

HEALTH

You're Likely to Get the Coronavirus

Most cases are not life-threatening, which is also what makes the virus a historic challenge to contain.

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In May 1997, a 3-year-old boy developed what at first seemed like the common cold. When his symptoms—sore throat, fever, and cough—persisted for six days, he was taken to the Queen Elizabeth Hospital in Hong Kong. There his cough worsened, and he began gasping for air. Despite intensive care, the boy died.

Puzzled by his rapid deterioration, doctors sent a sample of the boy's sputum to China's Department of Health. But the standard testing protocol couldn't fully identify the virus that had caused the disease. The chief virologist decided to ship some of the sample to colleagues in other countries.

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At the U.S. Centers for Disease Control and Prevention in Atlanta, the boy's sputum sat for a month, waiting for its turn in a slow process of antibody-matching analysis. The results eventually confirmed that this was a variant of influenza, the virus that has killed more people than any in history. But this type had never before been seen in humans. It was H5N1, or "avian flu," discovered two decades prior, but known only to infect birds.

By then, it was August. Scientists sent distress signals around the world. The Chinese government swiftly killed 1.5 million chickens (over the protests of chicken farmers). Further cases were closely monitored and isolated. By the end of the year there were 18 known cases in humans. Six people died.

This was seen as a successful global response, and the virus was not seen again for years. In part, containment was possible because the disease was so severe: Those who got it became manifestly, extremely ill. H5N1 has a fatality rate of about 60 percent—if you get it, you're likely to die. Yet since 2003, the virus has killed only 455 people. The much "milder" flu viruses, by contrast, kill fewer than 0.1 percent of people they infect, on average, but are responsible for hundreds of thousands of deaths every year.

[Read: The official coronavirus numbers are wrong, and everyone knows it]

Severe illness caused by viruses such as H5N1 also means that infected people can be identified and isolated, or that they died quickly. They do not walk around feeling just a little under the weather, seeding the virus. The new coronavirus (known technically as SARS-CoV-2) that has been spreading around the world can cause a respiratory illness that can be severe. The disease (known as COVID-19) seems to have a fatality rate of less than 2 percent—exponentially lower than most outbreaks that make global news. The virus has raised alarm not despite that low fatality rate, but because of it.

Coronaviruses are similar to influenza viruses in that they both contain single strands of RNA.* Four coronaviruses commonly infect humans, causing colds. These are believed to have evolved in humans to maximize their own spread—which means sickening, but not killing, people. By contrast, the two prior novel coronavirus outbreaks—SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome, named for where the first outbreak occurred)—were picked up from animals, as was H5N1. These diseases were highly fatal to

humans. If there were mild or asymptomatic cases, they were extremely few. Had there been more of them, the disease would have spread widely. Ultimately, SARS and MERS each killed fewer than 1,000 people.

COVID-19 is already reported to have killed more than twice that number. With its potent mix of characteristics, this virus is unlike most that capture popular attention: It is deadly, but not too deadly. It makes people sick, but not in predictable, uniquely identifiable ways. Last week, 14 Americans tested positive on a cruise ship in Japan despite feeling fine—the new virus may be most dangerous because, it seems, it may sometimes cause no symptoms at all.

[*Read: The new coronavirus is a truly modern epidemic*]

The world has responded with unprecedented speed and mobilization of resources. The new virus was identified extremely quickly. Its genome was sequenced by Chinese scientists and shared around the world within weeks. The global scientific community has shared genomic and clinical data at unprecedented rates. Work on a vaccine is well under way. The Chinese government enacted dramatic containment measures, and the World Health Organization declared an emergency of international concern. All of this happened in a fraction of the time it took to even identify H5N1 in 1997. And yet the outbreak continues to spread.

The Harvard epidemiology professor Marc Lipsitch is exacting in his diction, even for an epidemiologist. Twice in our conversation he started to say something, then paused and said, “Actually, let me start again.” So it’s striking when one of the points he wanted to get exactly right was this: “I think the likely outcome is that it will ultimately not be containable.”

Containment is the first step in responding to any outbreak. In the case of COVID-19, the possibility (however implausible) of preventing a pandemic seemed to play out in a matter of days. Starting in January, China began cordoning off progressively larger areas, radiating outward from the city of Wuhan and eventually encapsulating some 100 million people. People were barred from leaving home, and lectured by drones if they were caught outside. Nonetheless, the virus has now been found in 24 countries.

Despite the apparent ineffectiveness of such measures—relative to their inordinate social and economic cost, at least—the crackdown continues to escalate. Under political pressure to “stop” the virus, last Thursday the Chinese government announced that officials in Hubei province would be going door-to-door, testing people for fevers and looking for signs of illness, then sending all potential cases to quarantine camps. But even with the ideal containment, the virus’s spread may have been inevitable. Testing people who are already extremely sick is an imperfect strategy if people can spread the virus without even feeling bad enough to stay home from work.

Lipsitch predicts that within the coming year, some 40 to 70 percent of people around the world will be infected with the virus that causes COVID-19. But, he clarifies *emphatically*, this does not mean that all will have severe illnesses. “It’s likely that many will have mild disease, or may be asymptomatic,” he said. As with influenza, which is often life-threatening to people with chronic health conditions and of older age, most cases pass without medical care. (Overall, about 14 percent of people with influenza have no symptoms.)

Lipsitch is far from alone in his belief that this virus will continue to spread widely. The emerging consensus among epidemiologists is that the most likely outcome of this outbreak is a new seasonal disease—a fifth “endemic” coronavirus. With the other four, people are not known to develop long-lasting immunity. If this one follows suit, and if the disease continues to be as severe as it is now, “cold and flu season” could become “cold and flu and COVID-19 season.”

At this point, it is not even known how many people are infected. As of Sunday, there have been 35 confirmed cases in the U.S., according to the World Health Organization. But Lipsitch’s “very, very rough” estimate when we spoke a week ago (banking on “multiple assumptions piled on top of each other,” he said) was that 100 or 200 people in the U.S. were infected. That’s all it would take to seed the disease widely. The rate of spread would depend on how contagious the disease is in milder cases. On Friday, Chinese scientists reported in the medical journal *JAMA* an apparent case of asymptomatic spread of the virus, from a patient with a normal chest CT scan. The researchers concluded with stolid understatement that if this finding is not a bizarre abnormality, “the prevention of COVID-19 infection would prove challenging.”

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Even if Lipsitch's estimates were off by orders of magnitude, they wouldn't likely change the overall prognosis. "Two hundred cases of a flu-like illness during flu season—when you're not testing for it—is very hard to detect," Lipsitch said. "But it would be really good to know sooner rather than later whether that's correct, or whether we've miscalculated something. The only way to do that is by testing."

Originally, doctors in the U.S. were advised not to test people unless they had been to China or had contact with someone who had been diagnosed with the disease. Within the past two weeks, the CDC said it would start screening people in five U.S. cities, in an effort to give some idea of how many cases are actually out there. But tests are still not widely available. As of Friday, the Association of Public Health Laboratories said that only California, Nebraska, and Illinois had the capacity to test people for the virus.

With so little data, prognosis is difficult. But the concern that this virus is beyond containment—that it will be with us indefinitely—is nowhere more apparent than in the global race to find a vaccine, one of the clearest strategies for saving lives in the years to come.

Over the past month, stock prices of a small pharmaceutical company named Inovio have more than doubled. In mid-January, it reportedly discovered a vaccine for the new coronavirus. This claim has been repeated in many news reports, even though it is technically inaccurate. Like other drugs, vaccines require a long testing process to see whether they indeed protect people from disease, and do so safely. What this company—and others—has done is copy a bit of the virus's RNA that one day could prove to work as a vaccine. It's a promising first step, but to call it a discovery is like announcing a new surgery after sharpening a scalpel.

Though genetic sequencing is now extremely fast, making vaccines is as much art as science. It involves finding a viral sequence that will reliably cause a protective immune-system memory but not trigger an acute inflammatory response that would itself cause symptoms. (While the influenza vaccine cannot cause the flu, the CDC warns that it can cause "flu-like symptoms.") Hitting this sweet spot requires testing, first in lab models and animals, and eventually in people. One does not

simply ship a billion viral gene fragments around the world to be injected into everyone at the moment of discovery.

Inovio is far from the only small biotech company venturing to create a sequence that strikes that balance. Others include Moderna, CureVac, and Novavax. Academic researchers are also on the case, at Imperial College London and other universities, as are federal scientists in several countries, including at the U.S. National Institutes of Health. Anthony Fauci, the head of the NIH's National Institute of Allergy and Infectious Diseases, wrote in *JAMA* in January that the agency was working at historic speed to find a vaccine. During the SARS outbreak in 2003, researchers moved from obtaining the genomic sequence of the virus and into a phase 1 clinical trial of a vaccine in 20 months. Fauci wrote that his team has since compressed that timeline to just over three months for other viruses, and for the new coronavirus, "they hope to move even faster."

New models have sprung up in recent years, too, that promise to speed up vaccine development. One is the Coalition for Epidemic Preparedness (CEPI), which was launched in Norway in 2017 to finance and coordinate the development of new vaccines. Its founders include the governments of Norway and India, the Wellcome Trust, and the Bill & Melinda Gates Foundation. The group's money is now flowing to Inovio and other small biotech start-ups, encouraging them to get into the risky business of vaccine development. The group's CEO, Richard Hatchett, shares Fauci's basic timeline vision—a COVID-19 vaccine ready for early phases of safety testing in April. If all goes well, by late summer testing could begin to see if the vaccine actually prevents disease.

[*Read: Coronavirus is devastating Chinese tourism*]

Overall, if all pieces fell into place, Hatchett guesses it would be 12 to 18 months before an initial product could be deemed safe and effective. That timeline represents "a vast acceleration compared with the history of vaccine development," he told me. But it's also unprecedentedly ambitious. "Even to propose such a timeline at this point must be regarded as hugely aspirational," he added.

Even if that idyllic year-long projection were realized, the novel product would still require manufacturing and distribution. "An important consideration is whether the underlying approach can then be scaled to produce millions or even billions of doses in coming years," Hatchett said. Especially in an ongoing emergency, if

borders closed and supply chains broke, distribution and production could prove difficult purely as a matter of logistics.

Fauci's initial optimism seemed to wane, too. Last week he said that the process of vaccine development was proving "very difficult and very frustrating." For all the advances in basic science, the process cannot proceed to an actual vaccine without extensive clinical testing, which requires manufacturing many vaccines and meticulously monitoring outcomes in people. The process could ultimately cost hundreds of millions of dollars—money that the NIH, start-ups, and universities don't have. Nor do they have the production facilities and technology to mass-manufacture and distribute a vaccine.

Production of vaccines has long been contingent on investment from one of the handful of giant global pharmaceutical companies. At the Aspen Institute last week, Fauci lamented that none had yet to "step up" and commit to making the vaccine. "Companies that have the skill to be able to do it are not going to just sit around and have a warm facility, ready to go for when you need it," he said. Even if they did, taking on a new product like this could mean massive losses, especially if the demand faded or if people, for complex reasons, chose not to use the product.

Making vaccines is so difficult, cost intensive, and high risk that in the 1980s, when drug companies began to incur legal costs over alleged harms caused by vaccines, many opted to simply quit making them. To incentivize the pharmaceutical industry to keep producing these vital products, the U.S. government offered to indemnify anyone claiming to have been harmed by a vaccine. The arrangement continues to this day. Even still, drug companies have generally found it more profitable to invest in the daily-use drugs for chronic conditions. And coronaviruses could present a particular challenge in that at their core they, like influenza viruses, contain single strands of RNA. This viral class is likely to mutate, and vaccines may need to be in constant development, as with the flu.

"If we're putting all our hopes in a vaccine as being the answer, we're in trouble," Jason Schwartz, an assistant professor at Yale School of Public Health who studies vaccine policy, told me. The best-case scenario, as Schwartz sees it, is the one in which this vaccine development happens far too late to make a difference for the current outbreak. The real problem is that preparedness for this outbreak should have been happening for the past decade, ever since SARS. "Had we not set the

SARS-vaccine-research program aside, we would have had a lot more of this foundational work that we could apply to this new, closely related virus,” he said. But, as with Ebola, government funding and pharmaceutical-industry development evaporated once the sense of emergency lifted. “Some very early research ended up sitting on a shelf because that outbreak ended before a vaccine needed to be aggressively developed.”

On Saturday, *Politico* reported that the White House is preparing to ask Congress for \$1 billion in emergency funding for a coronavirus response. This request, if it materialized, would come in the same month in which President Donald Trump released a new budget proposal that would cut key elements of pandemic preparedness—funding for the CDC, the NIH, and foreign aid.

[Read: It's suddenly cold out. Am I going to get sick?]

These long-term government investments matter because creating vaccines, antiviral medications, and other vital tools requires decades of serious investment, even when demand is low. Market-based economies often struggle to develop a product for which there is no immediate demand and to distribute products to the places they're needed. CEPI has been touted as a promising model to incentivize vaccine development before an emergency begins, but the group also has skeptics. Last year, Doctors Without Borders wrote a scathing open letter, saying the model didn't ensure equitable distribution or affordability. CEPI subsequently updated its policies to forefront equitable access, and Manuel Martin, a medical innovation and access adviser with Doctors Without Borders, told me last week that he's now cautiously optimistic. “CEPI is absolutely promising, and we really hope that it will be successful in producing a novel vaccine,” he said. But he and his colleagues are “waiting to see how CEPI's commitments play out in practice.”

These considerations matter not simply as humanitarian benevolence, but also as effective policy. Getting vaccines and other resources to the places where they will be most helpful is essential to stop disease from spreading widely. During the 2009 H1N1 flu outbreak, for example, Mexico was hit hard. In Australia, which was not, the government prevented exports by its pharmaceutical industry until it filled the Australian government's order for vaccines. The more the world enters lockdown and self-preservation mode, the more difficult it could be to soberly assess risk and

effectively distribute tools, from vaccines and respirator masks to food and hand soap.

Italy, Iran, and South Korea are now among the countries reporting quickly growing numbers of detected COVID-19 infections. Many countries have responded with containment attempts, despite the dubious efficacy and inherent harms of China's historically unprecedented crackdown. Certain containment measures will be appropriate, but widely banning travel, closing down cities, and hoarding resources are not realistic solutions for an outbreak that lasts years. All of these measures come with risks of their own. Ultimately some pandemic responses will require opening borders, not closing them. At some point the expectation that any area will escape effects of COVID-19 must be abandoned: The disease must be seen as everyone's problem.

** This story originally stated that coronaviruses and influenza viruses are single strands of RNA; in fact, influenza viruses can contain multiple segments of single-strand RNA.*

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