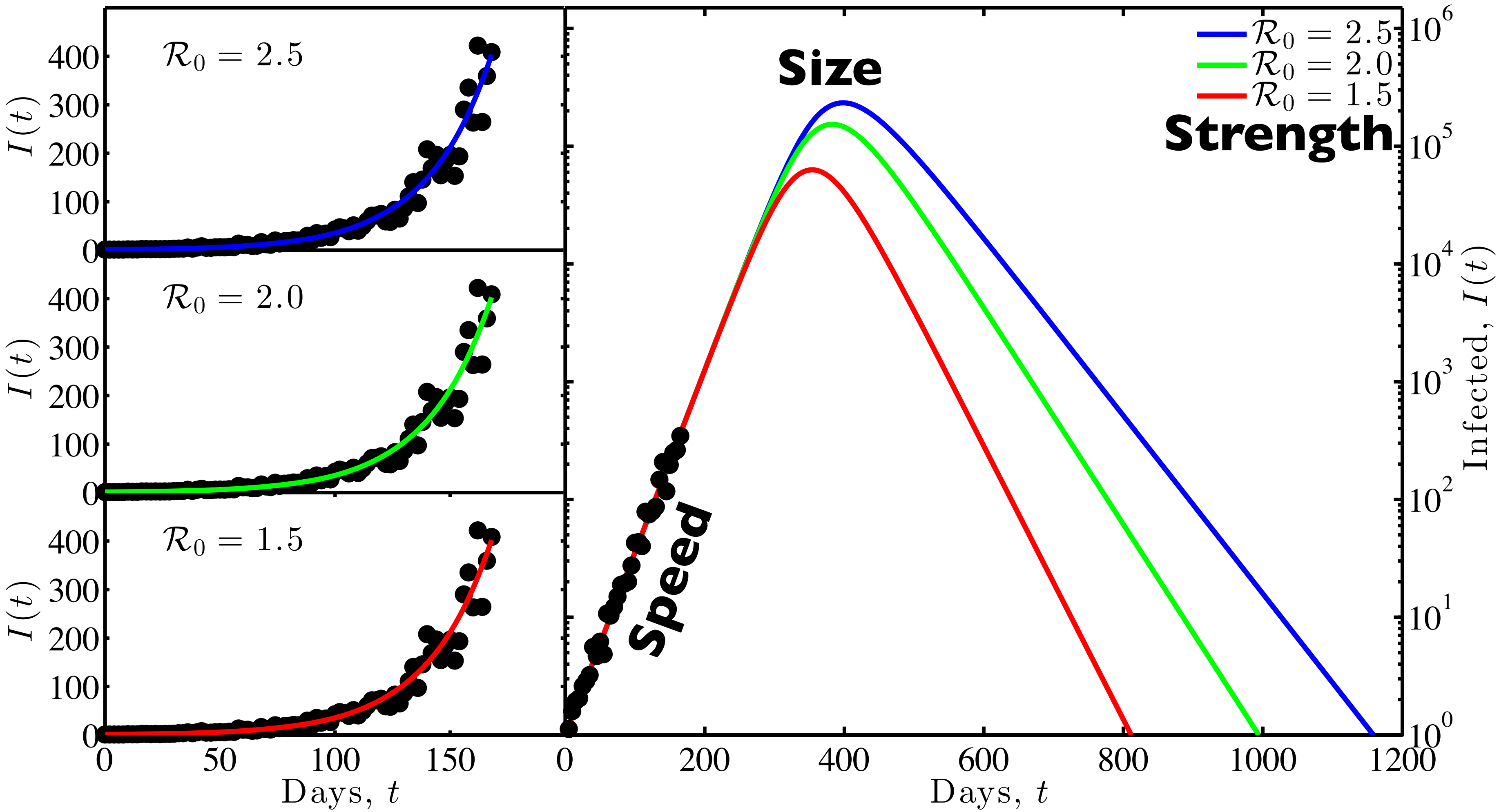
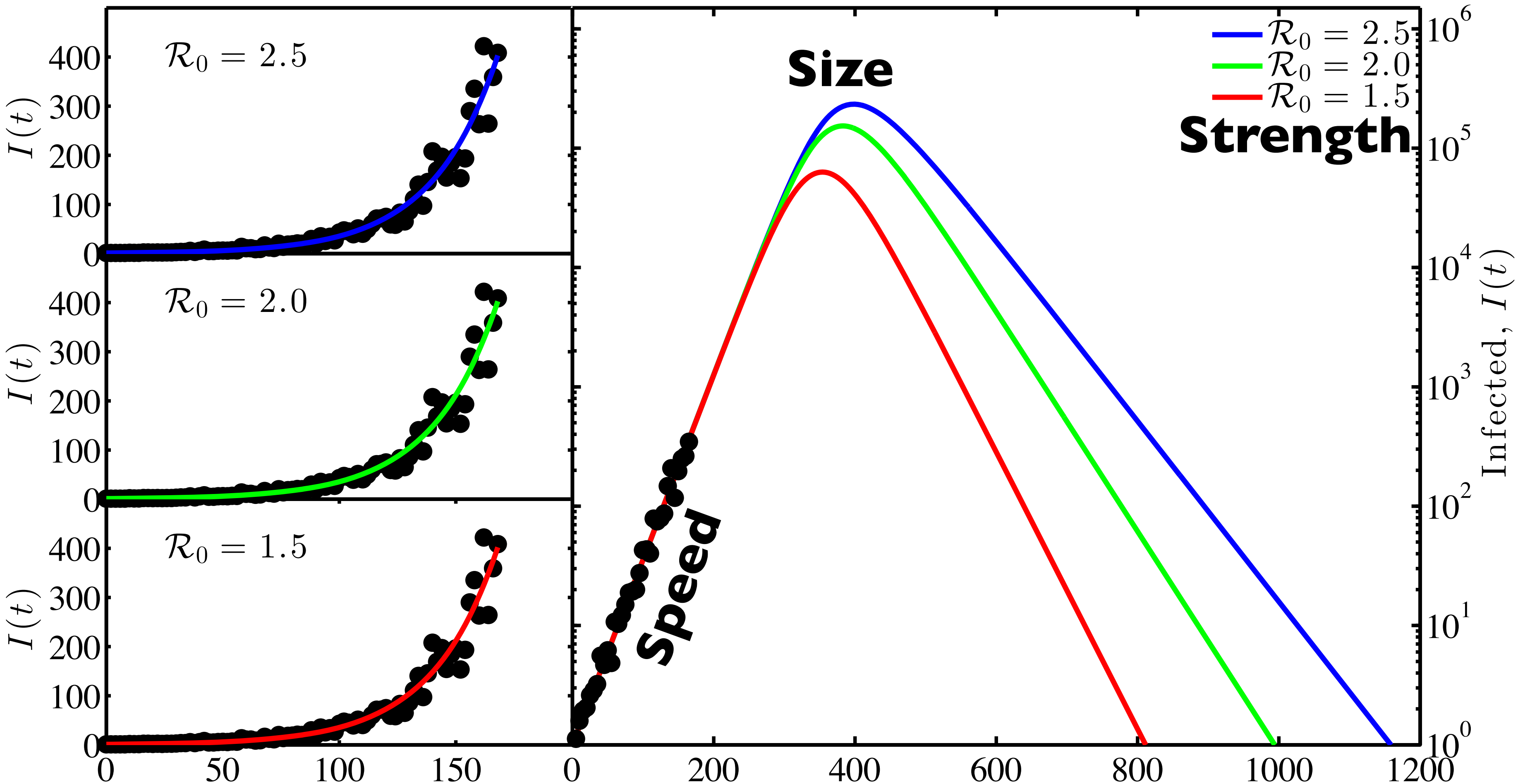


$\mathcal{R}_0 = 2.5$
$\mathcal{R}_0 = 2.0$
$\mathcal{R}_0 = 1.5$
$I(t)$
Days, t
Infected, $I(t)$

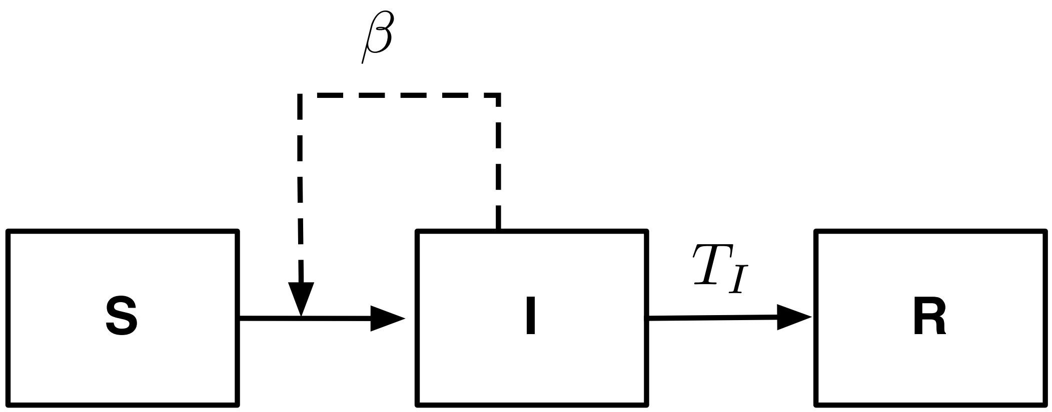


$\mathcal{R}_0 = 2.5$
$\mathcal{R}_0 = 2.0$
$\mathcal{R}_0 = 1.5$
$I(t)$
Days, t
Size
Strength
Speed
Infected, $I(t)$



Tentative conclusion: Many values of R0 can be compatible with the same observed rate of increase in cases – even if projected outbreak sizes are different.

SIR Model - Basics



Population "Classes"

S – The number of susceptible individuals

I – The number of infectious individuals

R – The number of "removed" individuals (through recovery or, possibly, death)

Mechanisms

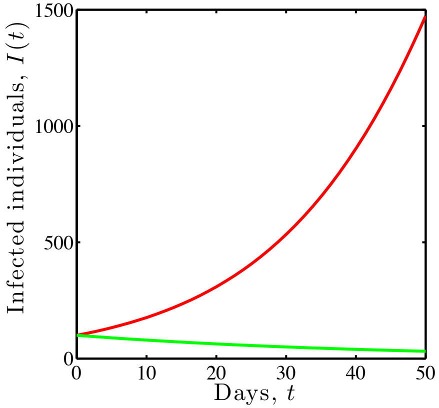
Infection: Requiring contact between a ***S*** and a ***I*** individual at rate β.

Recovery: After a period of infectiousness of average duration T_I.

SIR Model – Initial Dynamics Depend on Basic Reproductive Number, R_0

The expected number of cases, initially changes like:

$$\dot{I} = \frac{I}{T_I}\left(\mathcal{R}_0 - 1\right)$$



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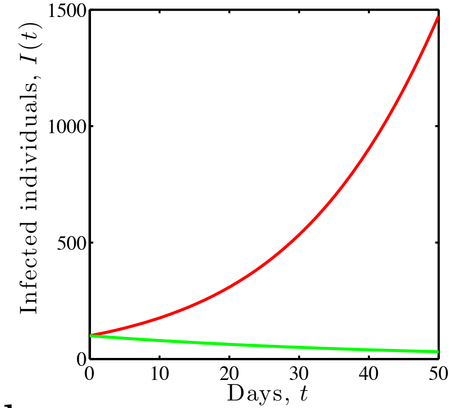

$$\dot{I} = \frac{I}{T_I}\left(\mathcal{R}_0 - 1\right)$$

where

$$\mathcal{R}_0 \equiv \overbrace{\beta}^{\text{infections per time}} \times \overbrace{T_I}^{\text{infectious period}}$$

SIR Model – Initial Dynamics Depend on Basic Reproductive Number, R_0

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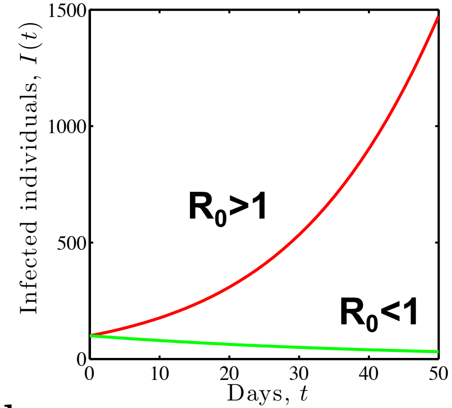

$$\dot{I} = \frac{I}{T_I}(\mathcal{R}_0 - 1)$$

where

$$\mathcal{R}_0 \equiv \overbrace{\beta}^{\text{infections per time}} \times \overbrace{T_I}^{\text{infectious period}}$$

such that

- Disease spreads whenever the average number of new cases exceeds unity, i.e: $\mathcal{R}_0 > 1$
- The increase is exponential

Estimating, R_0, for 2019-nCoV

	Basic reproductive number $\mathcal{R}_0$	
Study 1	1.5–3.5	Bedford *et al.* [4]
Study 2	2.5 (1.5–3.5)*	Imai *et al.* [5]
Study 3	2.92 (95% CI: 2.28–3.67)	Liu *et al.* [6]
Study 4	3.8 (95% CI: 3.6–4.0)	Read *et al.* [8]
Study 5	2.2 (90% CI: 1.4–3.8)	Riou and Althaus [10]
Study 6	5.47 (95% CI: 4.16–7.10)‡	Zhao *et al.* [9]
Study 7	2.0–3.1	Majumder and Mandl [7]

Many model choices:

Branching process

SEIR model (like SIR but with an asymptomatic class)

Exponential growth…

Estimating, R_0, for 2019-nCoV

	Basic reproductive number $\mathcal{R}_0$	Mean generation interval $\bar{G}$ (days)	Generation-interval dispersion κ	
Study 1	1.5–3.5	10	1	Bedford *et al.* [4]
Study 2	2.5 (1.5–3.5)*	8.4	unspecified†	Imai *et al.* [5]
Study 3	2.92 (95% CI: 2.28–3.67)	8.4	0.2	Liu *et al.* [6]
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Study 7	2.0–3.1	6–10	0	Majumder and Mandl [7]

Many model choices & latent assumptions:

Branching process

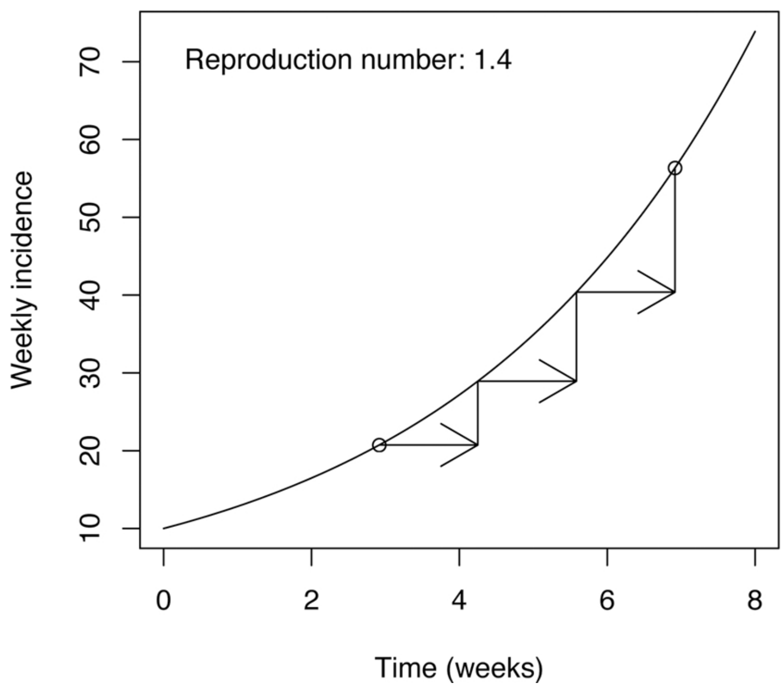
SEIR model (like SIR but with an asymptomatic class)

Exponential growth…

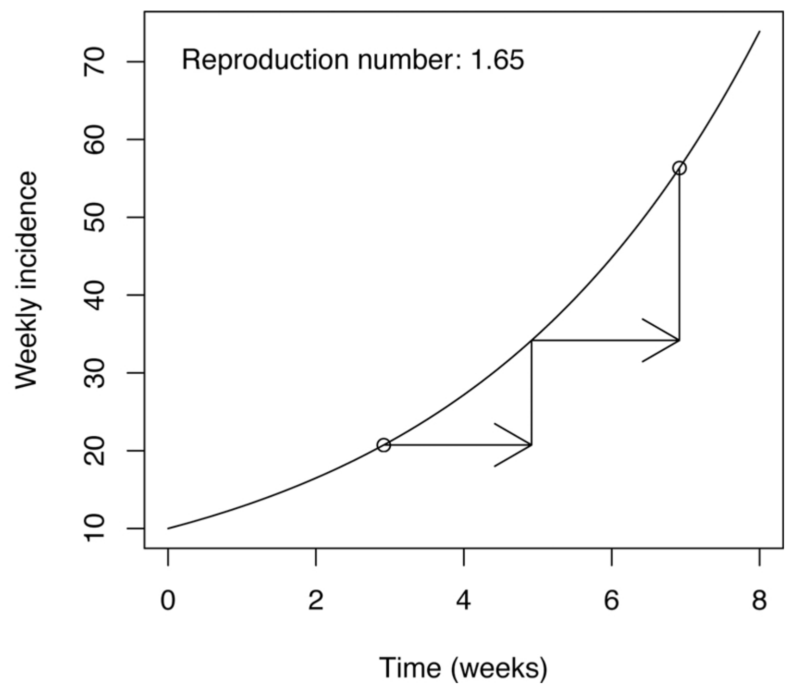
The brief answer is that speed and strength are linked.

The implicit link between speed and strength

Shorter generation intervals



Longer generation intervals



Epidemics 27 (2019) 12–18

Contents lists available at ScienceDirect

Epidemics

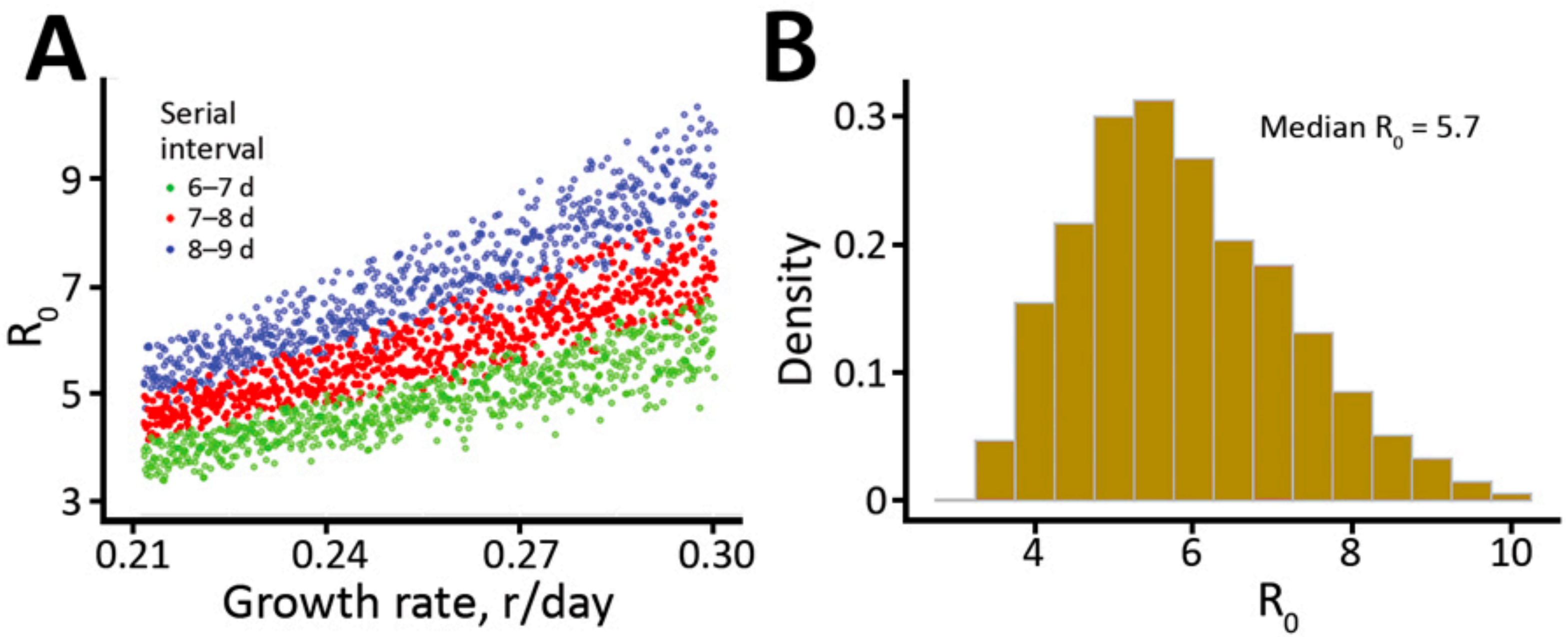
journal homepage: www.elsevier.com/locate/epidemics

ELSEVIER

A practical generation-interval-based approach to inferring the strength of epidemics from their speed

Sang Woo Park[a], David Champredon[b,c], Joshua S. Weitz[d,e], Jonathan Dushoff[b,*]

This link helps sort through putatively large R_0 claims (assumptions matter!)



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ISSN: 1080-6059
EID Journal > Volume 26 > Early Release > Main Article > Figure 5

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Volume 26, Number 7—July 2020

Research

High Contagiousness and Rapid Spread of Severe Acute Respiratory Syndrome Coronavirus 2

Steven Sanche[1], Yen Ting Lin[1], Chonggang Xu, Ethan Romero-Severson, Nick Hengartner, and Ruian Ke
Author affiliations: Los Alamos National Laboratory, Los Alamos, New Mexico, USA

Forbes

EDITORS' PICK | 107,243 views | Apr 7, 2020, 05:34pm EDT

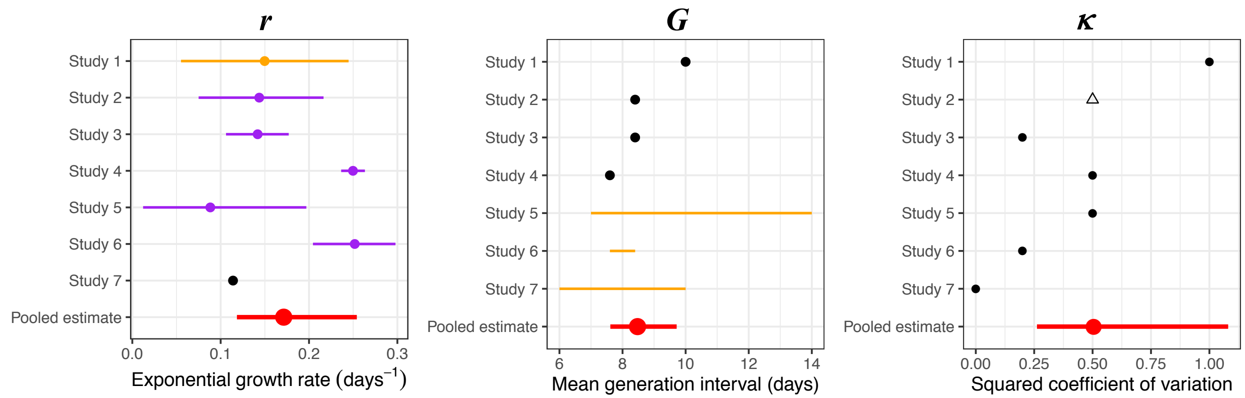
The COVID-19 Coronavirus Disease May Be Twice As Contagious As We Thought

Pooled estimates via a speed-strength relationship
(technically using generation intervals)

Sang Woo Park

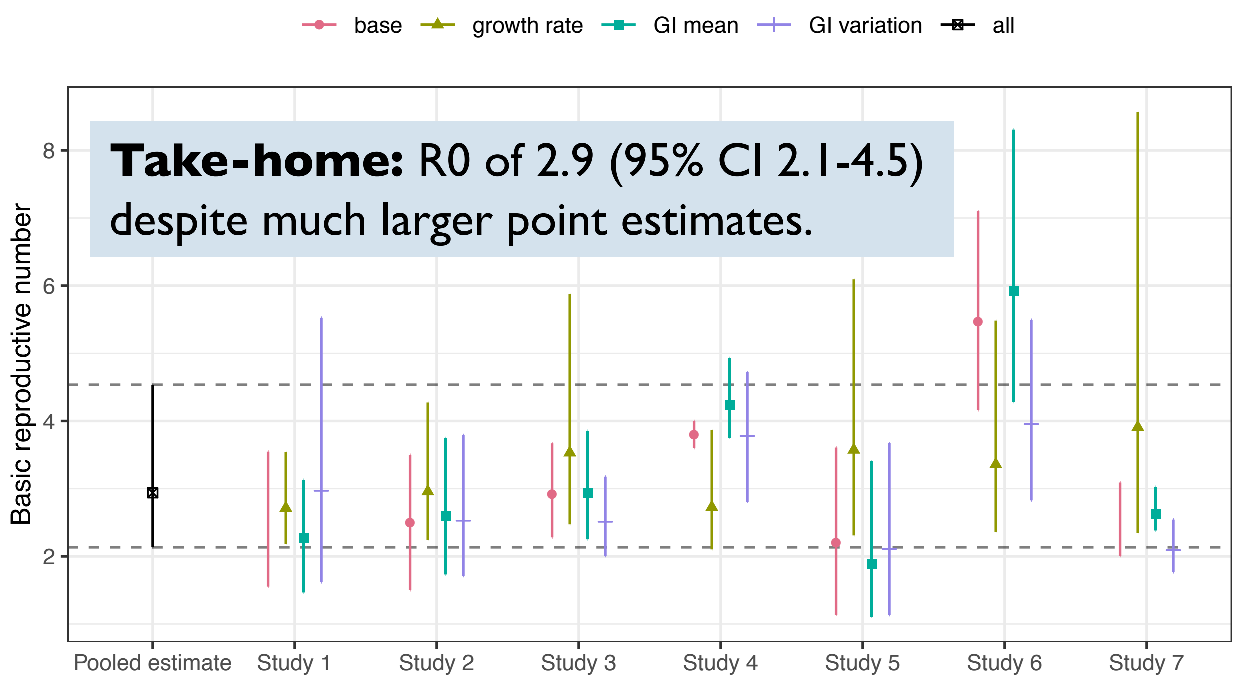
Jonathan Dushoff

Step 1: estimate latent uncertainty in 'parameters'.



Step 2: incorporate different types of uncertainty into R0 estimates by study or as part of a 'pooled' estimate (using a Bayesian multi-level model)

$$\mathcal{R}_0 = \left(1+\kappa r\bar{G}\right)^{1/\kappa}$$



Take-home: R0 of 2.9 (95% CI 2.1-4.5) despite much larger point estimates.

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Conditions for epidemic growth

$$\mathcal{R}_0 \equiv \overbrace{\beta}^{\text{infections per time}} \times \overbrace{T_I}^{\text{infectious period}}$$

Where infections per time, β, is a product of:

- Contacts by infectious individuals per unit time
- Probability of contact with a susceptible (S_0/N)
- Probability that the contact transmits the disease

Conditions for epidemic growth also suggest opportunities for **control**

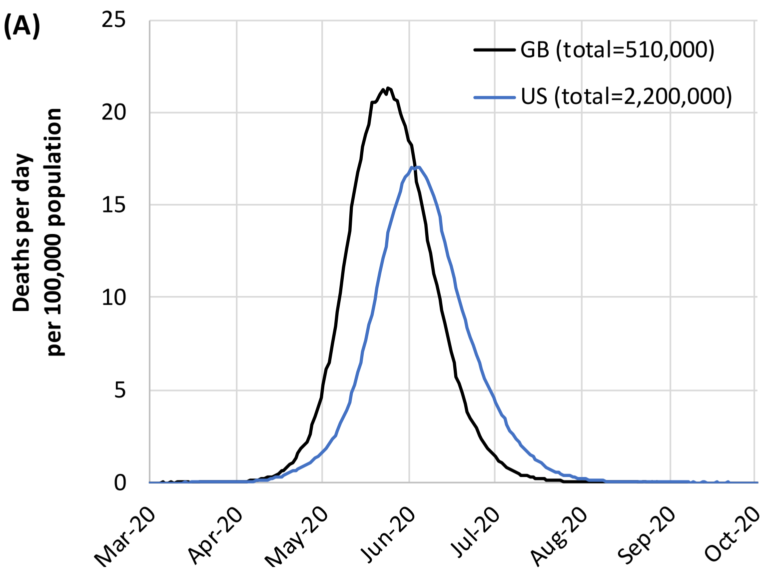
$$\mathcal{R}_0 \equiv \overbrace{\beta}^{\text{infections per time}} \times \overbrace{T_I}^{\text{infectious period}}$$

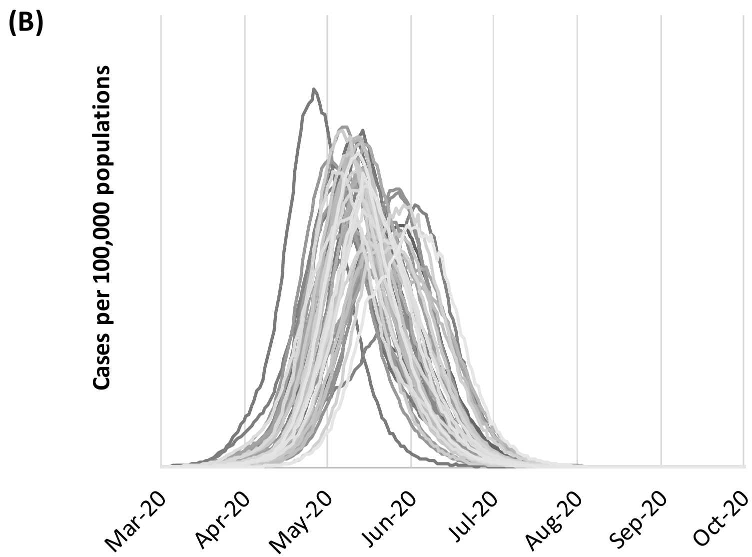
Hospitalization & treatment

Where infections per time, β, is a product of:

- Contacts by infectious individuals per unit time — **Contact tracing & targeted isolation**
- Probability of contact with a susceptible (S_0/N) — **Quarantine, travel control, closures**
- Probability that the contact transmits the disease — **Process engineering & PPE (masks)**

The Imperial Model Forecast – The Scale of the Problem





The unmitigated problem. This goes back to strength-size.

A strength of R0~2.4 implies ~80% infected (in a 'mean-field' scenario).

Population of 330M x 80% x ~0.8% IFR ~ 2M+ fatalities.

The reality of the Ebola outbreak is not reflected by model projections of high case numbers.

EPIDEMIOLOGY

Models overestimate Ebola cases

Rate of infection in Liberia seems to plateau, raising questions over the usefulness of models in an outbreak.

The reality of the Ebola outbreak is not reflected by model projections of high case numbers.

EPIDEMIOLOGY

Models overestimate Coronavirus cases

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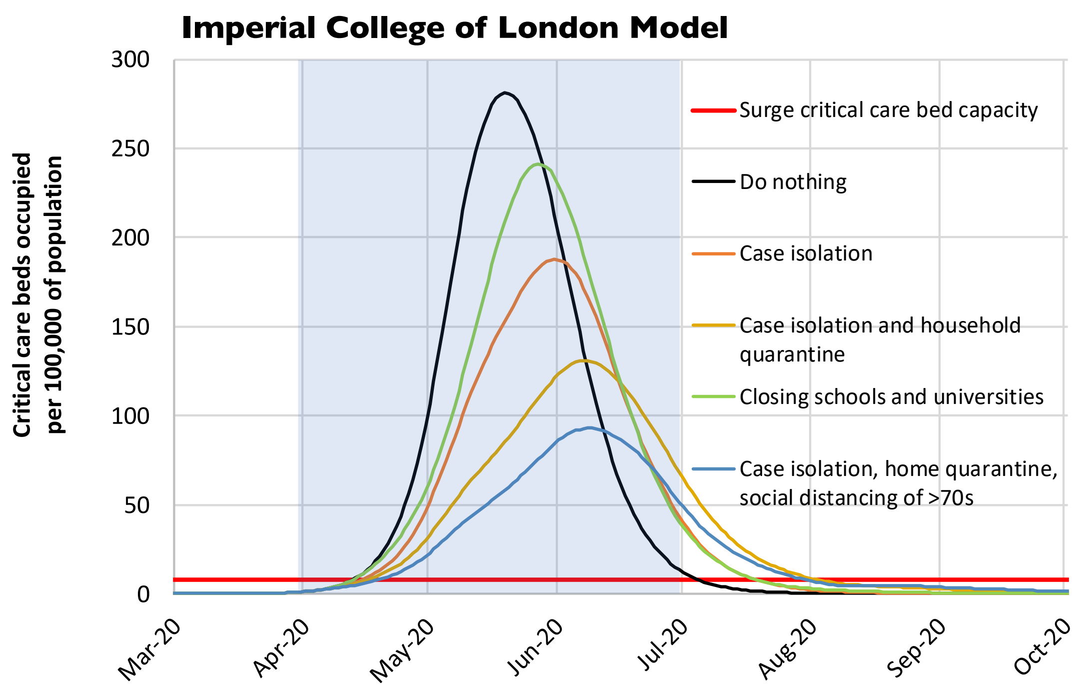

Model Purpose: to explain the need, scope, and potential outcome of **interventions.**

Different measures both reduce and ‘flatten’ the curve (i.e., reducing total burden)

TECHNOLOGY

Don't Believe the COVID-19 Models

That's not what they're for.

ZEYNEP TUFEKCI APRIL 2, 2020

TECHNOLOGY

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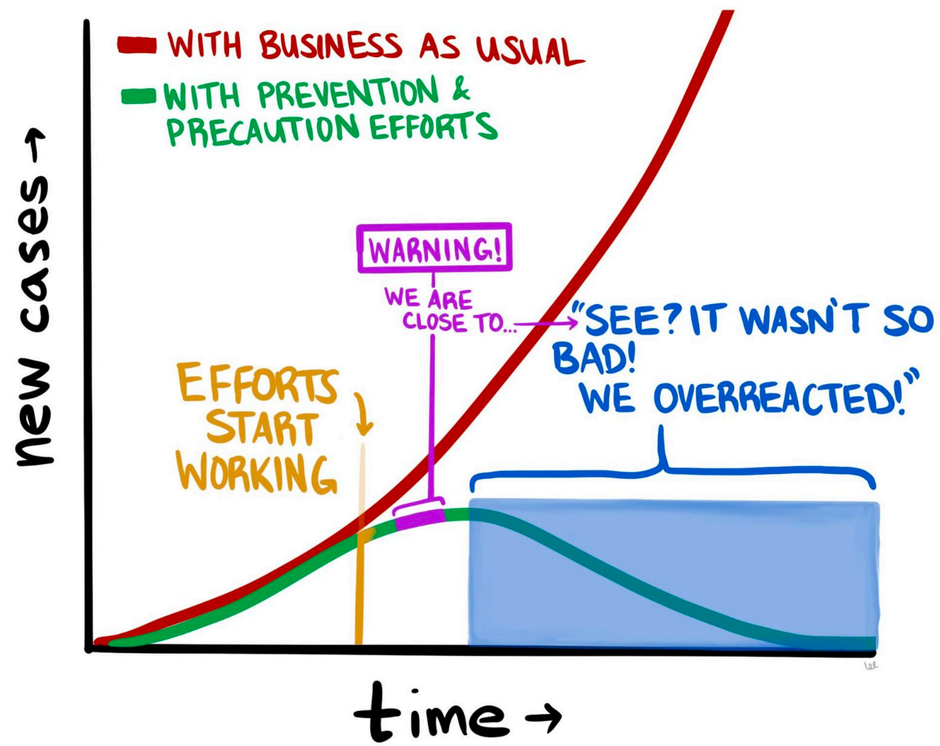
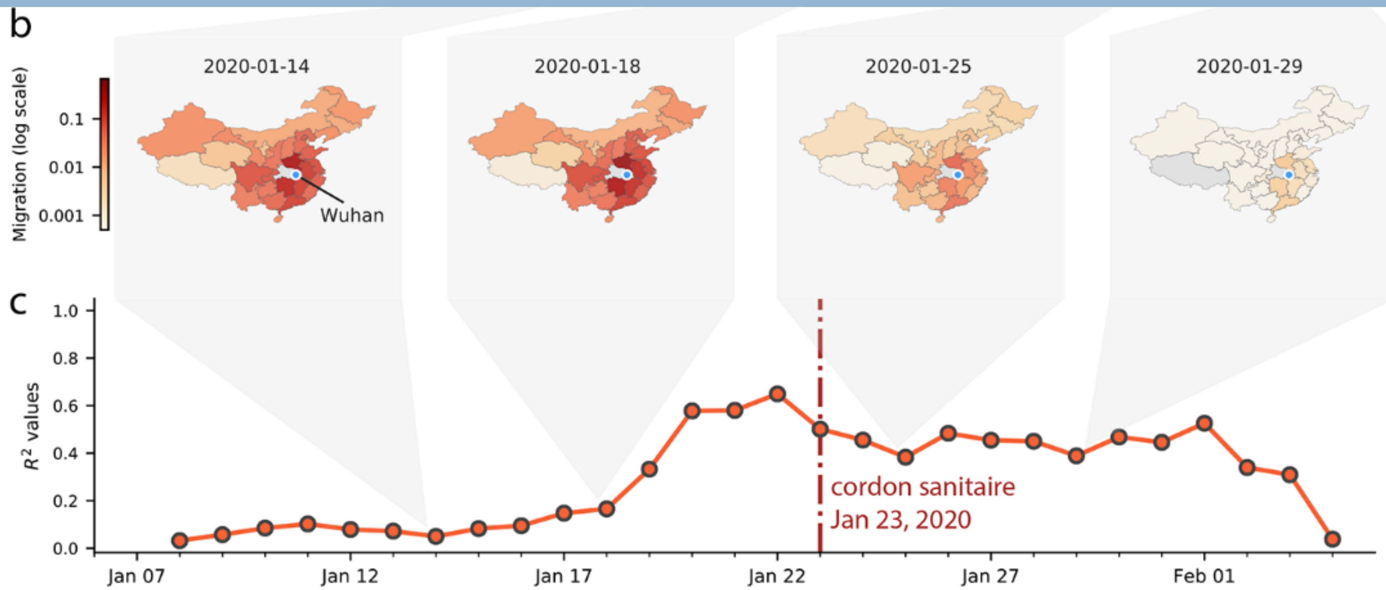
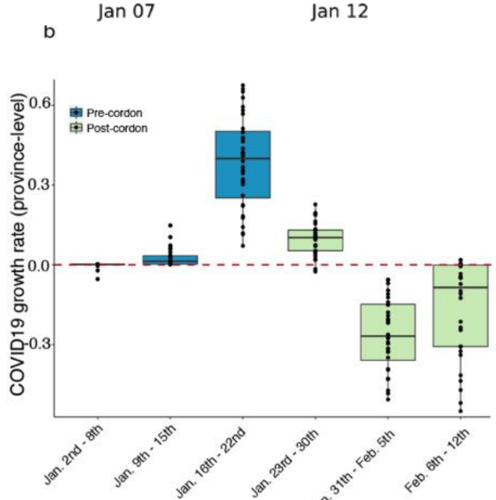


What Evidence Is There on the Impact of Interventions?

Measures of Impact of Interventions Scarpino and colleagues (Science 3/25/20)





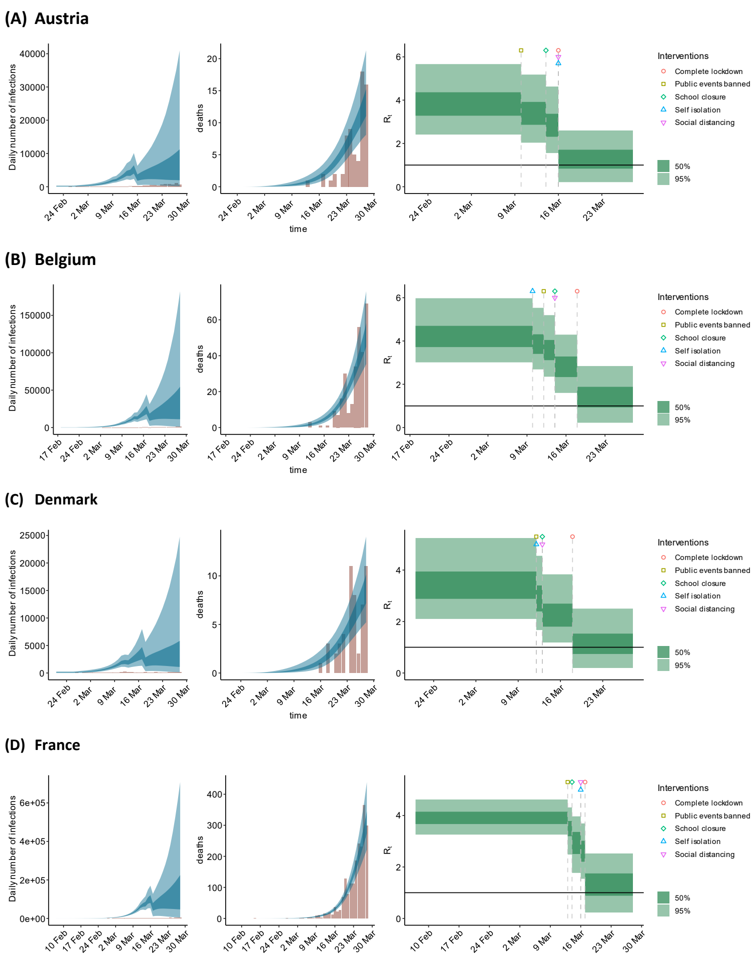
’Cordon sanitaire’ lead to rapid drop in export of cases, and control of outbreak.

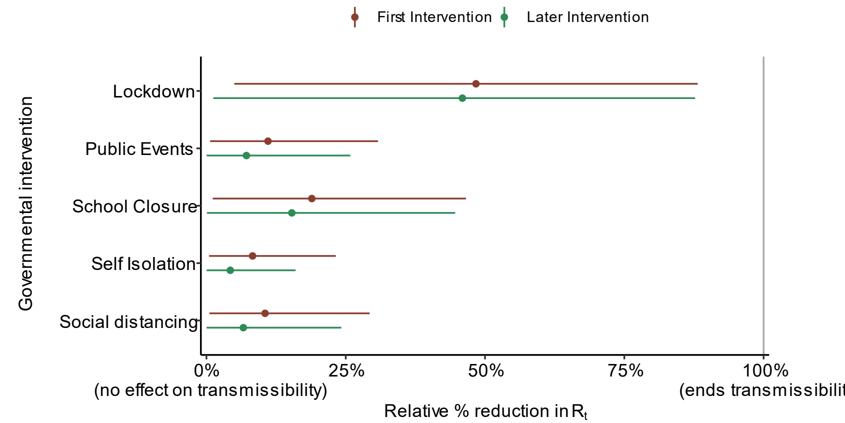
Early in an epidemic, stopping the import of cases can make a difference…

But soon – community transmission is the dominant factor.

M. U. G. Kraemer *et al.*, *Science* 10.1126/science.abb4218 (2020).

Measures of Impact of Interventions Imperial College London Report, 3/30/20



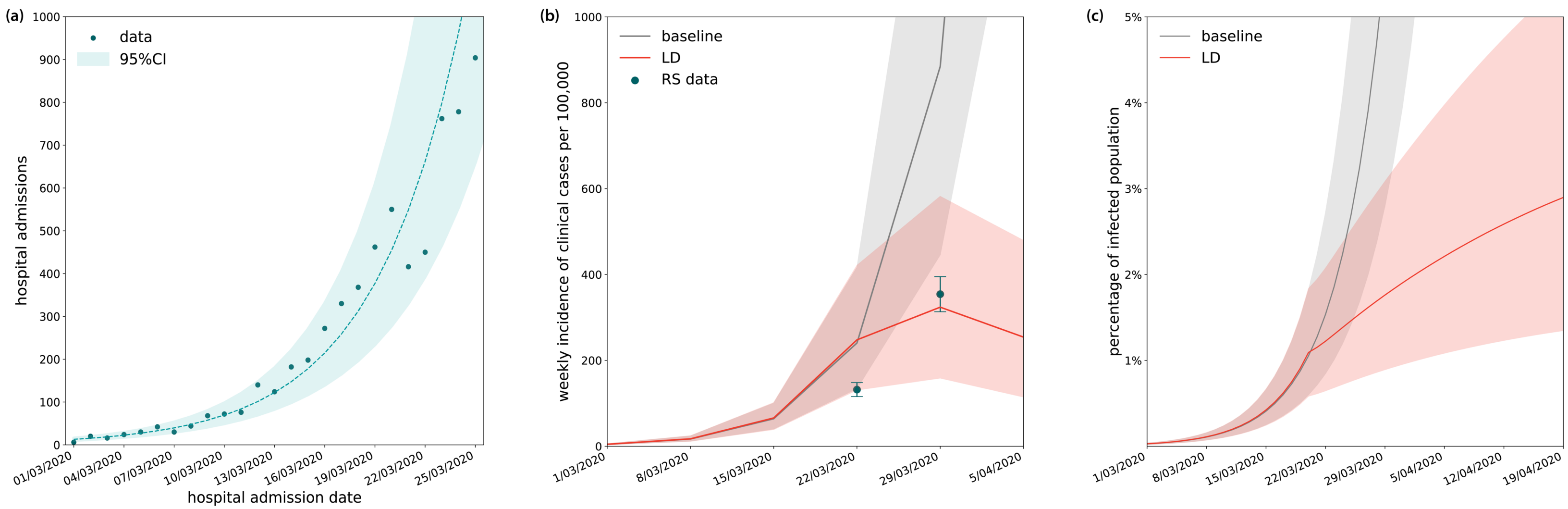


"[E]stimate that interventions across all 11 countries will have averted 59,000 deaths up to 31 March [95% credible interval 21,000-120,000].

Many more deaths will be averted through ensuring that interventions remain in place until transmission drops to low levels."

Flaxman et al.

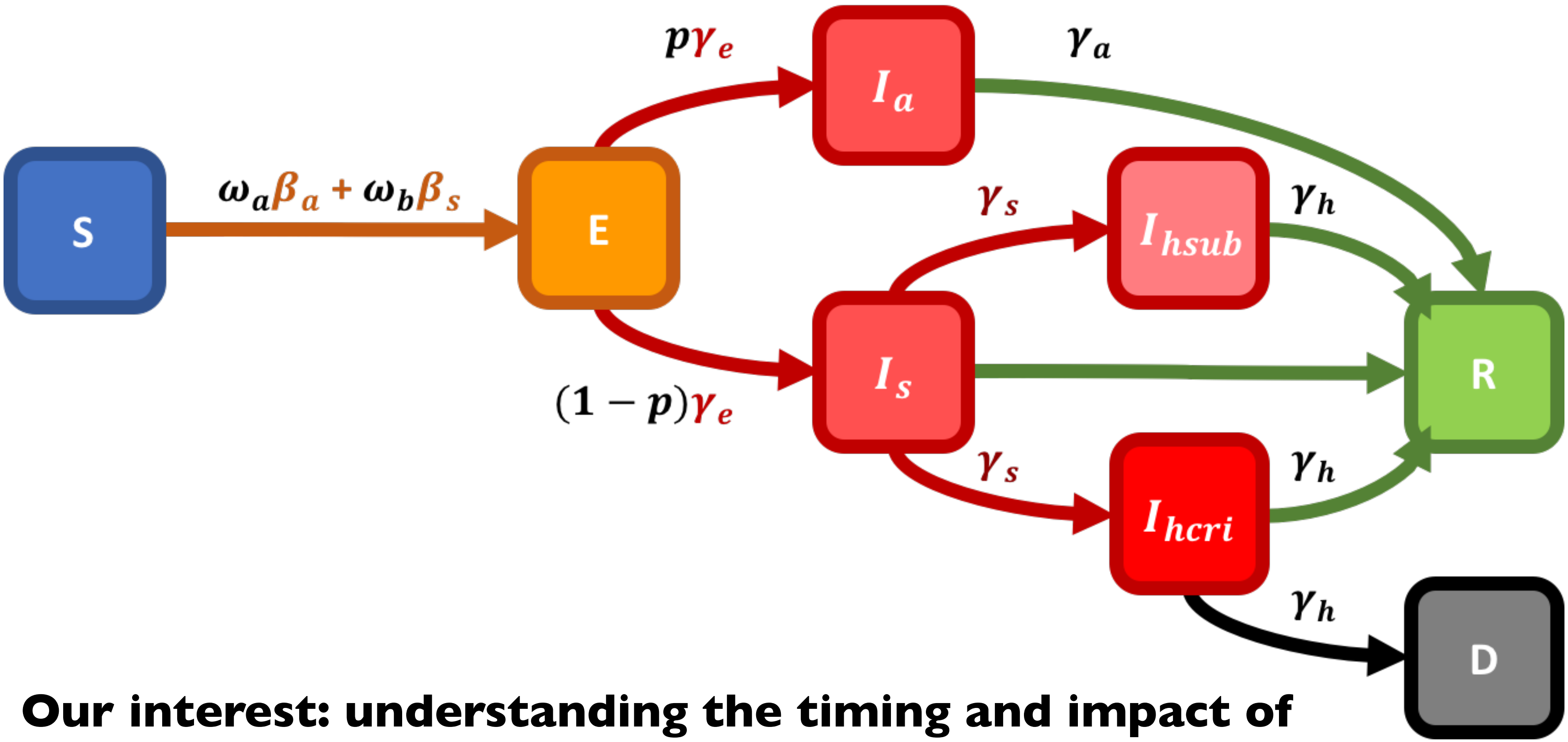
Measures of Impact of Interventions (4/12/20) INSERM – Ile De France (Vittoria Colizza & team)



Take-away:
Lockdown interventions have rapidly shifted the curve from perilous exponential-like growth to severe (2-5% infected).

Di Domenico et al. (EPICX Lab, V. Colizza)

But there are still deep uncertainties which make COVID-19 hard to predict and control



Our interest: understanding the timing and impact of asymptomatic cases on epidemic potential…

Asymptomatic cases may be a significant driver of transmission (and bias estimates of R0 and control)

Renewal equation formalism

$$\begin{aligned} \dot{S} &= -i(t) \\ i(t) &= \mathcal{R}_a S(t) \int_0^\infty i_a(t-\tau) g_a(\tau) \mathrm{d}\tau + \mathcal{R}_s S(t) \int_0^\infty i_s(t-\tau) g_s(\tau) \mathrm{d}\tau. \end{aligned}$$

and assuming exponential growth with an observed rate *r* yields:

$$\frac{1}{\mathcal{R}_0} = \int \exp(-r\tau) g(\tau) \mathrm{d}\tau.$$

Speed r : measured
Generation interval : assumed (and informed by clinical data)

Leads to an estimate of:

Strength R_0

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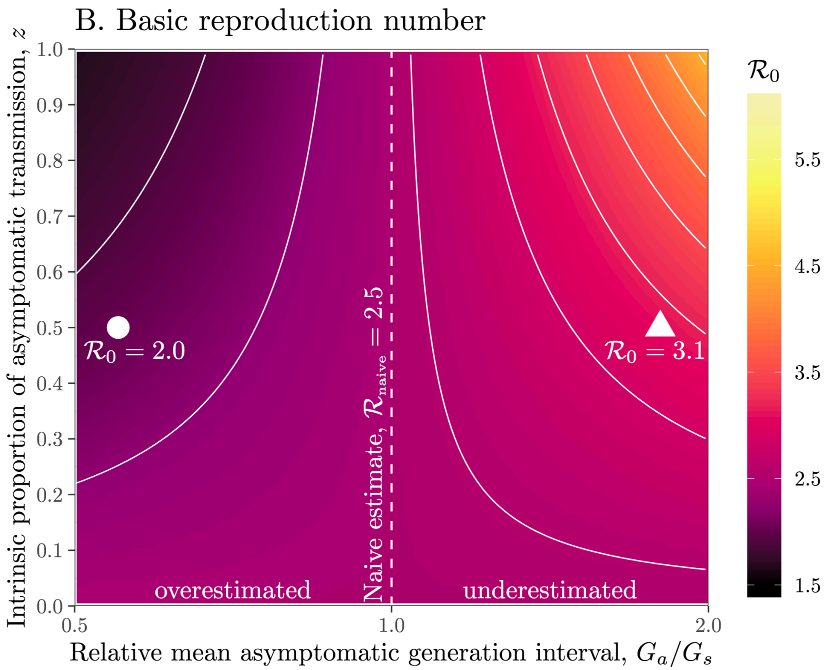

Asymptomatic cases may be a significant driver of transmission (and bias estimates of R0 and control)
Epidemics (in press) – w/SW Park, D. Cornforth & J. Dushoff

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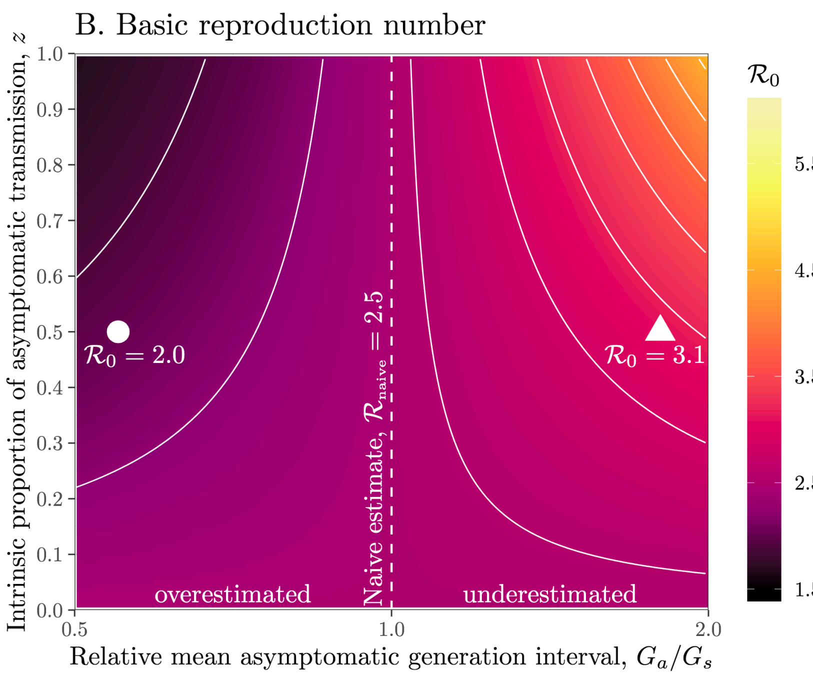


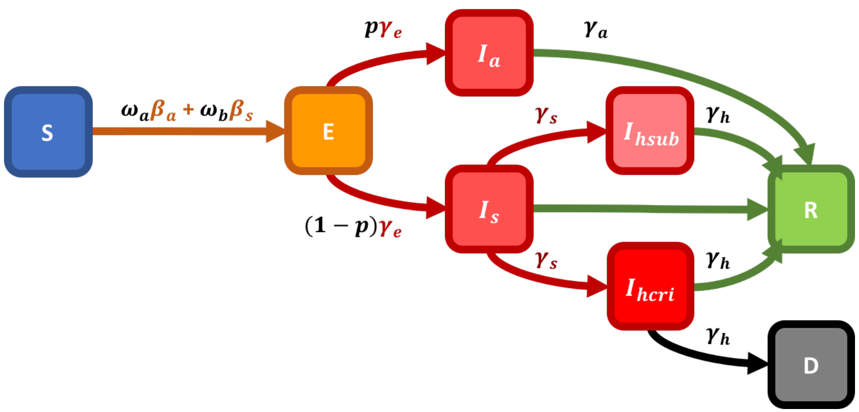
Asymptomatic transmission is a double-edged sword:

(i) Many more cases

(ii) Cases are not as bad

Measures of Impact of Interventions Georgia – Weitz Group Modeling

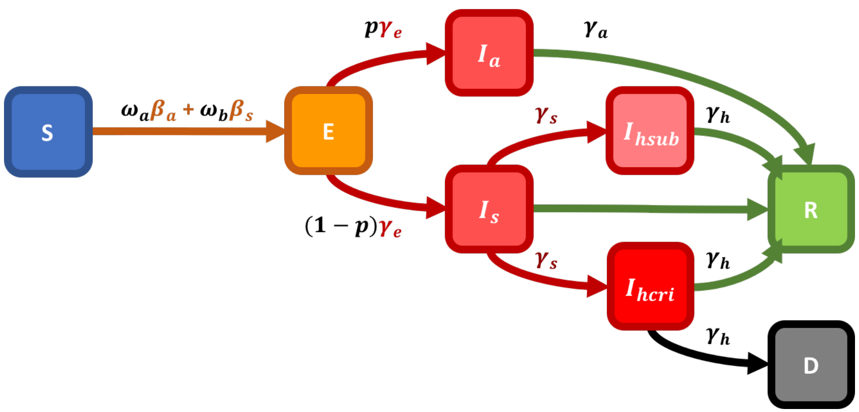
COVID-19 model
w/asymptomatic transmission



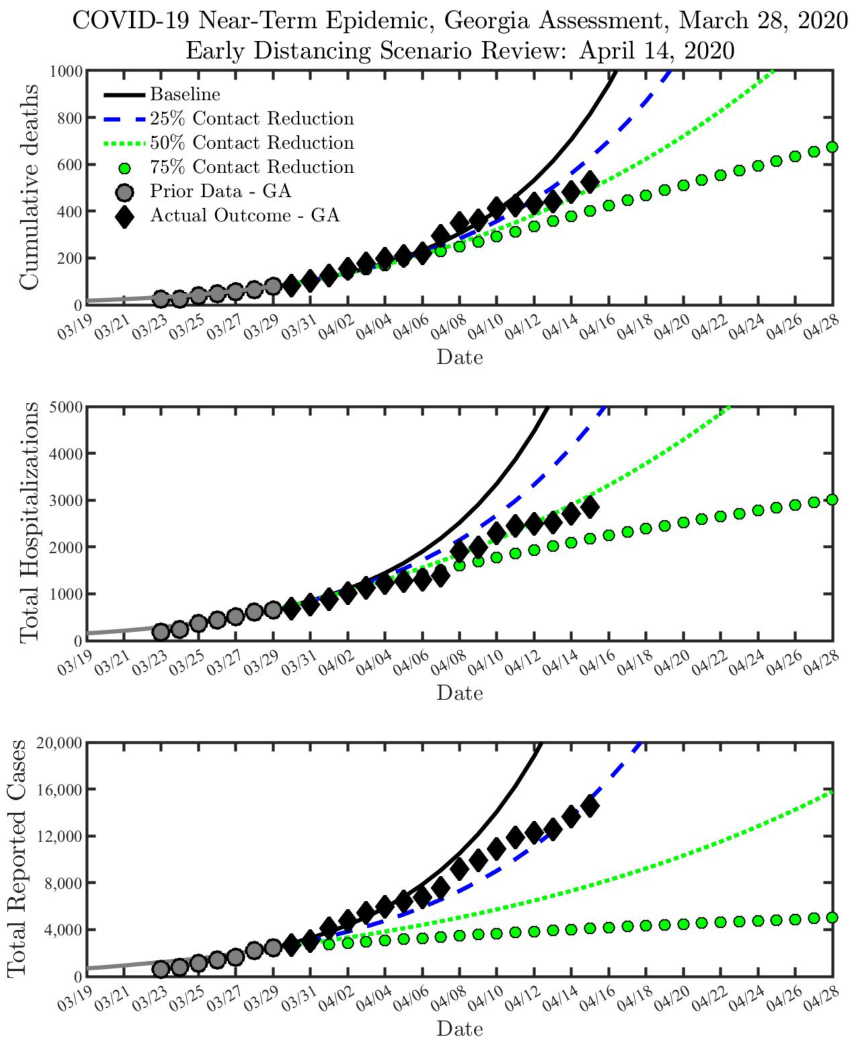
and GA age demographics
along with age-stratified risk
(via Imperial estimates).

Measures of Impact of Interventions Georgia – Weitz Group Modeling

COVID-19 model w/asymptomatic transmission

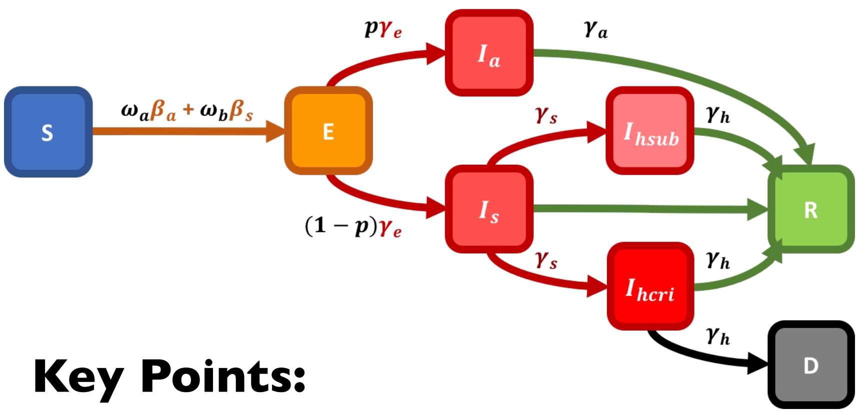


and GA age demographics along with age-stratified risk (via Imperial estimates).



Measures of Impact of Interventions Georgia – Weitz Group Modeling

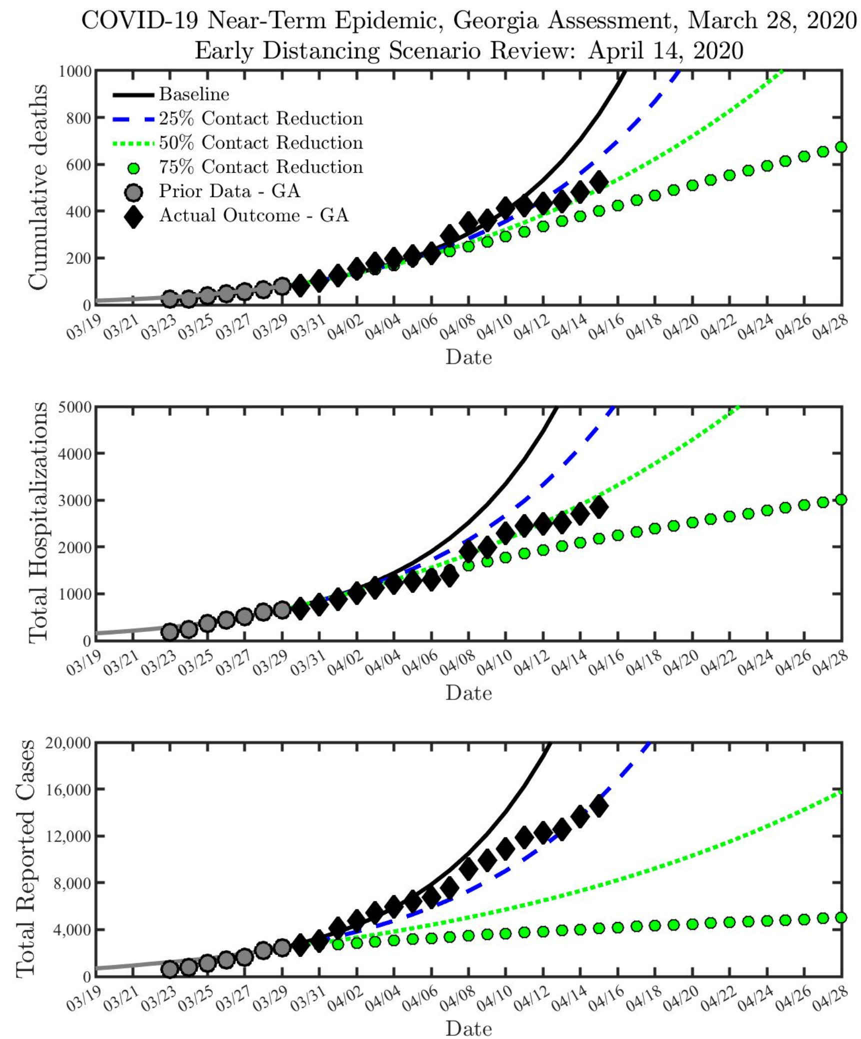
COVID-19 model w/asymptomatic transmission



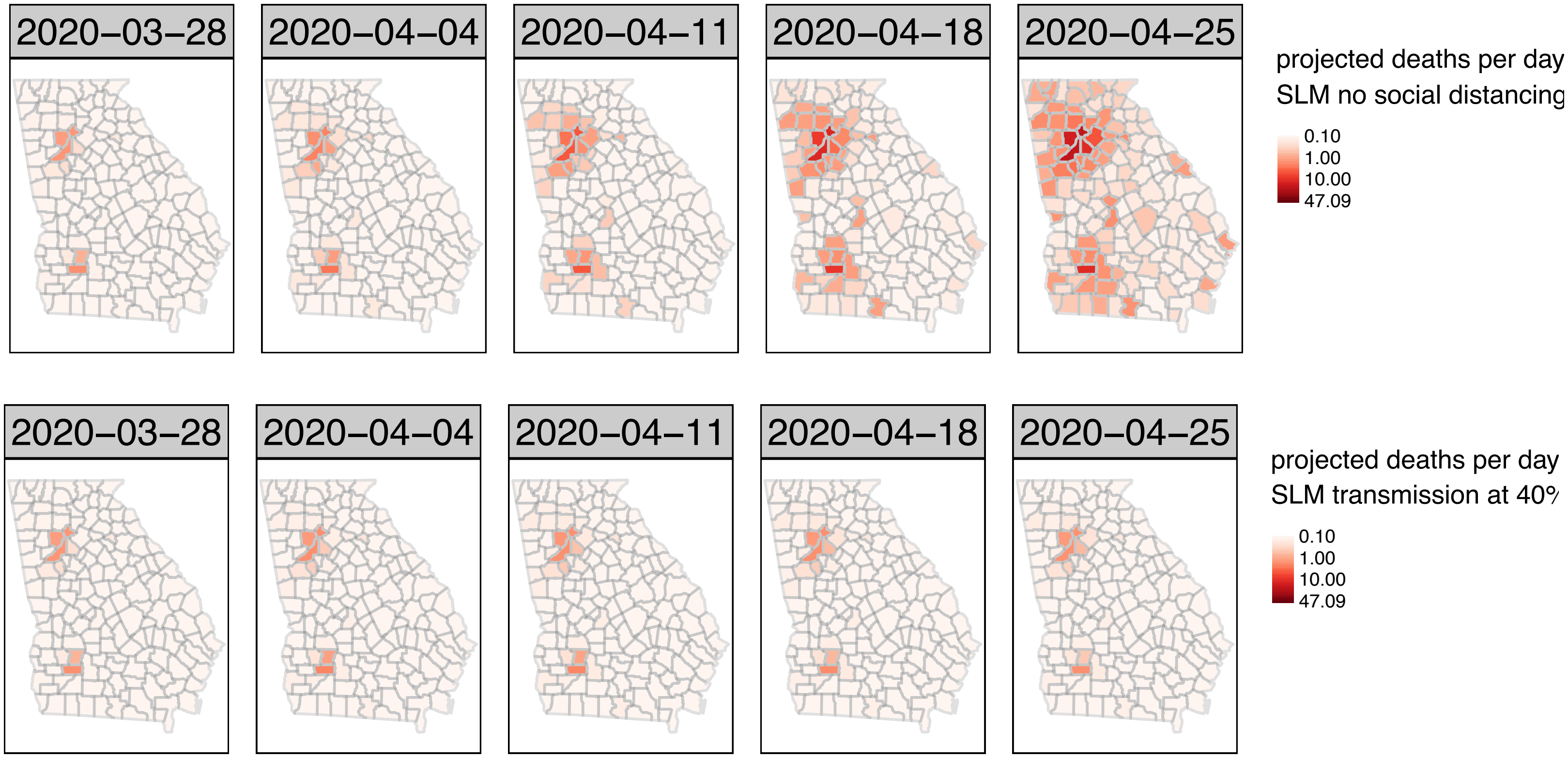
Key Points:

Reported deaths and hospitalizations show effect of large-scale orders (averting far worse outcomes)

Case ascertainment rate may be 1/10 to 1/30 suggesting prevalence ~1%-4% in Georgia vs. 'reported' prevalence of 0.1%.



Ongoing Work – Moving from State to County-Level Metapopulation Models

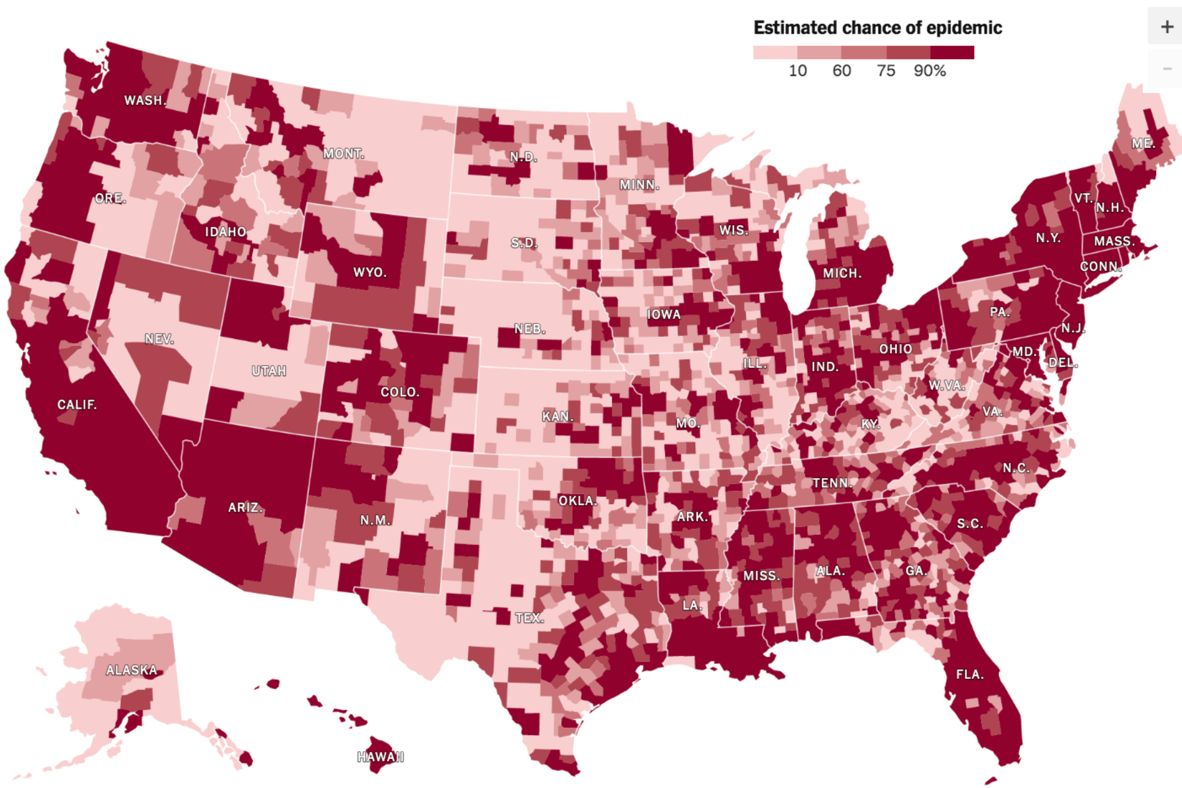


Dr. Stephen Beckett (GT, Bio Sci lead) w/Prof. Clio Andris (GT, IC and Design)
Report in progress – to be released at weitzgroup.github.io
See weitzgroup.github.io/cases.html & deaths.html for datasets by county.

Does "My" Country Have an Epidemic? Hint: Yes. (Lauren Meyers et al., UT-Austin)

Does My County Have an Epidemic? Estimates Show Hidden Transmission

By James Glanz, Matthew Bloch and Anjali Singhvi April 3, 2020



By The New York Times • Source: Emily Javan, Spencer Fox and Lauren Ancel Meyers, the University of Texas at Austin

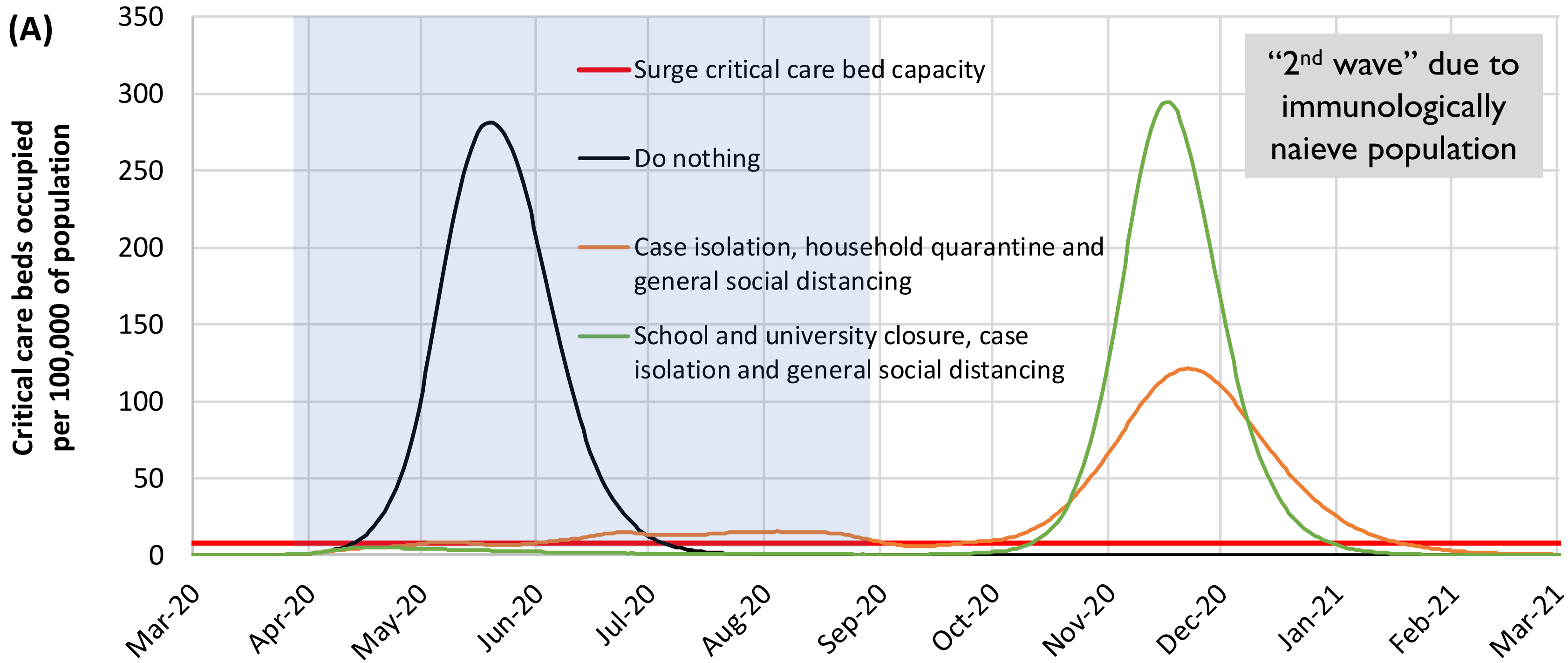
Today’s Talk

Part 1 – Dynamical Foundations of Epidemics
strength, speed, and size

Part 2 – Dynamics and Control
how we got to where we are now

Part 3 – Long-term strategies
how we might get out, in the absence of pharmaceutical interventions

Imperial: Long-Term Prospects in the Absence of a Vaccine



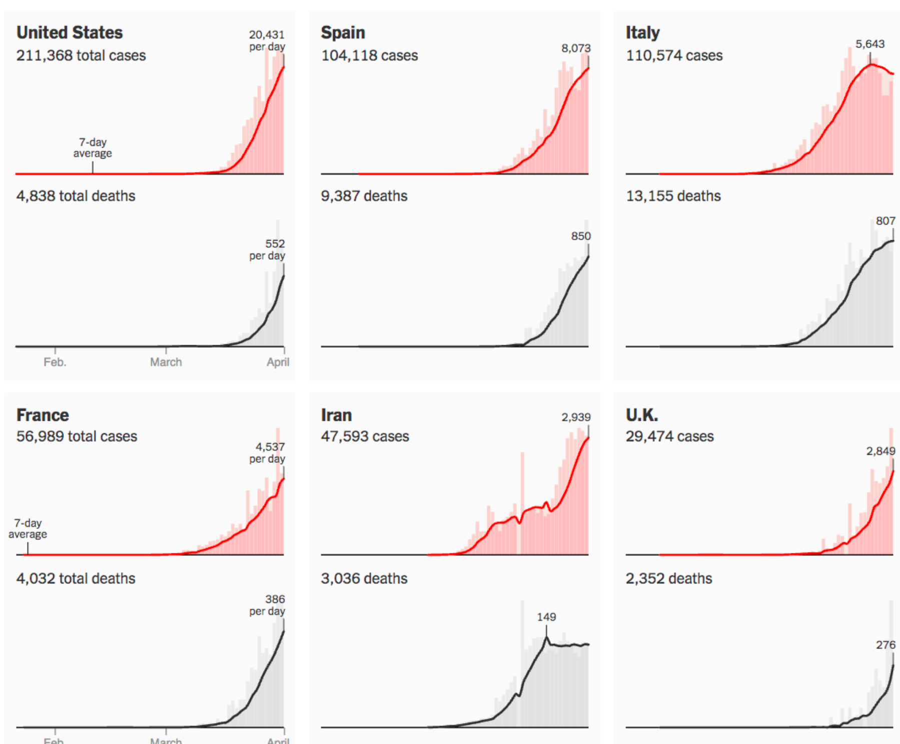
Source: Imperial College London, 3/16 Report

Current "Zero-Sum" Dichotomy: Infection Control or Economic Engagement

"Was the Dow to die for today, or what?!"

Source: Conde Nast

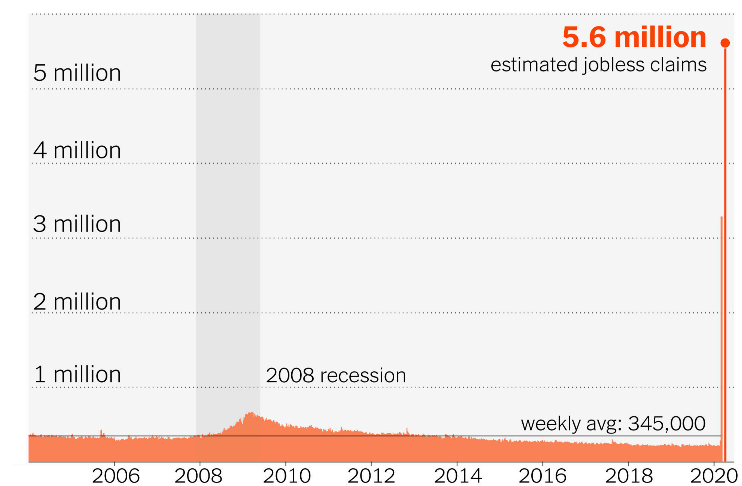
Are Countries Flattening the Curve for the Coronavirus?



TheUpshot

Jobless Claims Hit 3.3 Million in the Last Report. This Week's Will Probably Be Worse.

By Quoctrung Bui April 1, 2020



The Perils of 'Exit' Scenarios and Forecasting (IHME Model via U of Washington)

On March 28 – Predicted April 15th as Peak w/~2000 deaths per day

IHME Model Chris Murray

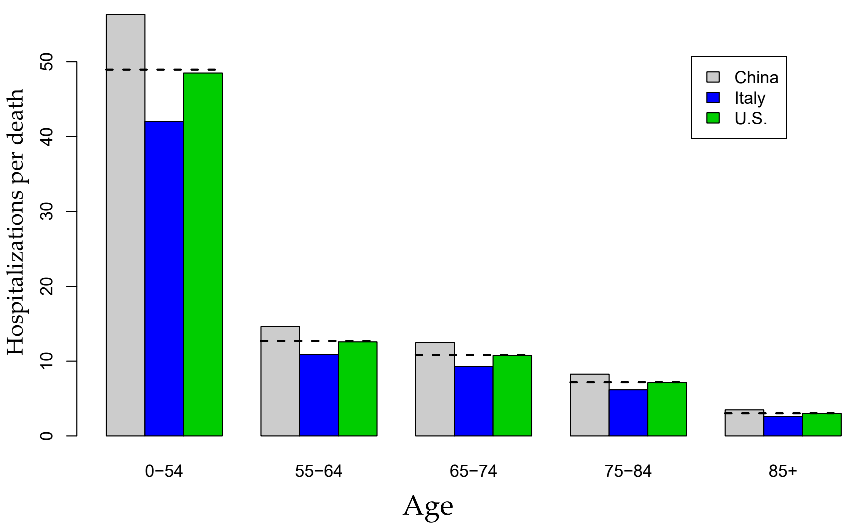
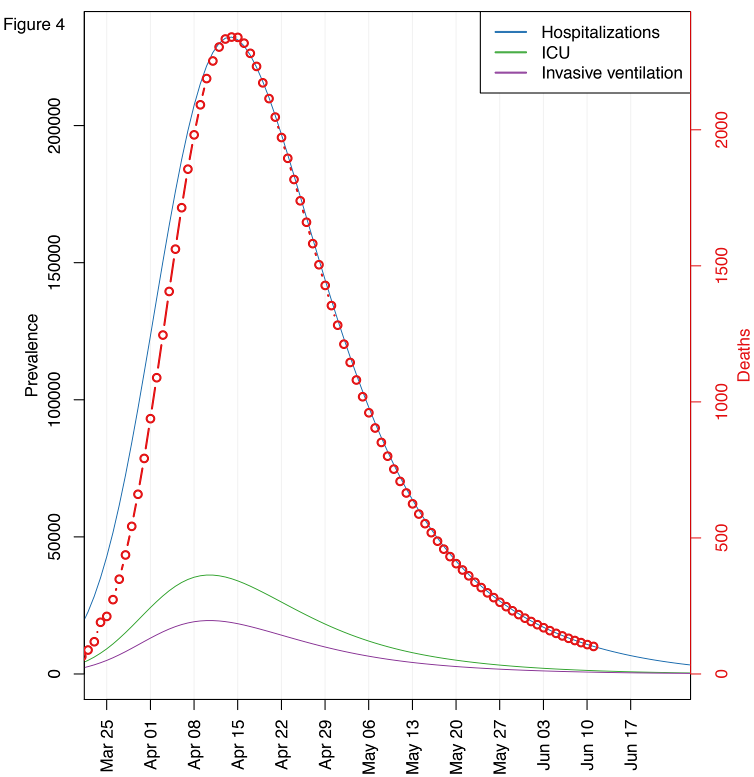


Figure 4



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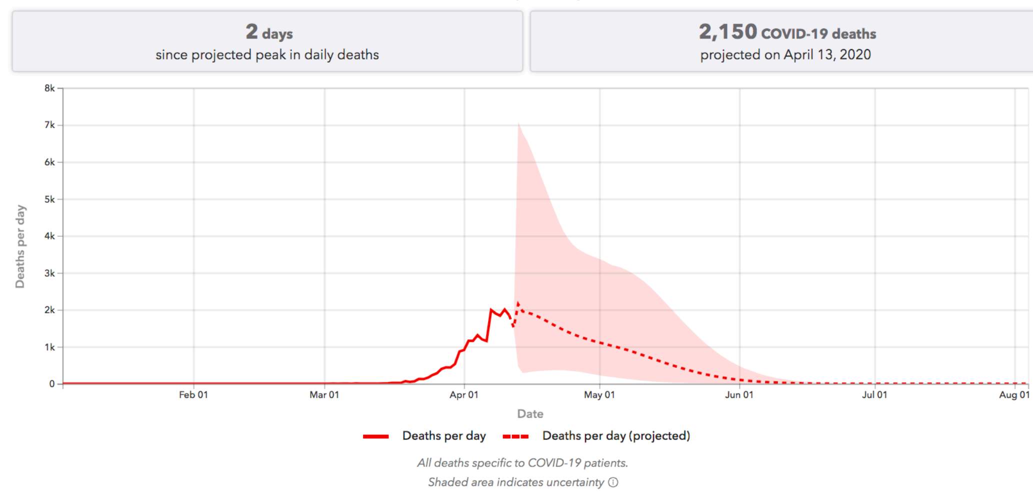
But now, the tail extends and there is no uncertainty after June 1 (!!)

IHME Model Chris Murray



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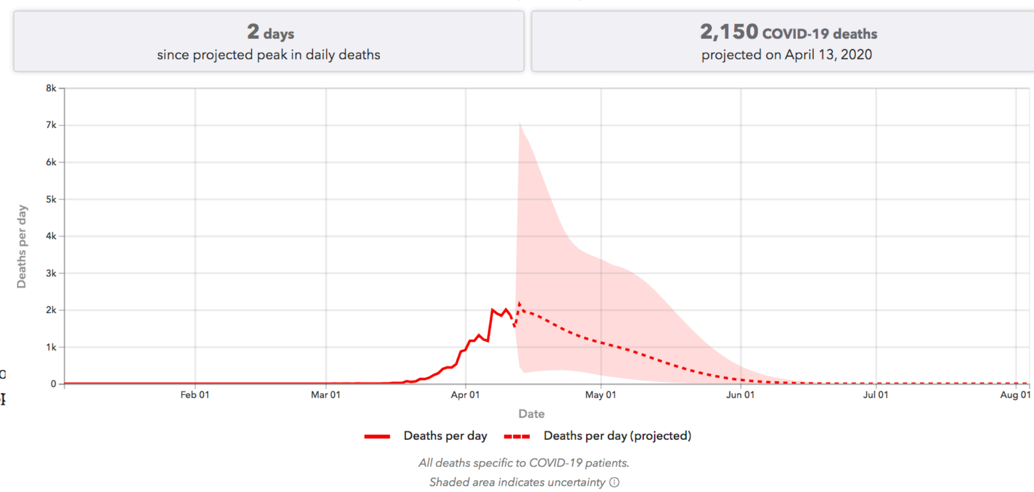


2. Functional Form for Covid-19

We considered several functional forms to model the death rate of the Covid-19 virus. Based both currently available data, the log rate starts slowly, increases quickly, and then flattens c again as either social distancing or saturation goes into effect. This is the classic sigmoid shap We first tried building the analysis using the sigmoidal function

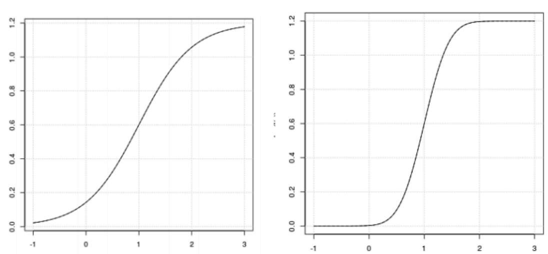


Figure 1. Expit function $\widetilde{D}$ (left) and ERF function D (right). The ERF function fits the available Covid-19 data better than Expit.

$$\widetilde{D}(t;\alpha,\beta,p) = \frac{p}{1+\exp(-\alpha(t-\beta))}$$

where p controls the level, β the shift, and α the growth. We quickly discovered that the ERF error function provided a better fit to the data:

$$D(t;\alpha,\beta,p) = \frac{p}{2}\left(\Psi(\alpha(t-\beta))\right) = \frac{p}{2}\left(1+\frac{2}{\sqrt{\pi}}\int_0^{\alpha(t-\beta)} \exp\left(-\tau^2\right) d\tau\right)$$

Buyer beware:

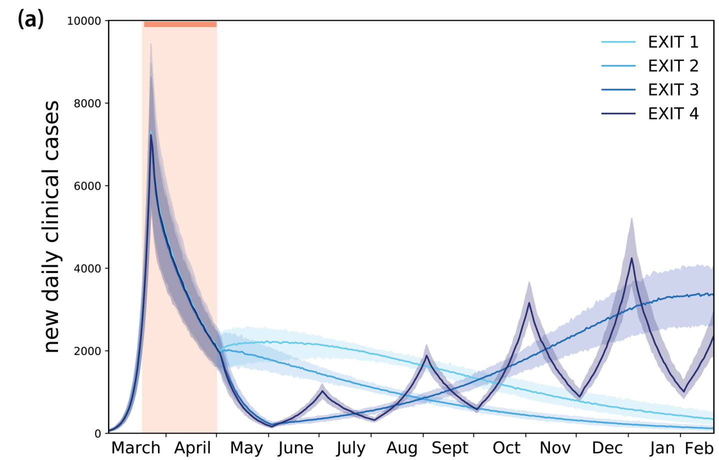
A curve fitting model based on an 'ERF' function should be used only for short-term predictions and its utility has already passed the expiration date.

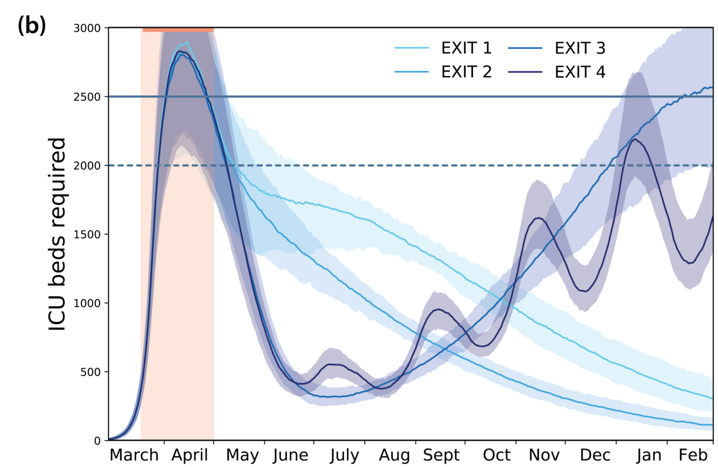
Hint: the future is not that certain.

Thoughtful Exit Scenarios and Forecasting (INSERM/EPICX Lab)

	March	April	May	June	July	Aug	Sept	Oct	Nov	Dec	Jan	Feb
LD(Apr)												
LD(May)												
LD(June)												
LD(Apr)+Strict			Strict interventions									
LD(Apr)+Mod			Moderate interventions									
LD(Apr)+Mild			Mild interventions									
LD(Apr)+SC,SI			School closure and senior isolation									
Exit 1			+50% CI	+50% CI	+50% CI	+50% CI	+50% CI	+50% CI	+50% CI	+50% CI	+50% CI	+50% CI
Exit 2			+25% CI	+25% CI	+25% CI	+25% CI	+25% CI	+25% CI	+25% CI	+25% CI	+25% CI	+25% CI
Exit 3			+75% CI	+75% CI	+75% CI	+75% CI	+75% CI	+75% CI	+75% CI	+75% CI	+75% CI	+75% CI
Exit 4			+75% CI	+50% CI	+50% CI	+50% CI	+50% CI	+50% CI	+50% CI	+50% CI	+50% CI	+50% CI
Exit 1 (1m after)				+50% CI	+50% CI	+50% CI	+50% CI	+50% CI	+50% CI	+50% CI	+50% CI	+50% CI
Exit 2 (1m after)				+25% CI	+25% CI	+25% CI	+25% CI	+25% CI	+25% CI	+25% CI	+25% CI	+25% CI
Exit 3 (1m after)				+75% CI	+75% CI	+75% CI	+75% CI	+75% CI	+75% CI	+75% CI	+75% CI	+75% CI
Exit 4 (1m after)				+75% CI	+50% CI	+50% CI	+50% CI	+50% CI	+50% CI	+50% CI	+50% CI	+50% CI

Figure 3. Scenarios (color code as in Table 1; CI refers to case isolation).

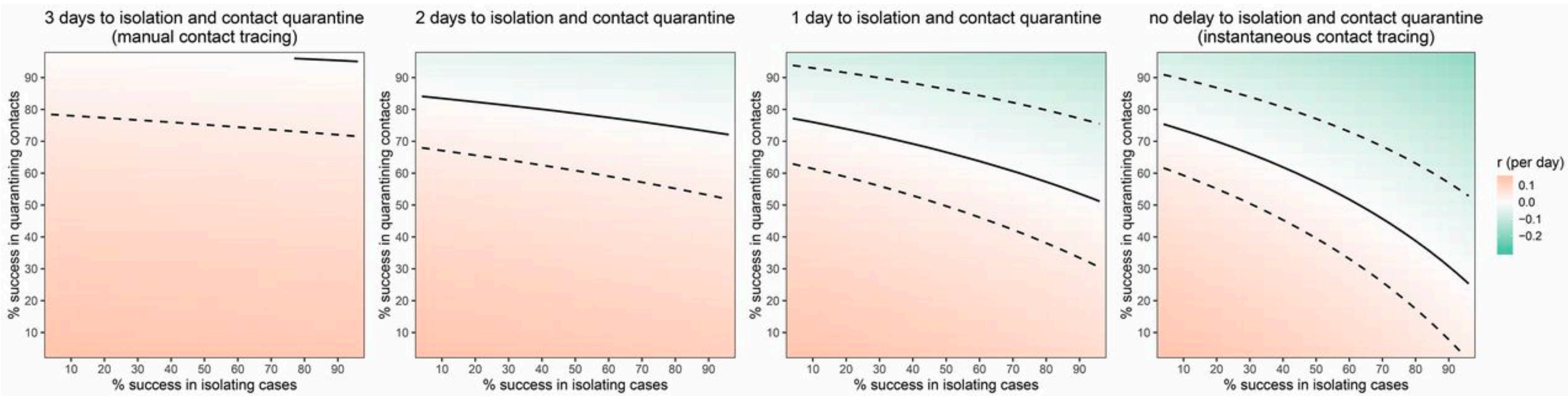


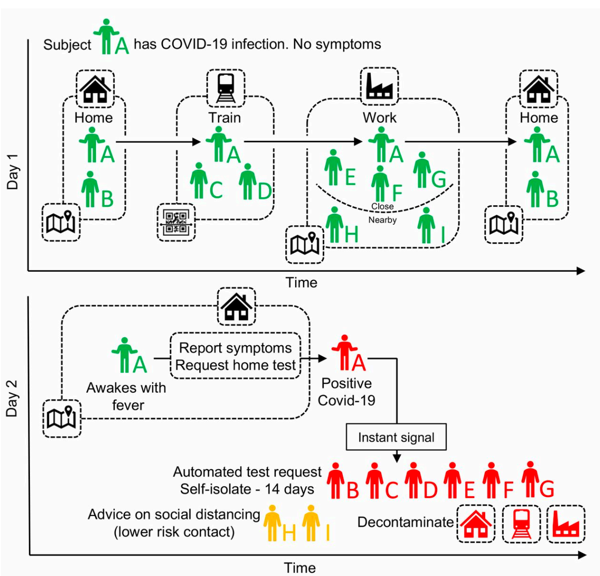


Take-away:

Sustained infection control is needed for ~1 year to prevent large-scale waves of new cases.

Testing and Tracing as a Means of Prevention not just Pathology





Science RESEARCH ARTICLES

Cite as: L. Ferretti *et al.*, *Science* 10.1126/science.abb6936 (2020).

Quantifying SARS-CoV-2 transmission suggests epidemic control with digital contact tracing

Luca Ferretti[1]*, Chris Wymant[1]*, Michelle Kendall[1], Lele Zhao[1], Anel Nurtay[1], Lucie Abeler-Dörner[1], Michael Parker[2], David Bonsall[1,3]†, Christophe Fraser[1,4]†‡

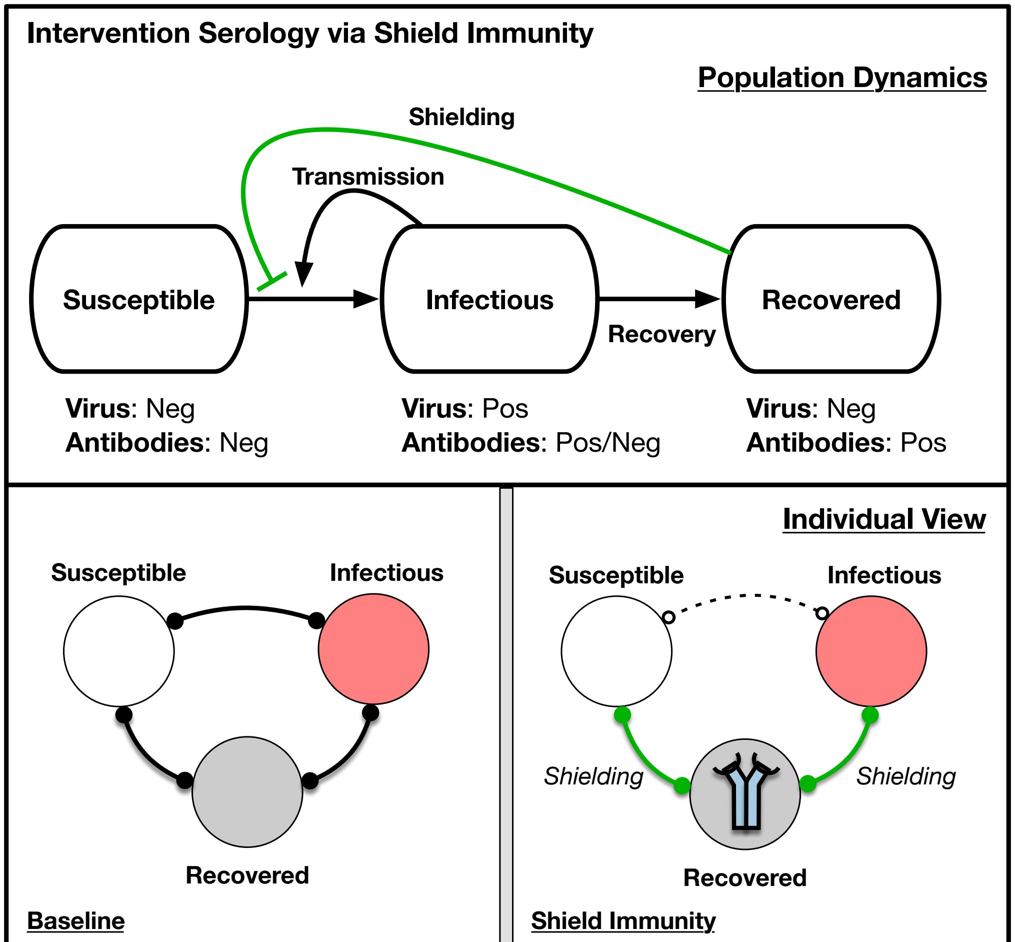
[1]Big Data Institute, Li Ka Shing Centre for Health Information and Discovery, University of Oxford, Oxford, UK. [2]Wellcome Centre for Ethics and the Humanities and Ethox Centre, University of Oxford, Oxford, UK. [3]Oxford University NHS Trust, University of Oxford, Oxford, UK. [4]Wellcome Centre for Human Genetics, University of Oxford, Oxford, UK.

The Bulk of Interventions
Focus on Reducing New Transmission
by Closures and/or Tracing

but what about all those who have already been sick and recovered…

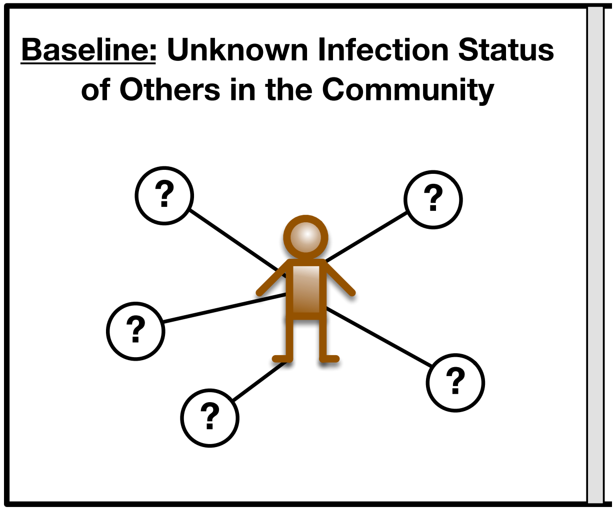
could these infections (far from herd immunity) help reduce collective risk?

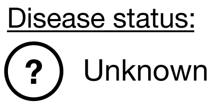
Our 'Shield Immunity' Proposal: Large-Scale Serological Testing to Reduce Transmission and Enable Economic Development



Weitz et al., medrxiv (in press, to be announced soon)

What is 'Shield Immunity'?





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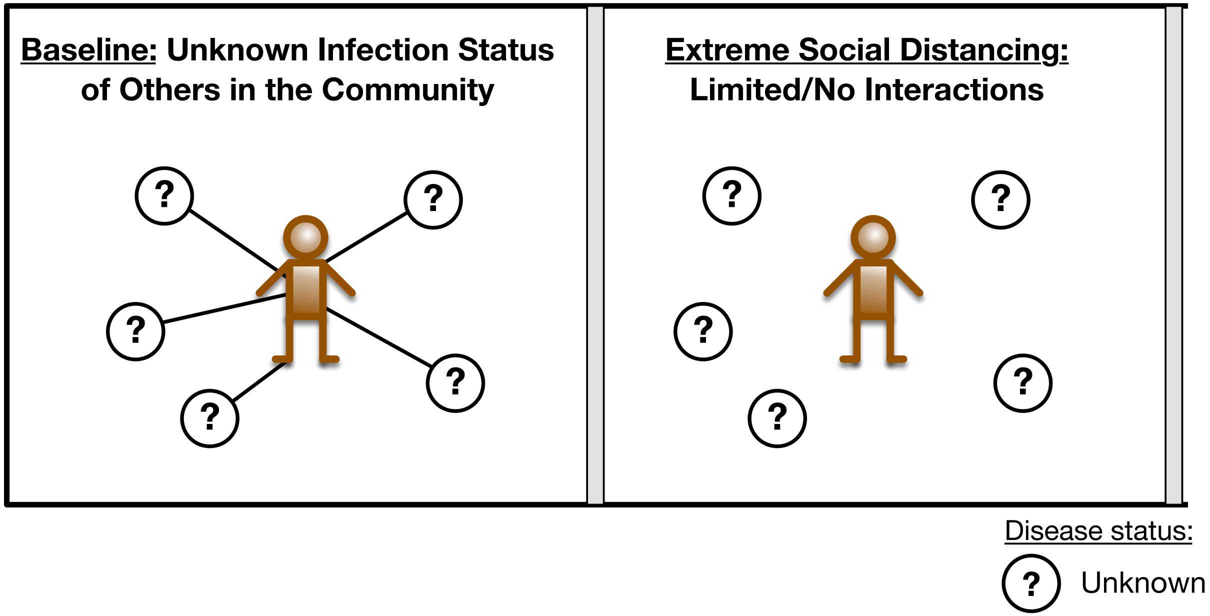

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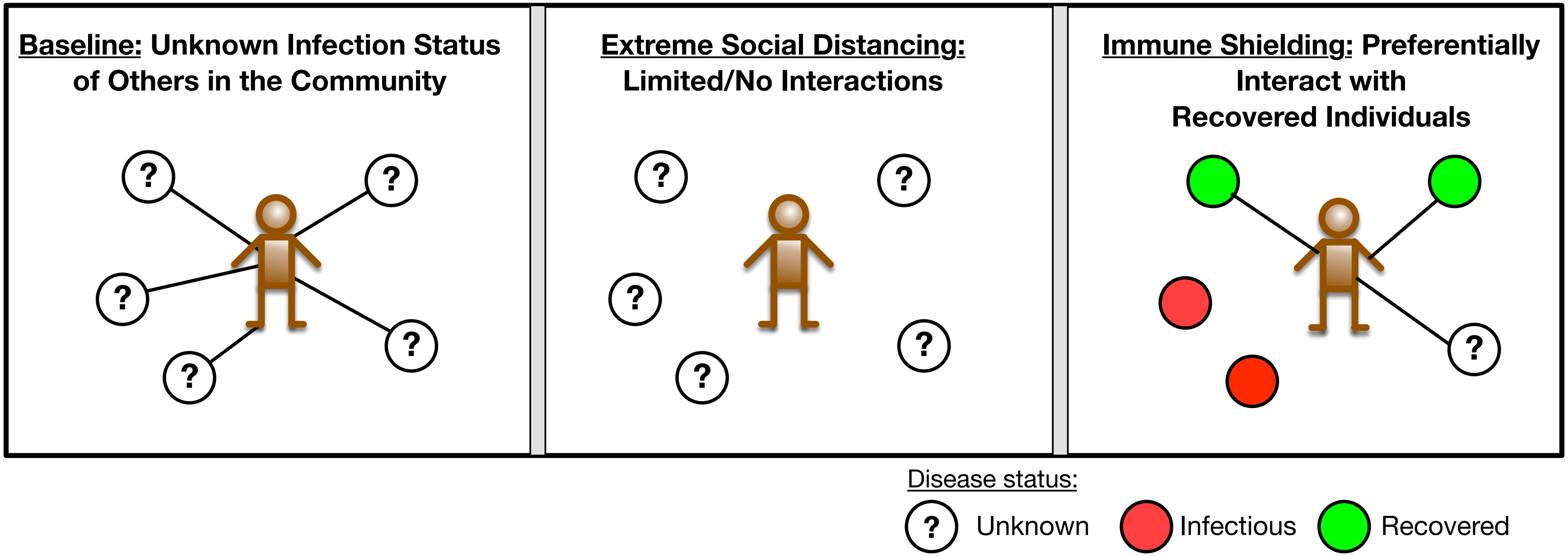

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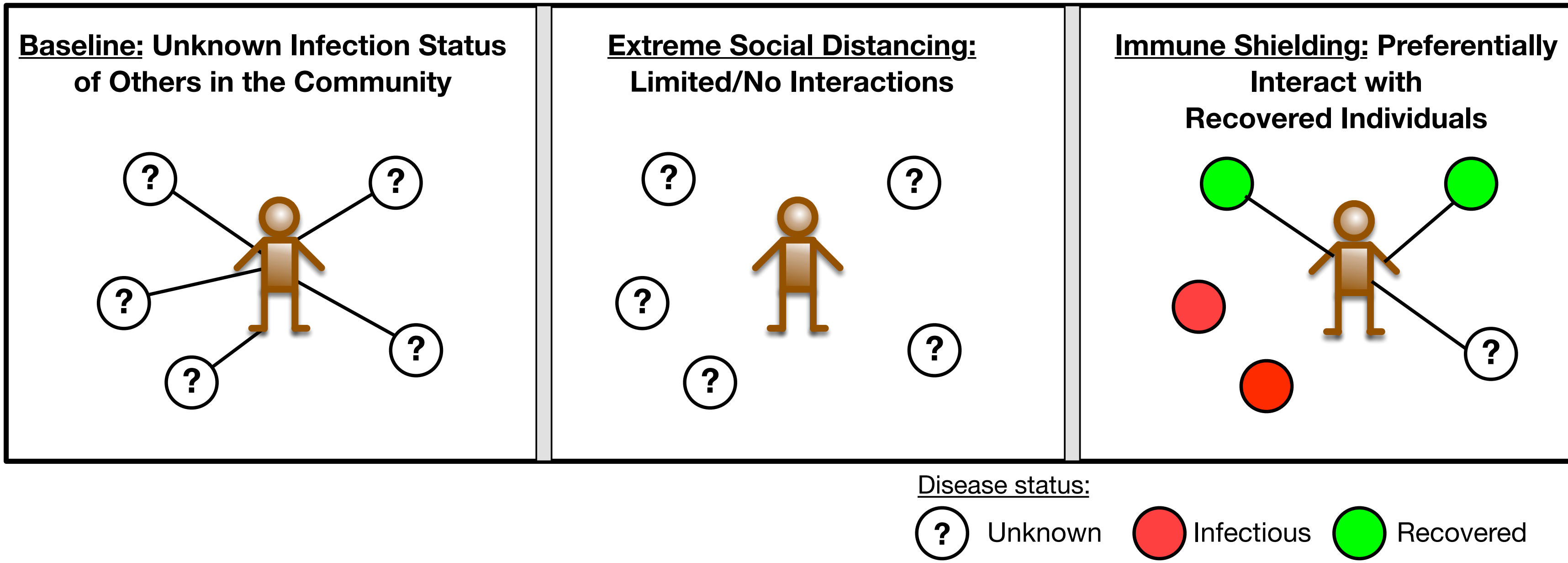


Take-away: the scale and type of testing matters

Infectious — PCR provides a snapshot, i.e., ‘are you shedding virus now’?

Recovered — Serological testing for antibodies provides a history, i.e., ‘have you been infected recently or in the past’? Recovered implies immune (duration still unknown).

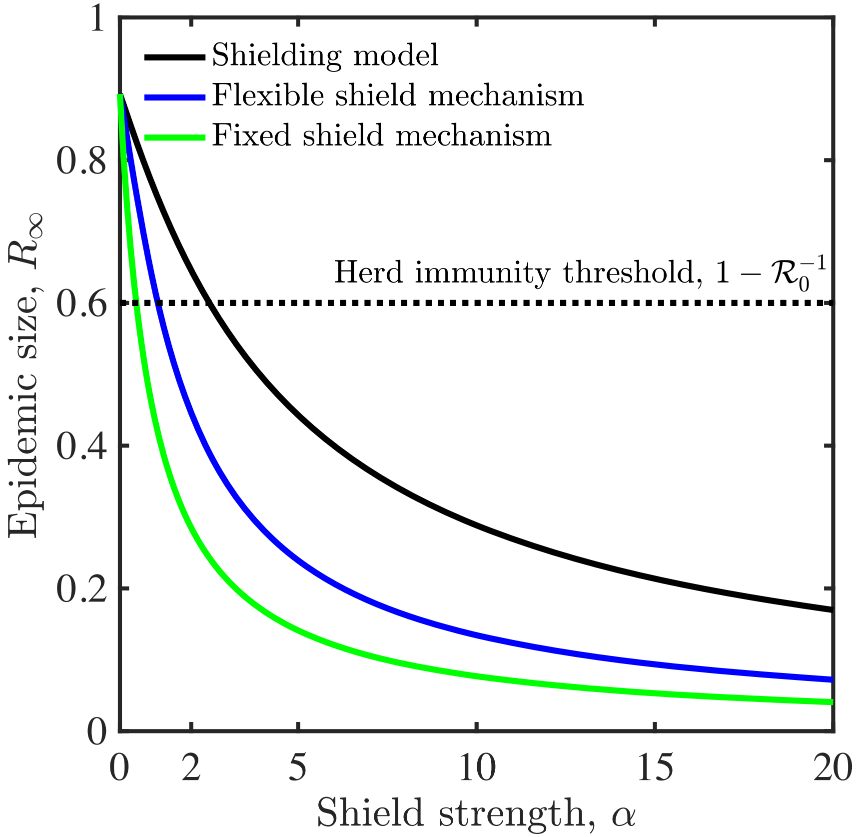
Shield Immunity Dynamics

SIR model w/shielding

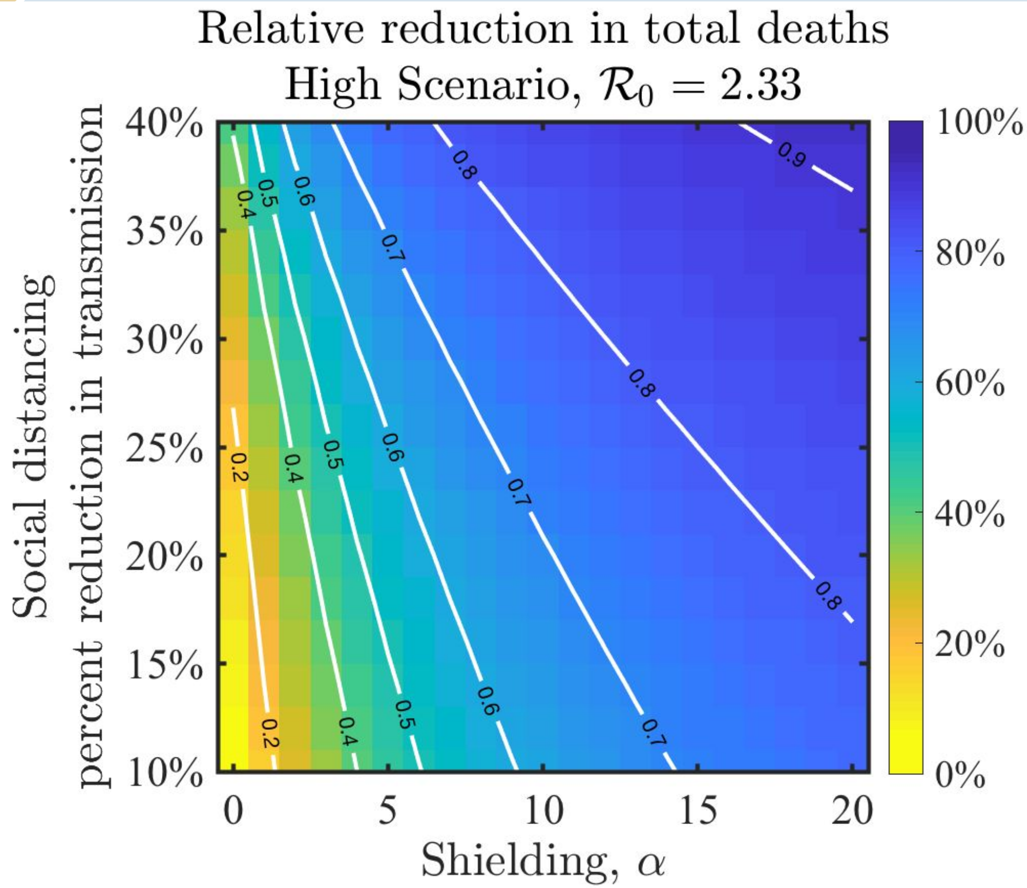
Recovered individuals have preferential interactions relative to other individuals.

This dilutes the susceptible fraction at levels well below the herd immunity threshold.

$$\begin{aligned}\dot{S} &= -\beta\frac{SI}{1+\alpha R}\\ \dot{I} &= \beta\frac{SI}{1+\alpha R} - \gamma I\\ \dot{R} &= \gamma I\end{aligned}$$



What could we do if we could identify recovered individuals?



Recovered individuals could elevate their interactions relative to other individuals – we call this 'shield strength'.

Combining (less intense) social distancing and shielding could have significant population-wide benefits.

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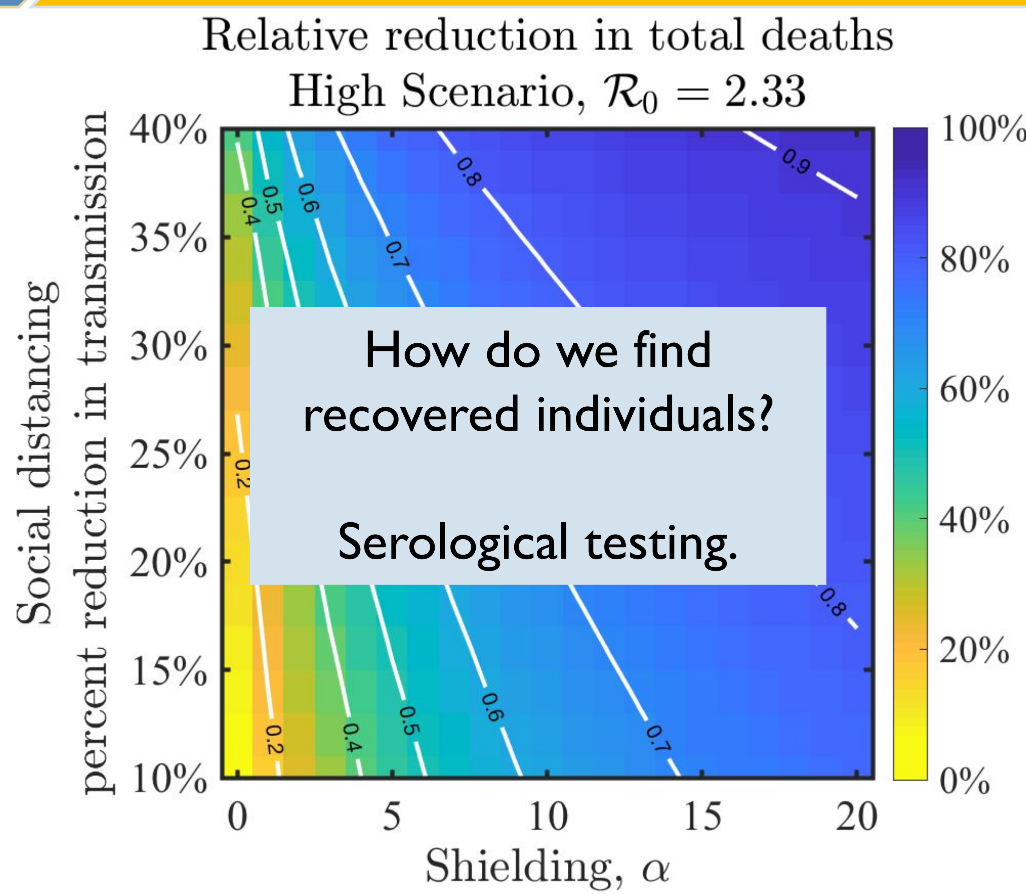

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Closing Thoughts

Part 1 – Dynamical Foundations of Epidemics

COVID-19 has epidemiological features of high R0, relatively fast spread, elevated fatality rates, and asymptomatic transmission that increase its epidemic potential.

Closing Thoughts

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Part 2 – Dynamics and Control

Interventions have made an enormous impact (averting tens/hundreds of thousands of fatalities). But, even if a peak has been averted, we remain immunologically naive.

Closing Thoughts

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COVID-19 has epidemiological features of high R0, relatively fast spread, elevated fatality rates, and asymptomatic transmission that increase its epidemic potential.

Part 2 – Dynamics and Control
Interventions have made an enormous impact (averting tens/hundreds of thousands of fatalities). But, even if a peak has been averted, we remain immunologically naive.

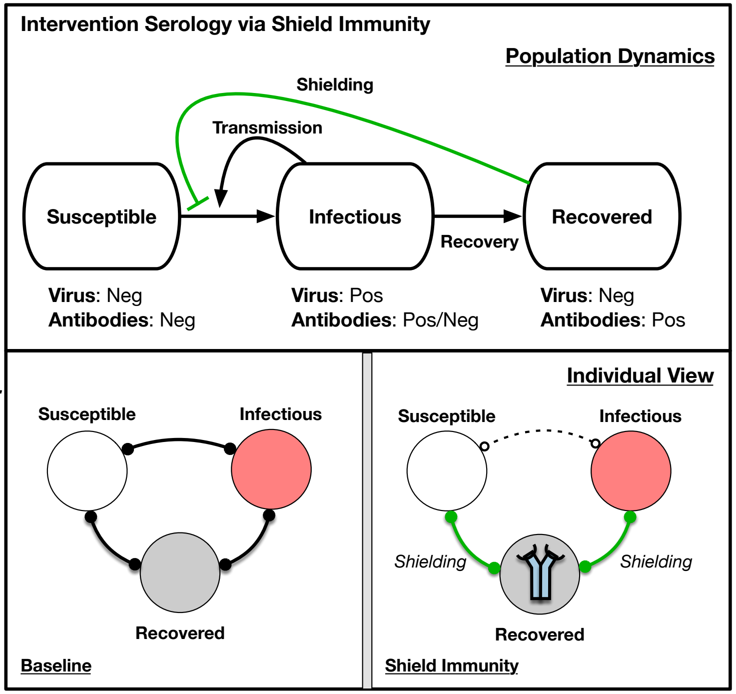
Part 3 – Long-term strategies
Testing (PCR and serology) & contact tracing are needed at scale! Strategic and coordinated responses – we have a long road ahead, we'll be better off working collectively.

Georgia Tech Team

Ashley Coenen
Dr. Stephen Beckett
Dr. David Demory
Marian Dominguez-Mirazo
Dr. Joey Leung
Guanlin Li
Andreea Magalie
Daniel Muratore
Rogelio Rodriguez-Gonzalez
Dr. Adriana Sanz
Shashwat Shivam
Conan Zhao

Collaborators

Clio Andris, GT
Daniel Cornforth, GT
Jonathan Dushoff, McMaster
Ceyhun Eksin, Texas A&M
Benjamin Lopman, Emory
Alicia Kraal, Emory
Kristen Nelson, Emory
Sang Woo Park, Princeton
Yorai Wardi, GT



Code:
https://github.com/WeitzGroup/covid_shield_immunity

Preprint (now in press, to be announced soon)
https://www.medrxiv.org/content/10.1101/2020.04.01.20049767v1

Tweet thread:
https://twitter.com/joshuasweitz/status/1245071163744645121?s=20

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