ADAM ROGERS MEGAN MOLTENI SCIENCE 03.30.2020 07:00 AM

The Mathematics of Predicting the Course of the Coronavirus

Epidemiologists are using complex models to help policymakers get ahead of the Covid-19 pandemic. But the leap from equations to decisions is a long one.

People at a supermarket in Barcelona, Spain, practice social distancing. PHOTOGRAPH: DAVID RAMOS/GETTY IMAGES

IN THE PAST few days, New York City's hospitals have become unrecognizable. Thousands of patients sick with the novel coronavirus have swarmed into emergency rooms and intensive care units. From 3,000 miles away in Seattle, as Lisa Brandenburg watched the scenes unfold —isolation wards cobbled together in lobbies, nurses caring for Covid-19 patients in makeshift trash bag gowns, refrigerated mobile morgues idling on the street outside—she couldn't stop herself from thinking: "That could be us."

It could be, if the models are wrong.

Until this past week, Seattle had been the center of the Covid-19 pandemic in the United States. It's where US health officials confirmed the nation's first case, back in January, and its first death a month later. As president of the University of Washington Medicine Hospitals and Clinics, Brandenburg oversees the region's largest health network, which treats more than half a million patients every year. In early March, she and many public health authorities were shaken by an urgent report produced by computational biologists at the Fred Hutchinson Cancer Research Center. Their analysis of genetic data indicated the virus had been silently circulating in the Seattle area for weeks and had already infected at least 500 to 600 people. The city was a ticking time bomb.

The mayor of Seattle declared a civil emergency. Superintendents started closing schools. King and Snohomish counties banned gatherings of more than 250 people. The Space Needle went dark. Seattleites wondered if they should be doing more, and they petitioned the governor to issue a statewide shelter-at-home order. But Brandenburg was left with a much grimmer set of questions: How many people are going to get hospitalized? How many of them will require critical care? When will they start showing up? Will we have enough ventilators when they do?

Read all of our coronavirus coverage here***.***

There's no way to know those answers for sure. But hospital administrators like Brandenburg have to hazard an educated guess. That's the only way they can try to buy enough ventilators and hire enough ICU nurses and clear out enough hospital beds to be ready for a wave of hacking, gasping, suffocating Covid-19 patients.

That's where Chris Murray and his computer simulations come in.

Murray is the director of the Institute for Health Metrics and Evaluation at the University of Washington. With about 500 statisticians, computer scientists, and epidemiologists on staff, IHME is a data-crunching powerhouse. Every year it releases the Global Burden of Disease study—an alarmingly comprehensive report that quantifies the incidence and impact of every conceivable illness and injury in each of the world's 195 countries and territories.

In February, Murray and a few dozen IHME employees turned their attention full-time to forecasting how Covid-19 will hit the US. Specifically, they were trying to help hospitals—starting with the UW Medicine system—prepare for the coming crisis. Brandenburg says the collaboration could turn out to be, quite literally, life-saving. "It's one thing to know you may be getting a surge of patients," she says. "If you can make that more tangible—here's what it's actually going to look like—then we're in a much better place in terms of being able to plan for the worst."

But it's a big if. During a pandemic, real data is hard to find. Chinese researchers have only published some of their findings on the spread of Covid-19 in Hubei. The ongoing catastrophe of testing for the virus in the United States means no researcher has even a reliable denominator, an overall number of infections that would be a reasonable starting point for untangling how rapidly the disease spreads. Since the 2009 outbreak of H1N1 influenza, researchers worldwide have increasingly relied on mathematical models, computer simulations informed by what little data they can find, and some reasoned inferences. Federal agencies like the Centers for Disease Control and Prevention and the National Institutes of Health have modeling teams, as do many universities.

As with simulations of Earth's changing climate or what happens when a nuclear bomb detonates in a city, the goal here is to make an informed prediction—within a range of uncertainty—about the future. When data is sparse, which happens when a virus crosses over into humans for the first time, models can vary widely in terms of assumptions, uncertainties, and conclusions. But governors and task force leads still tout their models from behind podiums, increasingly famous modeling labs release regular reports into the content mills of the press and social media, and policymakers still use models to make decisions. In the case of Covid-19, responding to those models may yet be the difference between global death tolls in the thousands or the millions. Models are imperfect, but they're better than flying blind—if you use them right.

THE BASIC MATH of a computational model is the kind of thing that seems obvious after someone explains it. Epidemiologists break up a population into "compartments," a sorting-hat approach to what kind of imaginary people they're studying. A basic version is an SIR model, with three teams: *susceptible* to infection, *infected*, and *recovered* or *removed* (which is to say, either alive and immune, or dead). Some models also drop in an E—SEIR—for people who are "exposed" but not yet infected. Then the modelers make decisions about the rules of the game, based on what they think about how the disease spreads. Those are variables like how many people one infected person infects before being taken off the board by recovery or death, how long it takes one infected person to infect another (also known as the interval generation time), which demographic groups recover or die, and at what rate. Assign a best-guess number to those and more, turn a few virtual cranks, and let it run.

"At the beginning, everybody is susceptible and you have a small number of infected people. They infect the susceptible people, and you see an exponential rise in the infected," says Helen Jenkins, an infectious disease epidemiologist at the Boston University School of Public Health. So far, so terrible.

The assumption for how big any of those fractions of the population are, and how fast they move from one compartment to another, start to matter immediately. "If we discover that only 5 percent of a population have recovered and are immune, that means we've still got 95 percent of the population susceptible. And as we move forward, we have much bigger risk of flare-ups," Jenkins says. "If we discover that 50 percent of the population has been infected—that lots of them were asymptomatic and we didn't know about them—then we're in a better position."

So the next question is: How well do people transmit the disease? That's called the "reproductive number," or R_0, and it depends on how easily the germ jumps from person to person—whether they're showing symptoms or not. It also matters how many people one of the infected comes into contact with, and how long they are actually contagious. (That's why social distancing helps; it cuts the contact rate.) You might also want the "serial interval," the amount of time it takes for an infected person to infect someone else, or the average time before a susceptible person becomes an infected one, or an infected person becomes a recovered one (or dies). That's "reporting delay."

And R_0 really only matters at the beginning of an outbreak, when the pathogen is new and most of the population is House Susceptible. As the population fractions change, epidemiologists switch to another number: the Effective Reproductive Number, or R_t, which is still the possible number of people infected, but can flex and change over time.

You can see how fiddling with the numbers could generate some very complicated math very quickly. (A good modeler will also conduct sensitivity analyses, making some numbers a lot bigger and a lot smaller to see how the final result changes.)

Those problems can tend to catastrophize, to present a worst-case scenario. Now, that's actually *good*, because apocalyptic prophecies can galvanize people into action. Unfortunately, if that action works, it makes the model look as if it was wrong from the start. The only way these mathematical oracles can be truly valuable is to goose people into doing the work to ensure the predictions don't come true—at which point it's awfully difficult to take any credit.

Models are helping scientists understand Covid-19 infections rates and hospitals plan for surges. This one—a generic version—illustrates the concept of how infection rates can be changed by social distancing measures.

Speaking at a White House briefing on Thursday, Deborah Birx, response coordinator for the Coronavirus Task Force, admonished the press against taking those models too seriously, even as New York governor Andrew Cuomo begged for federal help with acquiring ventilators and protective equipment for health care workers. “The predictions of the models don’t match the reality on the ground,” Birx said.

Responding to Birx in a thread on Twitter, Harvard infectious disease epidemiologist Marc Lipsitch said Birx had been talking about work from his lab, which the federal government had asked for two days prior. In a preprint (so not peer-reviewed), his team had used an SEIR model with numbers tweaked to simulate the tightening or loosening of social distancing measures, as well as a potential flu-like seasonal variation in Covid-19 infections. He was varying R_0, essentially. In the model, putting a stop to strict social distancing (without something like a vaccine or a cure coming along) allowed infections to climb right back up to their peak of about two critical cases per 1,000 people—which could be 660,000 Americans getting seriously ill or dying. And even with the strictest lockdown-type measures lasting from April through July, his team’s model finds that the disease surges back in autumn.

Remember, the whole point of social distancing is to *slow* the epidemic, to keep the numbers of sick people at any one time below the maximum that the health care system can handle and stall so scientists can work on treatments. If Lipsitch’s team is right, the characteristics of Covid-19 might require a cyclical flux between strict social distancing and viral resurgence, on and on, perhaps until 2022. If everything goes right, Lipsitch wrote—massive testing and quarantines of the ill, and aggressive social distancing—it’ll be possible to keep numbers down and maybe shorten the timeline. But, Lipsitch said on Twitter, he didn’t see any of that underway.

So in dismissing all that, was Birx making a policy determination to assume that the model’s most Panglossian all-is-well prediction will turn out to be correct? “That was my impression of her comment,” said Yonatan Grad, an infectious disease epidemiologist at the Harvard School of Public Health and a lead author with Lipsitch on that study, speaking at a press conference on Friday.

Birx also took aim at an influential report published earlier this month by disease modelers at Imperial College London that predicted the deadly coronavirus could kill 500,000 Brits before the year was out. These chilling forecasts jolted Boris Johnson’s UK government out of its plan to sit back and wait for herd immunity to take the British Isles.

The report, which also predicted 2.2 million American deaths if the government did nothing, got President Donald Trump's attention. Shortly after, the White House rolled out a 15-day social distancing challenge, encouraging Americans to stay home as an act of patriotism. Then the US economy tanked, and Trump got nervous about staying the course. So when one of the Imperial researchers, Neil Ferguson, brought new estimates to the UK parliament last Thursday that predicted a British death toll below 20,000, Trump's task force seized on the apparent walk-back. "Half a million to 20,000," Birx said during the Thursday press briefing. "We are looking at that, in great detail, to understand that adjustment."

Except Ferguson wasn't *really* walking back his estimates or his model. As he explained later in his own series of tweets, the new numbers resulted from two things: The UK government's implementation of social distancing measures, and a slightly higher R_0 gleaned from new data from around Europe that suggests the outbreak is moving faster than at first believed—so more people are infected than anyone knows, with milder symptoms. Ferguson said this should lend more evidence, not less, to the importance of social distancing measures.

To be clear, Ferguson was doing exactly what any good scientist would do when presented with new data: updating the model. But these revisions came at a politically dicey moment. Only days before, the British media had begun telling people that maybe they didn't have to worry after all. A new study said that half the country had already contracted the coronavirus and were already immune to it. This is, in fact, not what the study said. But the two things hitting headlines at the same time created the public perception that maybe the virus wasn't so worrisome after all.

Produced by a group of researchers at Oxford, that other study had examined the number of observed deaths that occured in Italy and the UK prior to any social distancing interventions. The scientists then tried to ascertain which hypothetical—*emphasis on hypothetical*—circumstances could have led to those rapidly rising death tolls. One plausible explanation, they found, is exactly what the Imperial group's models suggest: The virus has just begun to spread in the UK and it is causing severe symptoms among a significant percentage of people. But equally plausible, according to their models, is that SARS-CoV-2 could actually have been circulating since January, possibly infecting up to half the population. For this scenario to work, most people would only get a mild version of the disease—only a tiny fraction of those infected would wind up in the hospital. In other words, in the first scenario, the epidemic is just taking off. In the second, it's already swept through the population.

If it's the second scenario, says Sunetra Gupta, the theoretical epidemiologist who led the Oxford work, "that would be great news," because it would mean a substantial chunk of the UK population is already immune. Nevertheless, even though it's only one of the scenarios that Gupta's model implies, the fact that it seemed to contradict Ferguson's work at Imperial College was enough for commentators and some media to tell a story of conflicting (and therefore untrustworthy) models.

To be clear, it does seem like some number of people, possibly a large number, transmit the virus without being diagnosed. They're House Infected posing as House Susceptible. That seems clear from researchers showing that in January, the strict travel measures that China imposed on people trying to leave Wuhan, the center of the outbreak, slowed the spread of the disease. That shows up in location data drawn from mobile phone apps; the extent of the disease followed people's travel patterns. When Wuhan locked down, that spread almost completely stopped. It bought time for the world to prepare—which large parts of the world, including the United States, squandered.

One clever study even tried to use a complicated model to estimate exactly how many undiagnosed, or "undocumented," cases the Chinese population had in January. The researchers—some at Imperial College and others in the US—broke the infected population into two groups, diagnosed and undiagnosed. (Or, in the language of this particular study, "documented" and "undocumented.") Through surveys and an app-based data collection project, the US team had actual data on how many people were wandering around at any given time with a respiratory virus; their calculations see that number peaking at more than 10 percent.

Using that as a kind of baseline, and combining it with location data for travel among 375 Chinese cities including Wuhan, the researchers tried various models to infer, given the number of overall infections and where they happened, how many undiagnosed infections had to have been out there. Their conclusion was stunning. Just 14 percent of infections were diagnosed, they wrote. Fully 86 percent of infected people were the walking ill, stealth transmitters of the virus. "Those undocumented infected people were about half as infectious.

However, because there are many more of them, they are the dominant driver of the outbreak," says one of the creators of the model, Jeffrey Shaman, director of the Climate and Health Program at the Columbia University School of Public Health. "This virus needs these undocumented cases to successfully move through a society. If you're identifying cases, you're going to have a better handle on it."

For now, there's really only one way to figure that out: tests. Specifically, that means gathering blood from infected people, which would contain their antibodies to the virus. That's what Gupta has concluded, too. "Our motivation was to explore, conceptually, the extreme variation that could be underlying what we see," says Gupta. "What we see is just the tip of the iceberg. And the only way to see under the surface is to go out there and look for these antibodies."

One of her collaborators has already developed one of these so-called serological tests, which can tell scientists who has been exposed to the virus and therefore now has immunity. Over the weekend, the researchers began testing blood samples collected from healthy Brits over the previous two months. (Gupta declined to say where the samples came from, citing confidentiality.) She says it could be just a matter of weeks before they have a much better picture of how vulnerable the UK population really is. But until then, at least in the UK, it will continue to be a tale of two models.

ONE THING THAT models will try to predict next, given the tranche of new data that these first 80,000-plus cases in the US will yield, is when social distancing and shelter-in-place measures can end. "You don't make the timeline. The virus makes the timeline," Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases told CNN. But how will anyone determine that timeline? The role of children as spreaders of the disease still isn't clear. Nor is the role of adults with mild symptoms.

"One of the crucial things that has to happen is serology tests, testing large numbers of the population for antibodies," Jenkins says. This data would show whether a person has been infected—whether or not they had symptoms. Population wide, that can give you more certainty on the numbers of susceptible and recovered people. The tests really only work a week or so after a person contracts the virus, but that's valuable enough that the UK has purchased 3.5 million blood tests already, and researchers in the Netherlands have begun testing blood bank donations.

How Long Does the Coronavirus Live on Surfaces?

Plus: What it means to "flatten the curve," and everything else you need to know about the coronavirus.

BY MEGHAN HERBST

"The modeling is going to be absolutely key for how we come out of this and what things look like longer-term. But for places in Western Europe and the United States, the scientific evidence is not particularly complicated. If you act soon, with a firmer response, you limit early deaths and get through the initial phase more quickly," Jenkins says. That's based less on models, she says, and more on research like a 2007 article about the "non-pharmaceutical interventions" different US cities used to respond to the 1918 influenza pandemic. Places that locked down more quickly had death rates half as high as ones that waited—and one of the coauthors of that study was the same Marc Lipsitch who tangled with the White House last week.

That paper's a lot clearer than a model, especially when so much about Covid-19 remains unknown. "One of the big dangers of modeling is that a model can get quite complicated quite quickly," Jenkins says. "And it's only as good as the data that go into it."

That's not the only barrier, either. The channels for model-makers to get to policymakers aren't clear. Even though governors across the US are touting models to justify their shelter-in-place orders and build-outs of critical care beds, it's just as easy for political leaders like Birx, a representative of the federal coronavirus response, to dismiss them—as a report from the Center for Health Security at Johns Hopkins points out.

Just as happens with models of climate change, the presentation of a range of possible futures in epidemiological models provides a lever for political opposition. Conservative commentators and allies of President Trump, *The Washington Post* reports, are increasingly describing social distancing orders and pleas for medical aid as part of a deep state plot. On his radio show Friday, ultraconservative provocateur Rush Limbaugh said,"We didn't elect a president to defer to a bunch of health experts that we don't know. And how do we know they're even health experts?"

The president seems to share these sentiments. After Governor Andrew Cuomo based a request for tens of thousands of ventilators on model projections, the president told television personality Sean Hannity, "I don't believe you need 40,000 or 30,000 ventilators." He based that opinion, he said, on "a feeling." Or maybe the president *doesn't* feel this way; two days later he tweeted that Ford and GM should start mass-producing ventilators, and he obliquely threatened to invoke the law he could use to make this happen. Maybe.

LISA BRANDENBURG THOUGH, would take the models over a feeling any day. University of Washington Medicine hospitals got their first confirmed Covid-19 patient on March 7. Three days later, she reached out to Murray and the Institute for Health Metrics and Evaluation. The following Tuesday, his team delivered a first round of projections for three scenarios: best, middle, and worst case. The worst case was bad. According to the models, UWM would have to accommodate an additional 950 Covid patients per day during the surge, which was due to arrive April 7. With around 1,500 beds across four hospitals, they would be overrun.

So Brandenburg's team got to work. They had already begun ordering more masks, gloves, face shields, and ventilators. They had opened a drive-thru testing station. Now they moved to deploy a surge plan, canceling all elective surgeries and trying to clear out as many beds as possible. They built wedding-party-size triage tents outside hospitals' emergency room departments to keep potential Covid-19 patients away from others seeking care. They called up ICU nurses who'd retired within the past five years. They began shuffling in nurses, respiratory therapists, and technicians from other departments, training them up on the specifics of critical care.

Murray's team embedded with Brandenburg's, providing them with daily updated projections as new data came in. In the most recent models from late last week, things started to take a turn—and for the first time, they were for the better. The curve is flattening out. In the new worst-case scenario, the number of patients has dropped by 20 percent compared with IHME's first report. The peak is now 10 days later, on April 17.

Across UWM's four hospitals, Covid-19 cases are down too. At the end of last week, doctors and nurses were caring for just over 60 Covid-19 patients, down from about 75 a few days prior. "It looks like the social distancing is helping," says Brandenburg.

She knows the projections can change any time, for the worse. And that's still what they're preparing for. But for the first time, she says, looking at those graphs she allowed herself to think that maybe, *maybe*, it was no longer a question of when Seattle would become the next Spain, the next Italy, the next New York. "For the first time I feel like, 'OK, maybe we are actually going to have all our plans in place,'" she says.

Other hospital administrators and local public health officials should take note. After word got out about the work IHME was doing for hospitals in Seattle, other health care providers around the US began sending Murray emails, asking for help with their own preparedness plans. As the individual requests piled up, his team decided to go public with their work last week, providing interactive state-by-state projections for how the nation's supply of hospital beds, intensive care units, and ventilators will hold up over the next few months.

The new coronavirus will spread through different regions at different speeds—depending on population density, transit patterns, and how well people are adhering to whatever social distancing measures are in place. So Murray's hope is that local policymakers can use the models to get a more fine-grained view on when their particular wave might be cresting. "We want to help them figure out when their worst week will be and to prepare accordingly, however they can," says Murray. His team plans to update their models every Monday, pulling in the latest death counts and adjusting for any changes to statewide social distancing policies. It's still too soon to say if Washington will be a success story. But at least right now, it appears to be an outlier.

According to IHME's models, 41 states will need more hospital beds than they currently have. Twelve states will need to boost their numbers of ICU beds by 50 percent or more. The models predict that over the next four months, these shortfalls will contribute to the deaths of 81,000 Americans, with the number of deaths per day peaking as soon as mid-April.

Even this estimate is generous. As epidemiologists have been pointing out on Twitter, Murray's models assume that states that haven't yet enacted strict stay-at-home orders will do so in the next week, in light of what's happening in New York—and that they'll achieve Wuhan-level lockdowns, which many public health experts are skeptical Americans can pull off. Indeed, plenty of states, mostly conservative-leaning and where case counts so far remain low, have resisted taking those steps. Even before Covid-19, scientists had trouble getting policymakers to pay attention to their warnings. Now they can't get enough data to make those warnings specific, and politicians are working to undermine what little the scientists are sure of. What was already a tragedy has evolved into a disaster, reaching toward catastrophe. And all of it was predictable.

WIRED is providing free access to stories about public health and how to protect yourself during the coronavirus pandemic. Sign up for our Coronavirus Update newsletter for the latest updates, and subscribe to support our journalism.

More From WIRED on Covid-19

- It's time to do the things you keep putting off. Here's how
- What isolation could do to your mind (and body)

- Bored? Check out our video guide to extreme indoor activities
- Blood from Covid-19 survivors may point the way to a cure
- How is the virus spread? (And other Covid-19 FAQs, answered)
- Read all of our coronavirus coverage here

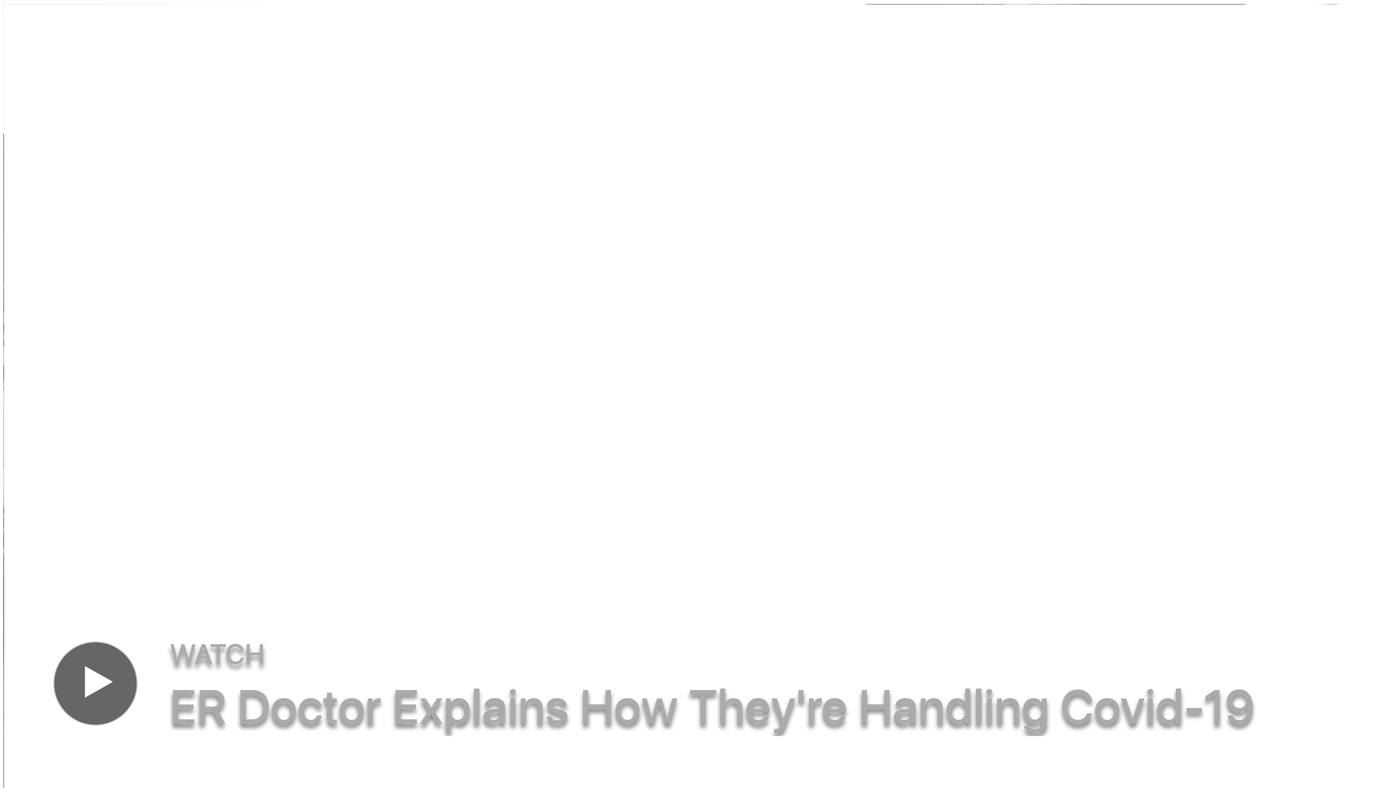
Adam Rogers writes about science and miscellaneous geekery. Before coming to WIRED, Rogers was a Knight Science Journalism Fellow at MIT and a reporter for *Newsweek*. He is the author of the *New York Times* science bestseller *Proof: The Science of Booze*.

SENIOR CORRESPONDENT

Megan Molteni is a staff writer at WIRED, covering biotechnology, public health, and genetic privacy. Previously, she freelanced as a reporter, audio producer, and fact-checker. Her work has appeared in Popular Science, Discover, Undark, Nautilus, and Aeon. She studied biology and ultimate frisbee at Carleton College and has a graduate... Read more

STAFF WRITER

Featured Video



ER Doctor Explains How They're Handling Covid-19

Epidemic expert Dr. Seema Yasmin interviews emergency room physician Dr. Cedric Dark about COVID-19's effect on the city of Houston, Texas. Dr. Dark talks about how the city is handling the pandemic, and what measures they are beginning to take in preparation for the worst.

TOPICS CORONAVIRUS COVID-19 MODELING EPIDEMIOLOGY WIRED FREE ACCESS