Mike Famulare, PhD.

Bill and Melinda Gates Foundation

Senior Research Manager and head of the Epi team at the Institute for Disease Modeling (IDM), an institute within Global Health at the Bill & Melinda Gates Foundation

Worked closely with partners in the Global Polio Eradication Initiative to assess the impacts of polio vaccination policies on poliovirus transmission

Founding co-Principal Investigator of the Seattle Flu Study, an innovative collaboration in at-home, multi-pathogen, self-testing that identified the first case of community transmission of COVID-19 in the United States

Co-led IDM's COVID-19 response, with a focus on analytics and modeling to inform COVID-19 control strategy in collaboration with the Washington State Department of Health and Governor

IDM: a research institute in the Bill & Melinda Gates Foundation

- Mission: to shape global efforts to eradicate infectious disease and to achieve permanent improvements in the health of those most in need.

- IDM is a team of ≈ 90
    - Research scientists, software engineers, technical writers, PMs, Admin, and IT

- Embedded research institute within BMGF that serves to support researchers and policymakers in global health and develops computational tools for that mission

- We are a research partner and do not operate as a funder

- We work with a wide ecosystem of partners: universities, NGOs, government ministries, research and public health institutions, and other divisions within BMGF

- **We are opening a few new roles (limited and unlimited term), so reach out and let your people know about us if interested.**

Colleagues closest to today's stories

Roy Burstein · Stewart Chang · Dennis Chao · Jamie Cohen · Greer Fowler

Niket Thakkar · Gov. Jay Inslee · Me · Dan Klein · Jeff Duchin

Brittany Hagedorn · Gregory Hart · Hao Hu · Mandy Izzo

Cliff Kerr · Rafael Nunez · Katherine Rosenfeld · Jenn Schripsema · Marita Zimmermann

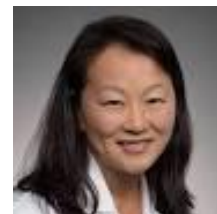Cathy Wasserman · Ian Painter · Ruth Etzioni · Juan Lavista Ferres
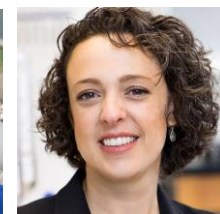
Trevor Bedford · Michael Boekh · Helen Chu · Jan Englund

Peter Han · Mark Rieder · Jay Shendure · Lea Starita

Reports and papers at covid.idmod.org

What is this talk about?

- "Lectures… can be on <u>any topic you prefer that is related to the secondary consequences of the COVID-19 pandemic or the data science challenges associated with it.</u>" – Jeanna Kamdar

- This is a talk about
  - uncertainty, thinking clearly through uncertainty, decision-making under uncertainty.
  - the challenges we face as individuals during highly uncertain times.
  - our responsibilities as scientists.

- This is a chance for you to
  - enjoy a few stories.
  - evaluate my credibility as an expert and colleague.
  - reflect on your work in relation to society.

What, *specifically*, is this talk about?

- I'll try to put you in my shoes during three critical periods of the COVID-19 pandemic
  - Figuring out the dynamics and epidemiology of 2019-nCoV
  - **Building a shared mental model** with the gov't, media, and public in Washington state
  - Deciding how to care for myself—a person on immunosuppressive therapy for MS—as the vaccines arrived

- Throughout, I hope to illustrate general principles of working through uncertainty when the stakes and pace are very high.

- I hope it prompts reflection on who and what you and your research program serve.

- *All opinions expressed are my own. I am not speaking on behalf of BMGF.*

It's January 2020, and you read "strange pneumonia out of Wuhan."

You want to know what's happening and what's going to happen, because:

- **You feel compelled to as a scientist.**
- You think your work is somehow related.

You ask yourself, **"are we capable of helping?"**

- Do I have a relevant research program?
- Do I want to help in any way I can?
  - Including filling sandbags?
- or do I want to keep doing my thing but in this new area?
  - find my niche in this disrupted ecosystem?
- Are we prepared to do the grunt work before opening our mouths?
- Are we prepared for the scientific discomfort? The risks of being wrong?
- Can we pay for the work?
- *Are we driven by FOMO or chasing clout?*

The line lists were "epistemic infrastructure" of January 2020

人民日报 人民日报
2020-1-21 来自 微博 weibo.com 已编辑

【#天津确诊2例新型冠状病毒感染肺炎#病例 曾赴武汉】天津确诊2例新型冠状病毒感染的肺炎病例。患者为60岁女性，近日曾赴武汉旅游，返津后因发热、干咳等症状，于1月19日在本市一发热门诊就诊后即被收治入院隔离治疗；另一位患者为58岁男性，近日曾到武汉出差，返津后因发热、咳嗽等症状，于1月14日在本市一发热门诊就诊后即被收治入院隔离治疗。目前，两名患者生命体征平稳，其在津密切接触者正在接受医学观察。@津云#天津确诊2例新型肺炎#

People's Daily
2020-1-21 From Weibo weibo.com edited

【#Tianjin confirmed 2 cases of new coronavirus pneumonia#cases went to Wuhan】 Tianjin confirmed 2 cases of pneumonia infected by new coronavirus. The patient is a 60-year-old female who recently traveled to Wuhan, and after returning to Tianjin, due to fever, dry cough and other symptoms, she was admitted to the hospital for isolation treatment after visiting a fever clinic in the city on January 19; Another patient, a 58-year-old man, recently went to Wuhan on a business trip, and after returning to Tianjin, due to fever, cough and other symptoms, he was admitted to the hospital for isolation treatment after visiting a fever clinic in the city on January 14. At present, the vital signs of the two patients are stable, and their close contacts in Zimbabwe are under medical observation. @Jinyun#Tianjin confirmed 2 cases of new pneumonia#

Kudos to DXY.cn Last update: 03/13/2020, 8:00 PM (EST)
File Edit View Insert Format Data Tools Extensions Help

100%   Comment only

6:6   =ROW(A6)-2

	A	B	C	E	F	G	H	I	J	K	L	M	N
1	Email	contact.sunky@gmail.com											
2	id	case_in_country	reporting date	location	country	gender	age	symptom_onset	f_onset_approximated	hosp_visit_date	ernational_traveler	domestic_traveler	exposure_start
3	1		1/20/2020	Shenzhen, Guangdong	China	male	66	1/3/2020	0	1/11/2020			12/29/2019
4	2		1/20/2020	Shanghai	China	female	56	1/15/2020	0	1/15/2020			NA
5	3		1/21/2020	Zhejiang	China	male	46	1/4/2020	0	1/17/2020			NA
6	4		1/21/2020	Tianjin	China	female	60	NA	NA	1/19/2020			NA

"I spent last night watching Schitt's Creek and adding ten thousand cases to the line list." – David Pigott
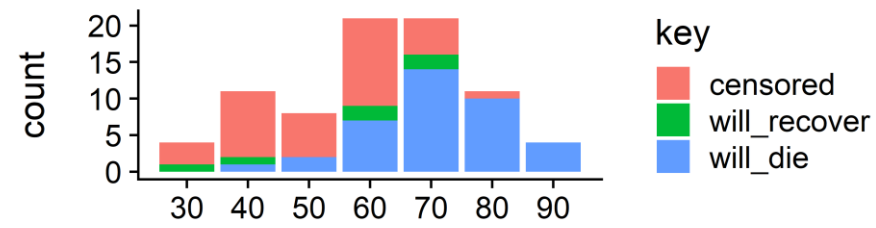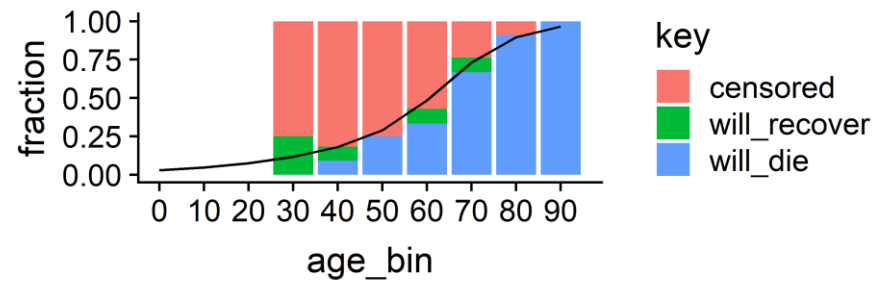
With prior knowledge of how viral infections work, it was possible to independently derive an accurate understanding of the *acute* disease course by the end of January 2020.
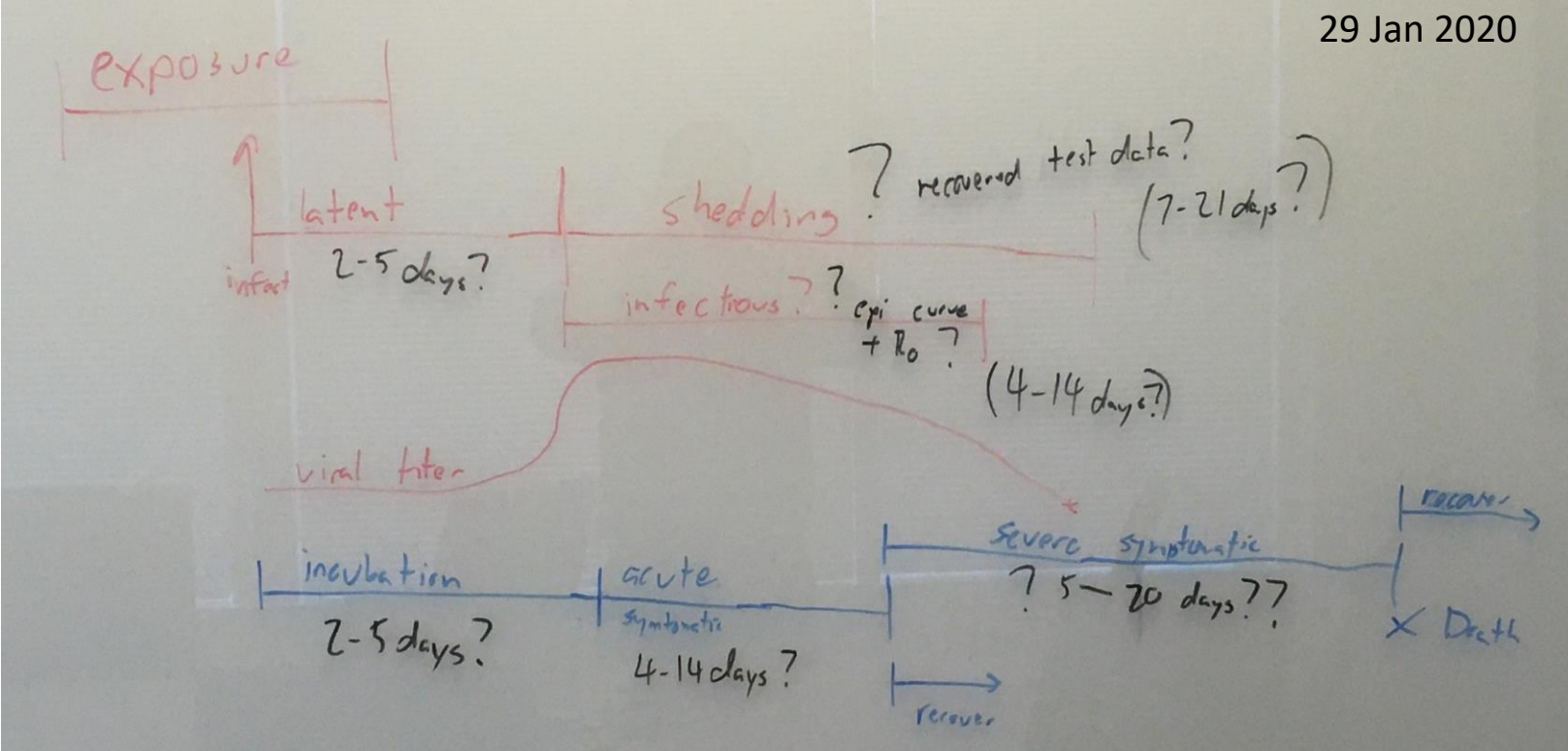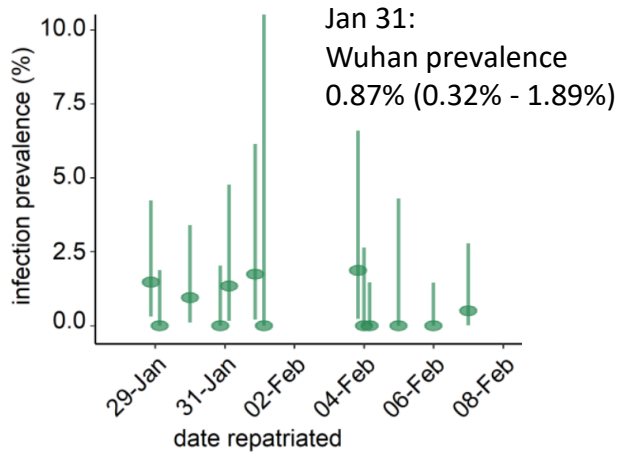
From the line lists, we could know a lot about case-fatality.


Early case-fatality rate by age

The flight network provided independent confirmation of model-based prevalence estimates from Wuhan, and thus told us there was lots of unseen transmission globally.

Jan 31:
Wuhan prevalence
0.87% (0.32% - 1.89%)

Exploring infection prevalence in repatriated individuals from Wuhan City, China (imperial.ac.uk)

Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study - The Lancet

Relative risk of case importation
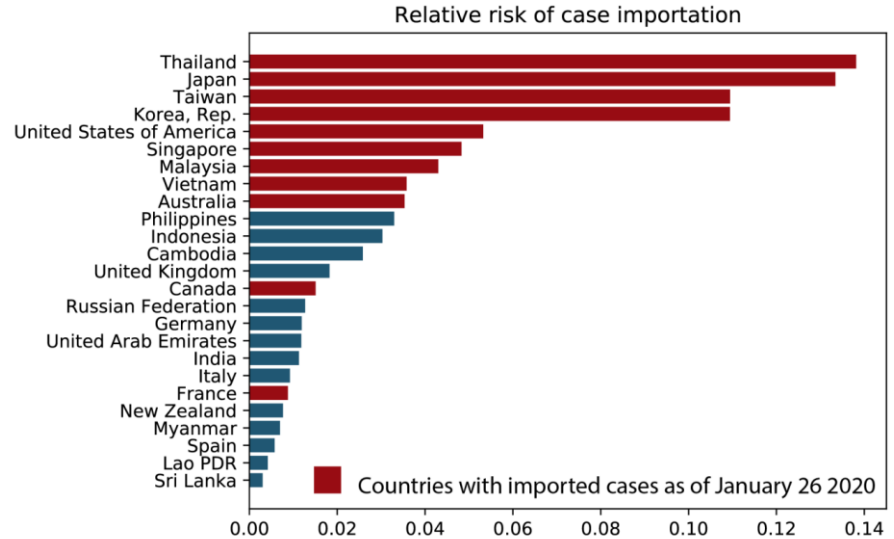
wuhan_novel_coronavirus_jan26.pdf (mobs-lab.org)

Hard to quantify but important:
Transmission must be easy for the virus and hard-to-see for the people, or it wouldn't be so per-population random.

Three independent estimates arrived at 0.3-1.0% IFR in China by Feb 19.

Coronavirus disease 2019 (COVID-19)
Situation Report – 30

World Health Organization

Data as reported by 19 February 2020*

[10] Jung S, Akhmetzhanov A, Hayashi K , Linton N, Yang Y , Yuan B, et al. Real-Time Estimation of the Risk of Death from Novel Coronavirus (COVID-19) Infection: Inference Using Exported Cases, *J. Clin. Med.* **2020**, *9*(2), 523

[11] Dorigatti I, Okell L, Cori A, Imai N, Baguelin M, Bhatia S, et al. Report 4: Severity of 2019-novel coronavirus (nCoV), https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/news--wuhan-coronavirus/

[12] Famulare M. 2019-nCoV: preliminary estimates of the confirmed-case-fatality-ratio and infection-fatality-ratio, and initial pandemic risk assessment, https://institutefordiseasemodeling.github.io/nCoV-public/analyses/first_adjusted_mortality_estimates_and_risk_assessment/2019-nCoV-preliminary_age_and_time_adjusted_mortality_rates_and_pandemic_risk_assessment.html

With a strong age-dependence that would mean many things like
- Italy would have a higher mortality rate. (First documented death in Italy was 22 Feb.)
- sub-Saharan Africa would have a lower mortality rate.

Feb 19, 2020
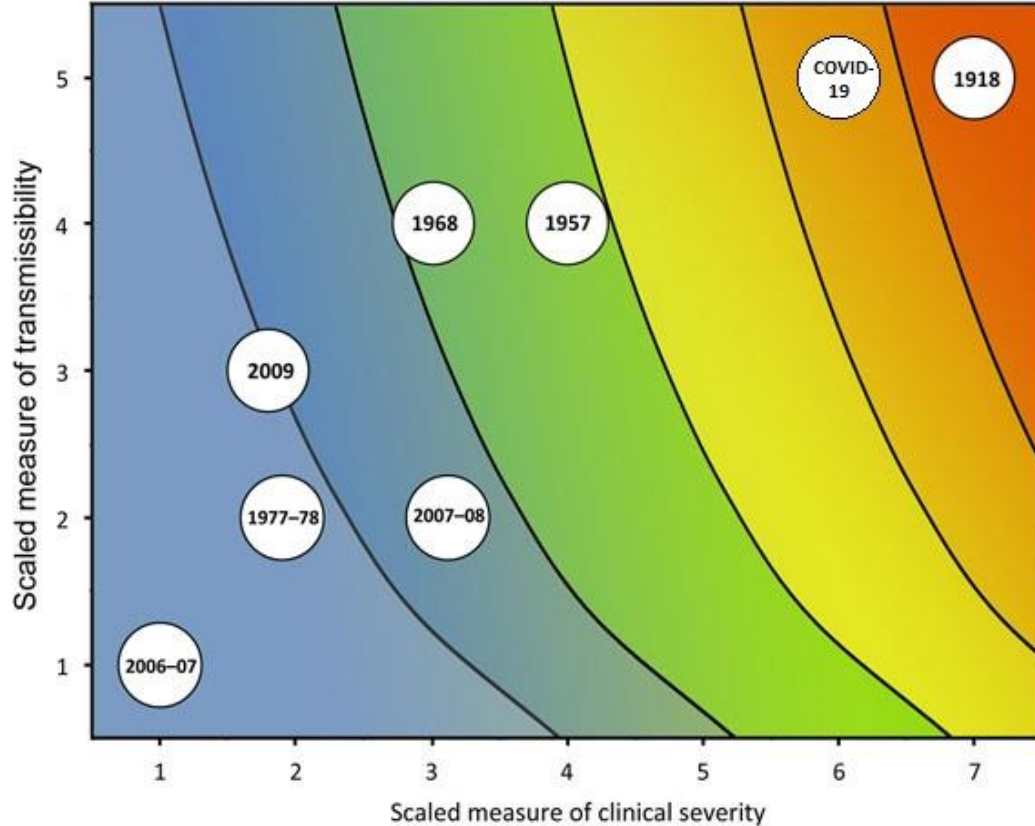
All of my work on this topic was hosted on Github between Jan 31 and Feb 19, 2020 and made public from Feb 14, 2020.
2019-nCoV: preliminary estimates of the confirmed-case-fatality-ratio and infection-fatality-ratio, and initial pandemic risk assessment

Interlude: Systems thinking

"Systems thinking is a way of exploring and developing effective action by looking at connected wholes rather than separate parts." Intro to Systems Thinking: Report of UK GSE and GORS seminar (2012)

Key concepts

- Context and beliefs
- Parts, wholes, and layers
- Connections and loops
- Processes

I contend that complex problem solving under high uncertainty *requires* systems thinkers in key places.

As you develop your research programs, ask yourself how you want to relate to the systems around you.

March 2020: "should the Seattle area close schools?"

It's March 2020, and we know we have widespread undetected community transmission in the Seattle Metro area.

The New York Times

Coronavirus May Have Spread in U.S. for Weeks, Gene Sequencing Suggests

Two cases detected weeks apart in Washington State had genetic links, suggesting that many more people in the area may be infected.

By Sheri Fink and Mike Baker

Published March 1, 2020   Updated March 9, 2020   6 MIN READ

HEALTH

First Covid-19 outbreak in a U.S. nursing home raises concerns

By Eric Boodman and Helen Branswell   Feb. 29, 2020

MyNorthwest

≡

LOCAL NEWS

How Seattle Flu Study defied federal government to test for coronavirus

Mar 12, 2020, 11:40 AM | Updated: 11:55 am

* As throughout this presentation, these are my professional opinions and do not reflect official positions of BMGF.

Models exist to inform decisions

Working paper – model-based estimates of COVID-19 burden in King and Snohomish counties through April 7, 2020

Dan Klein[1], Brittany Hagedorn[1], Cliff Kerr[1], Hao Hu[2], Trevor Bedford[3], Mike Famulare[1]*

[1]Institute for Disease Modeling; [2]Bill & Melinda Gates Foundation; [3]Fred Hutchinson Cancer Research Institute; *mfamulare@idmod.org

Results as of March 10, 2020 at 4:00 pm.
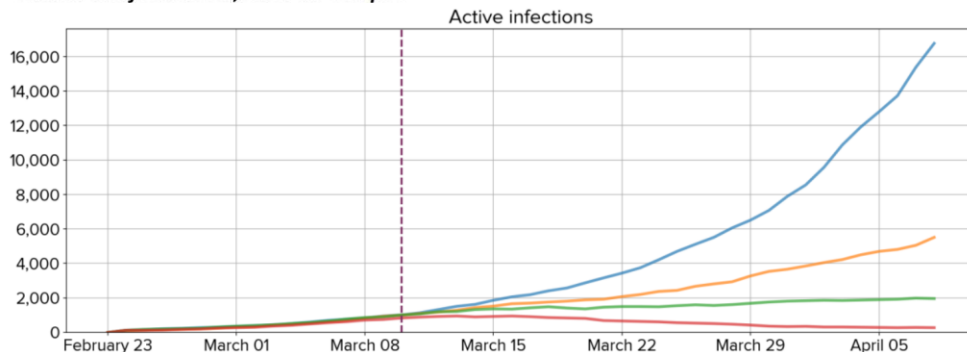
Figure 1. Scenarios for the possible cumulative burden of COVID-19 infection in King and Snohomish counties. Based on data from China and other countries, deaths occur in approximately 1 percent of the infected population (averaged across all ages) with an average three week delay relative to infection.

Seattle-ish transmission model, informed by all our knowledge about COVID-19, and matched to local case and fatality data through March 10.

Because COVID is controllable through our collective behavior, we decided to never publish a projection without highlighting a choice.

How was this first round of modeling used by our community?

What happened over the next week?

- Imagine our surprise seeing this on the TV!
- Public health officials asked us about the work.

What we said to them on a stressful call with many people we'd never met

- If we somehow cut at least 75% of possible transmission links, then prevalence will fall.
- We can't tell you how to do that, or what specifically school closures will accomplish, but they would disrupt a lot of social contacts across all ages.

What gov't, schools, and people decided

- **close schools**
- **transition as much work to home as possible**

Without 'social distancing,' 400 could die from coronavirus in Western Washington by April 7, study suggests

March 11, 2020 at 10:50 pm | Updated March 12, 2020 at 10:36 pm
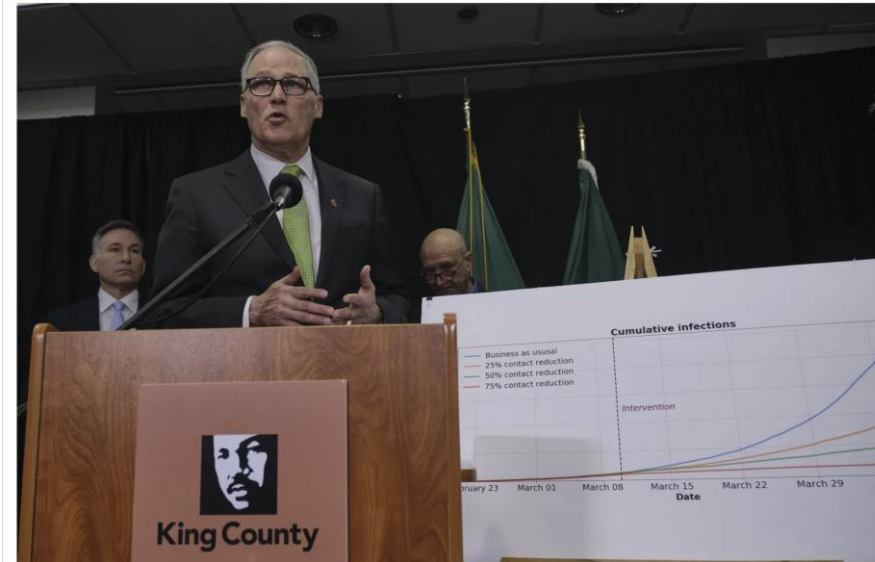
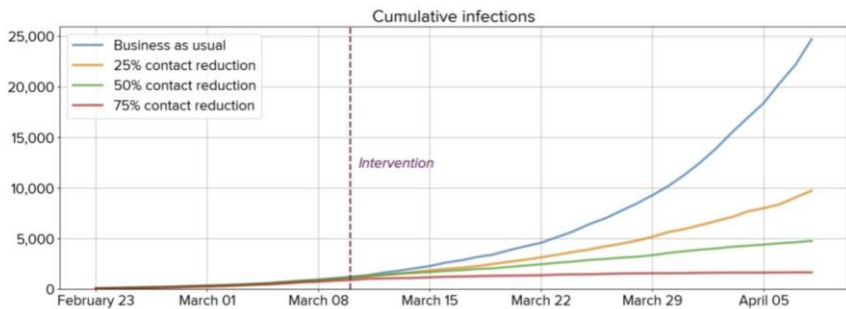# Gov't, press, and public worked together to build a shared mental model.

brewbooks

Social distancing is reducing Covid-19 burden in King and Snohomish counties

There's a plot that has been stuck in my brain for about 10 days:

### COVID-19 projections, King + Snohomish counties

Now, I realize that it's difficult to see much from this curve. I looked at the change in new daily infections, I believe that's a better metric to visualize how we are improving. Figure 2 provides this visualization with the yellow data points show the daily increase in new cases compared to the baseline (blue) and 25% reduction (red) lines. I realize that there's not very much data yet but we are seeing new data being published daily (and I will update this analysis sheet daily). Still, this made me realize that **we are likely achieving 25% reduction level due to social distancing in Sno-King!**

Increase in daily new cases (First difference) updated 25 March 2020
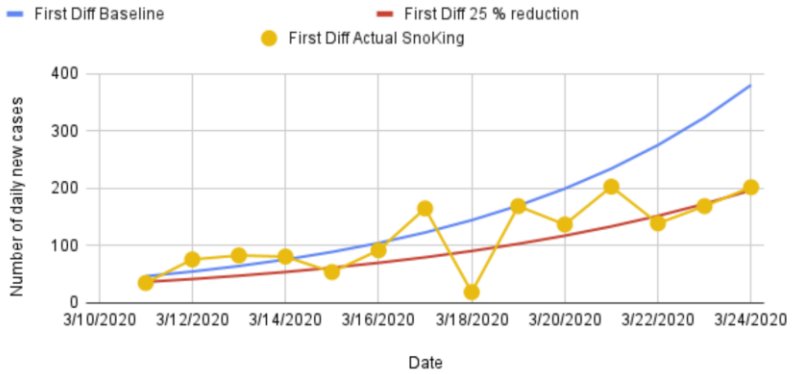
Building a shared mental model with policymakers and the community
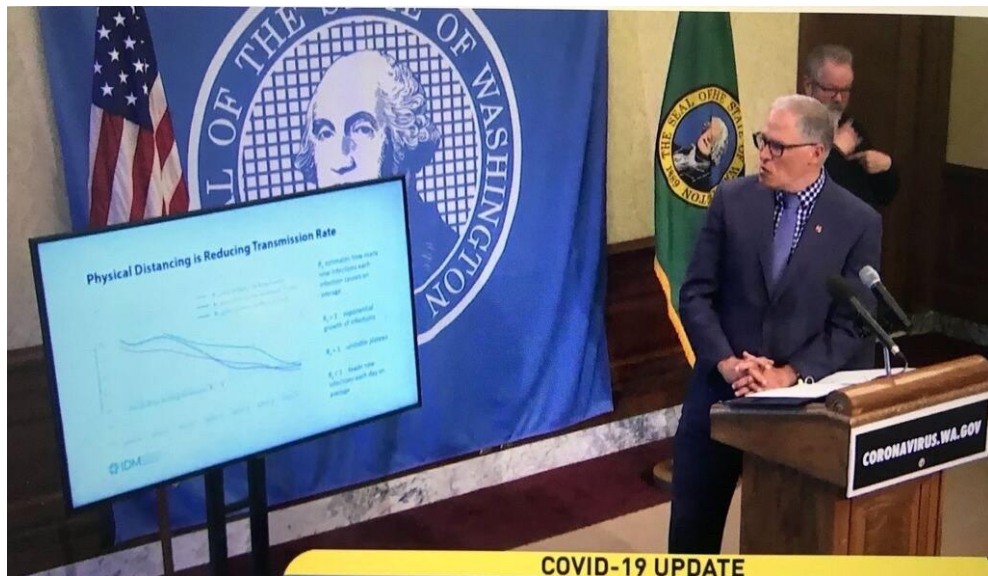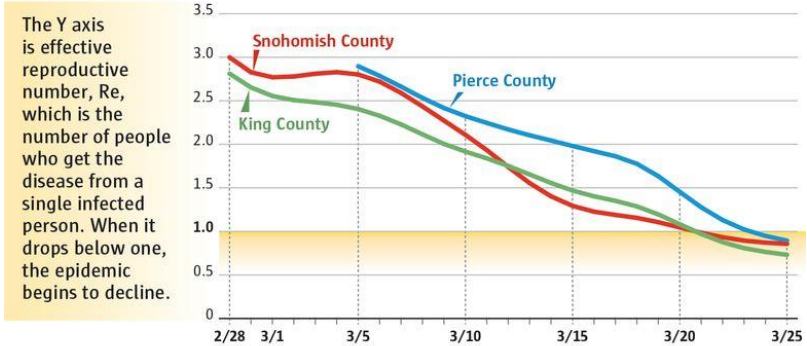
After achieving R near 1 with school and voluntary business closures, Gov. Inslee introduced the Stay Home, Stay Healthy orders that went into effect on March 23.

Prevalence fell shortly thereafter.

COVID-19 prevalence in King County
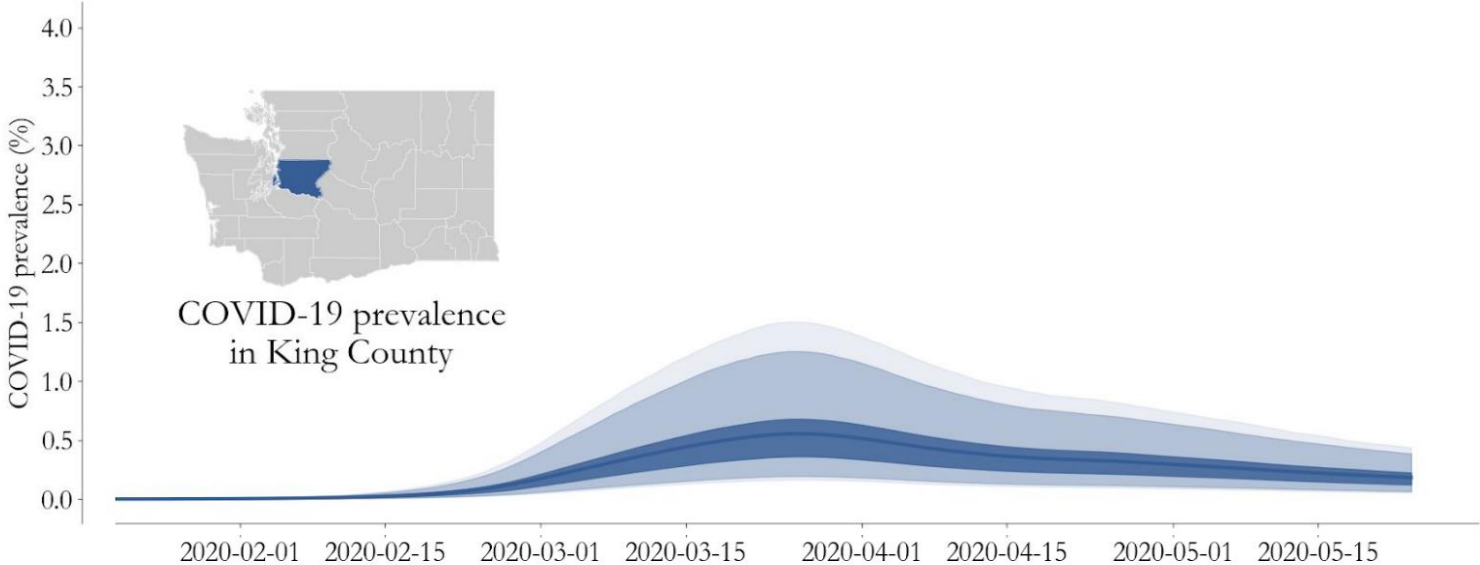
This first month set the structure for all of our public engagement.

Our roles

- Build a team to stay up-to-date on as much relevant science as possible
- Incorporate that into models – mental and computational – to serve various stakeholders
    - Ourselves as scientists
    - Local gov't, media, and community
    - International partners and academic community
- Never say anything without some description of accompanying uncertainty
- Always enumerate multiple options for the future.
- Carefully express opinions if requested but avoid pushing for a personal preference.
- Emphasize we will all learn together as we go.
- Put everything on the internet.

Our partners' roles

- **Use our input, alongside anything else they value, to act as they see fit.**

As of 21 Mar 2023, per NY Times, Washington state is ranked 46th in total COVID-19 deaths per capita among US states.

Building a shared mental model is the point.

- Computational modeling is essential for disciplining mental models, and for driving specific, mechanistic learning about how the complex system under study is working

- The best use of computational modeling is to fill the niches where it contributes unique value.

- "Good modeling" is impossible without understanding its interaction with other parts of the system.

- Good modeling is only useful if people make better decisions because of it.

- You cannot model every dynamic and every decision.

My personal experience with MS and COVID-19

Put yourself in my situation and imagine with me what we should do.

My situation in February 2021

- I have multiple sclerosis (MS)
    - I use an immunosuppressive b-cell-depleting therapy to delay progression.
    - This is known to blunt vaccine responses, but the degree for a novel antigen is unknown.
- People like me are probably at higher risk of severe COVID-19, but not much higher.
- I'm due for my next treatment.
- I do not yet know when I will be eligible for vaccination.
- Standard of care is to consider MS and COVID separately and in isolation.
- Professionally, I am as up-to-date as possible on COVID-19 pathogenesis and vaccinology.
- There will not be direct data on vaccine effectiveness for people like me for a very long time.

The choices

- I can change my treatment to influence vaccine response, at elevated risk for MS progression.
- I can vaccinate as soon as eligible or delay in coordination with my MS therapy.

Break down the problem

The studies with "the answer" don't exist. So how do we think through this?

- Immunology
  - What can we predict about my immune response?
  - What can we predict about the impact of immune response on COVID-19 protection?
  - Can I alter my treatment to change my immune response?
- MS progression
  - How might altering my immune response affect my MS risk?
- Values
  - How do I weigh MS risk vs COVID risk?
- Decisions
  - Do I change my treatment?
  - When do I vaccinate?

If you want to read the most useful single paper on this topic, choose **Baker *et al* 2020(!)**
COVID-19 vaccine-readiness for ocrelizumab and other anti-CD20-depleting therapies in multiple sclerosis and other autoimmune diseases

What could be guessed from proxies?

- What can we predict about my immune response?
    - *Won't get any antibody response. Will get a normal t-cell response.*
- What can we predict about the impact of immune response on COVID-19 protection?
    - *More antibodies is more better.*
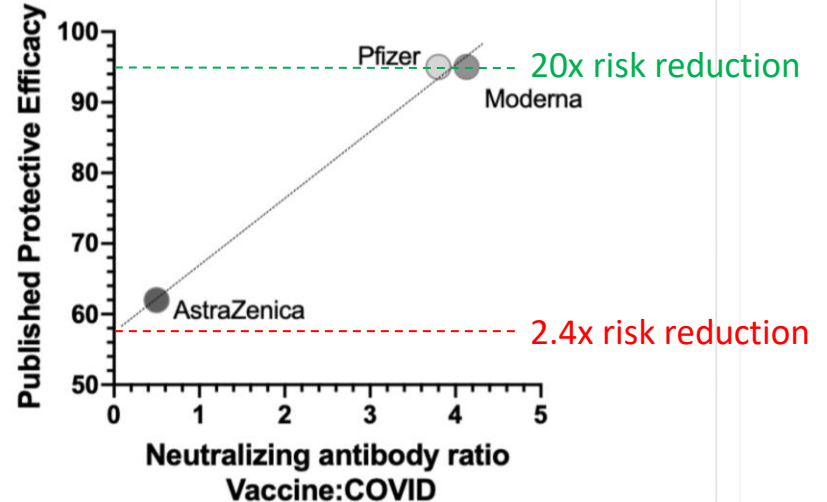
Jamie Triccas
@TricckyLab

3) The analysis:
- Compare level NAbs in human trials and with that of COVID patients (from same study)
- Results in a ratio comparing relative fold difference between vaccinees and COVID samples
Can then plot against efficacy for the 3 vaccines with published data.
Get this:

4:45 PM · Jan 28, 2021

What could be guessed from proxies?

- What can we predict about my immune response?
  - *Won't get any antibody response. Will get a normal t-cell response.*
- What can we predict about the impact of immune response on COVID-19 protection?
  - *More antibodies is more better.*
- Can I alter my treatment to change my immune response?
  - *B-cells recover with time. My personal data pre-COVID shows I replenish fast.*
- How might altering my immune response affect my MS risk?
  - *~3x increased MS relapse rate and worse relapses and progression w/o treatment,*
  - *Can guess this applies once memory b-cells return, but very limited data.*
- How do I weigh MS risk vs COVID risk?
  - *Estimate risk of ending up in hospital from COVID or MS, given what I know of my life, my community, and the literature on both diseases.*
  - *Result: point estimates give equal risks over a 6-month period! Large uncertainty.*

DECISION COMES DOWN ENTIRELY TO WHAT I VALUE, HOPE FOR, AND FEAR.

Interlude: There is rarely "an answer".
Or rather, there is often no answer to the question you wish was the right one to ask.

- Easy decisions
  - dichotomous outcomes
    - small uncertainty relative to difference
- Hard easy decisions
  - Very asymmetric outcomes
    - decision dominated by large risks for any finite probability
  - Minor differences in outcomes
    - decision doesn't matter even if it feels like it does

  Agita is often about wanting to feel in control.

- Hard decisions
  - Insufficient evidence for outcomes that are meaningfully different.

  Actually a science problem.

  - "Wicked Problems"
  - Overcoming strong beliefs

  Most disagreements are about values, not data.

The art of decision-making under uncertainty is finding ways to avoid hard decisions.

Decisions and outcomes

Round 1 (Feb-June 2021)

- Model: similar expected risk and reward for delaying MS treatment or not, with huge uncertainty.
- Decision: **Standard of care**—go thru with MS treatment & get vaccinated when eligible.
- Outcome: No covid antibodies. Positive COVID t-cells. No MS progression.

Round 2 (Sept 2021-Jan 2022)

- Model: COVID exposure risk is higher (Delta + less distancing); data confirms I can predict vax result.
- Decision: **Delay MS treatment.** Take advantage of lax record keeping to **initiate new 3-dose vax course.**
- Outcome: **Better than standard of care for what I value.**
  - Maximum achievable vaccine response. No MS change. *Developed mild eczema.*

Round 3 (Aug-Dec 2022)

- Model: COVID exposure risk higher still. Omicron makes novel response to new bivalent important.
- Decision: **Delay MS treatment.** Take advantage of lax record keeping to **get 2 bivalents.**
- Outcome: **Meh.**
  - Maximum achievable vaccine response. *Minor MS relapse that has only 80% recovered.*

Upon reflection, how do I think I did?

Round 1

- **A little wrong** to go ahead with my MS treatment instead of delaying.
  - Expert opinion was I would be eligible by May, but my frustration with our public health response made me unwilling to consider it carefully.

Round 2

- **Right choice**

Round 3

- **Got greedy**. Going for the second booster, and spending the extra time at MS risk, was a mistake.
  - *Contemporaneous signal:* I got really worried toward the end of my waiting period…
  - Inability to for vaccines to keep up with Omicron variants changed the value of antibodies.
  - I published on this(!), but I didn't update my personal beliefs because of my fear of COVID.
  - I didn't update my personal evidence for reactive autoimmunity, indicating higher MS risk.

Was it ethical to take advantage of lax vaccine record keeping to get extra doses above policy?

This reveals an enormous and complex space for personalized medicine

Millions of Americans have multiple comorbidities AND personalized risk factors.

- a novel infectious disease differentially affecting people with different risk factors is just an obvious example.

For MS and related diseases, the scientific community *does produce* much of the necessary data to model out many relevant individual choices, with individual preference accounted for.
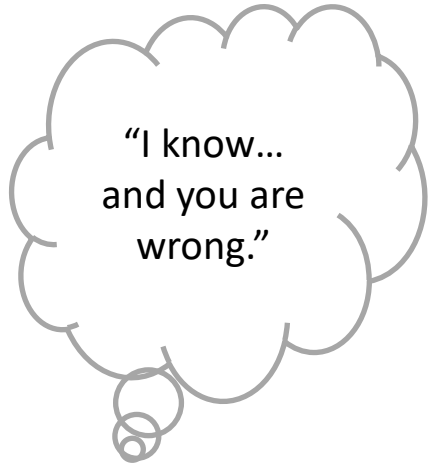
It is nearly impossible for anyone to reason through these issues alone.

It would be *revolutionary* to demonstrate that a personalized care system can generate better outcomes on average than current standard of care.
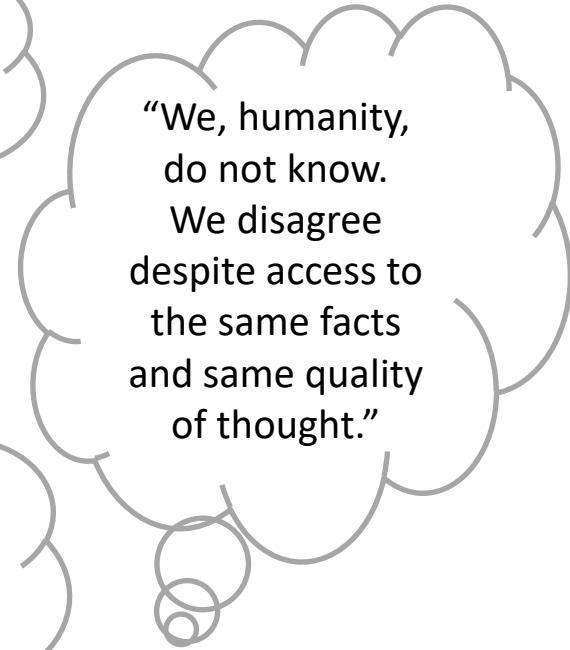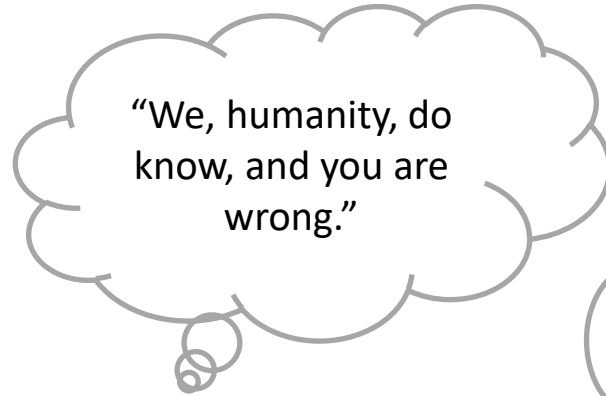
- Lower clinical morbidity and improved patient satisfaction

Requires innovation in care delivery, doctor-patient interaction, point-of-care modeling, and regulatory frameworks.

What does it mean when we say…?

"I know… and you are wrong." = ?

"We, humanity, do know, and you are wrong."

"We, humanity, do not know. We disagree despite access to the same facts and same quality of thought."

"We, humanity, do know. Both of us are making factual statements. We're really disagreeing about values."

What do I hope to leave you with?

- As data scientists, it's often tempting to focus on "here's the data I have, and here's the question I have, so what's the answer within my data?" This, alone, is bad.

- As natural philosophers, it's often tempting to focus on "here's how I think the world works. How does the evidence to support my model?" This, alone, is bad.

- As human animals, it's often tempting to focus on "here's what I think (avoiding what I feel), and this is what we should do (that I hope will make me feel differently)."
  This, alone, is worthy of love and compassion. But, with motivation obscured, it is not a sound basis for action.

- Maintaining dynamic balance on top of all these and other… selves… is essential to being good scientists.

Thank you!