

Why Do Some Young, Healthy People Die From COVID-19?

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In the worst cases of COVID-19, the virus not only attacks and destroys tissue in the lungs but also triggers an overreaction of the immune system, creating dangerous levels of inflammation. Many of these patients are left unable to breathe on their own, and some die in a hospital intensive care units, or at home.

For others with milder COVID-19 cases, a hospital stay might end without the need for artificial ventilation, and they go home after being treated for pneumonia. Many more are riding out this illness at home, in bed with fevers, striving to isolate themselves from the rest of their household. Still more people — perhaps between 25 and 50 percent of all infected — feel no COVID-19 symptoms at all.

This huge range of severity of COVID-19 cases is part of what makes it such a horrific health crisis. The mild or asymptomatic cases can spread the disease to the most vulnerable, who may suffer greatly and, in some cases, even die. Because COVID-19 is such a new disease, much still needs to be learned about it. Among the top questions:

“What leads one person with the virus to severe disease, and another to have no or few symptoms?”

There are a few clear risk factors, including age and underlying medical conditions. But among younger healthy people, the risk factors aren't known.

“A lot of young patients without comorbidities are getting very sick, and we wish we knew who was going to deteriorate,” Dr. Rochelle Walensky, chief of infectious diseases at Massachusetts General Hospital and a professor of medicine at Harvard, told reporters last week. “We do know it happens precipitously. One day they're okay, the next day they require intubation. [It's] one of scariest parts of this disease.”

Potential risk factors need a lot more research: Are there some genetic variations that make one person more susceptible than another? And why are men dying in higher numbers than women? Here's what we know so far about risks for the worst forms of COVID-19 — and what we ought to learn.

The “infection enigma”

While the most severe COVID-19 cases are concerning, it's actually not unusual to have a big range. Doctors routinely see the same virus wreak havoc on one person and leave another unharmed.

“What we're seeing here is the same for tuberculosis, malaria, all infectious disease of

humankind,” says Dr. Jean-Laurent Casanova, a pediatrician who studies the genetics of disease severity. “Some people control the infectious agent very well, others die, and there’s everything in between. It’s what we call the infection enigma.”

What’s frustrating, he explains, is that the answer to the enigma may be different for each illness. The biological pathways that lead to severe disease for one virus might not be the same pathways that lead to severe disease with another virus. Each infection requires its own investigation.

Individual differences in immune response could lead one person to severe disease and another one to be fine. Scientists already have some hypotheses to test, and some leads to follow, in answering the infection enigma of COVID-19. For one, it’s thought that some of the difference between mild COVID-19 and severe cases may have to do with how the person’s immune system reacts (or overreacts) to the virus.

After an infection sets in, the immune system rallies to create antibodies — proteins that hunt down and kill foreign invaders like viruses in our bodies.

In some cases, “those antibodies can also backfire,” Akiko Iwasaki, a Yale immunobiologist, says. Some antibodies bind to the virus, she explains, and instead of blocking the virus, they’re taken up by white blood cells. Those white blood cells then go haywire, producing molecules called cytokines. These are the chemicals that, among other things, promote inflammation throughout the body. “And that ultimately makes the disease as bad as it is,” she says.

It’s unclear why a “cytokine storm,” as this reaction is called, might impact one person severely and not occur at all in another. Thankfully, though, doctors do have some insights into how to treat this overreaction. It’s possible sex differences play a role too. In the United States, and around the world, it appears COVID-19 is killing more men than women. The reason isn’t completely understood.

Men could have more underlying health risk factors than women. They could also be engaging in more risky behaviors (perhaps greater rates of smoking and drinking alcohol among men are in play.) There’s also evidence women may have a stronger immune response than men (and are also more at risk for autoimmune diseases because of it), as the Washington Post explains. We just need more research here.

Scientists will soon start to search for genetic clues, too, that might signal a person is more at risk than another. In Casanova’s lab, he and his team look for single genetic changes that cause one person to get sicker with an infection than another.

Herpes, for example, is a common infection that many people don’t even know they have, but in rare cases, it can lead to encephalitis (swelling of the brain). Casanova and colleagues have found genetic mutations that make brain cells more prone to herpes infections, he says. So if you have these mutations, “the virus replicates in the brain,” he says. “Whereas if you don’t, your neurons your brain remains protected.”

This genetic detective work has already begun for COVID-19. Casanova’s lab has been collecting genetic data on the few people under the age of 50 without underlying conditions in the ICU to see if

there are any genes that might explain the course their illness took in them.

He stresses that his approach is not guaranteed to find quick answers. “It may be three weeks, three months, three years, or 30 years, I don’t know,” he says.

Many things are not guaranteed here. It’s also possible that the genetics that underlie severe disease in an otherwise healthy person may not necessarily play the same role in one with an underlying condition like diabetes. The results of the genetic investigations may reveal more about the biology of the disease, rather than produce a reliable genetic counseling test for COVID-19.

Other groups of scientists will also search for polygenetic (many-gene) associations between genetic variation and disease severity. These studies will help scientists understand the biology of this illness better, and could potentially be used to figure out who is most at risk.

Perhaps the amount of virus a person is exposed to makes them sicker

Scientists also wonder if the circumstances of how a person was first infected play a role in how sick they get. Data from China reveals that health care workers are getting sicker from COVID-19 than you might expect based on their age.

It’s possible these workers are being exposed to high concentrations of the virus, which may lead a person to more severe illness. “The more virus you are exposed to, the more likely you are going to replicate higher levels of virus [in the body], and that’s not going to help you cope with such an infection,” Iwasaki explains. “And, of course, if you’re a health care worker, inhaling someone coughing in your face —that’s a very high level of exposure.”

This is one scientists still need to figure out. “We don’t really know at this time if dose, or dosing route has an effect” on severity, Angela Rasmussen, a Columbia University virologist, says. “I would imagine that it probably does.”

One thing is clear: Age is a risk factor for severe disease and death

Scientists may not yet understand the genetics, and exposure factors that lead someone to severe illness, but they’re not completely in the dark when it comes to risk factors. We know COVID-19 is an illness that disproportionately impacts some groups more than others. Namely, older people are most clearly at risk.

Last week, the journal *Lancet Infectious Diseases* published the latest estimates of the death rate of COVID-19. The paper found that globally, the case fatality rate for those under age 60 was 1.4 percent. For those over age 60, the fatality rate jumps to 4.5 percent. The older the population, the higher the fatality rate. For those 80 and over, COVID-19 appears to have a 13.4 percent fatality rate.

In the US, the CDC reports, “overall, 31% of cases, 45% of hospitalizations, 53% of ICU admissions, and 80% of deaths associated with COVID-19” are among adults older than 65. “With the highest percentage of severe outcomes among persons aged ≥85 years.” (To note: This CDC data is compiled from February 12 to March 16, when there were just 4,226

confirmed cases in the United States.)

Why are older people more at risk? There's no one reason. It's believed immune function declines with age, and older people have more of the underlying conditions that also appear to be risk factors for severe COVID-19. Young people also should not feel invulnerable. There have been disturbing reports of young, otherwise healthy people falling seriously ill with COVID-19 and dying.

In New York City — which currently has the largest outbreak of COVID-19 in the United States — there have been 12 deaths of people ages 19 to 44 who had no reported underlying medical conditions as of April 7, of 3,202 deaths total. And 11 percent of more than 19,000 hospitalizations were for those ages 18 to 44 as of April 5. So we should all do our part to protect ourselves from the virus, regardless of our age.

Underlying conditions like diabetes and heart disease appear to be risk factors

This is also showing up in US hospital data reported to the CDC: Many of the sickest patients also have underlying medical conditions. Seventy-eight percent of all people put into intensive care for COVID-19 in the US have had an underlying condition like diabetes or heart disease: 32 percent had diabetes, 29 percent had heart disease, 21 percent had chronic lung disease, and 9 percent had compromised immune systems.

We know that certain communities are disproportionately affected by these chronic conditions. In Chicago, 70 percent of those who have died from COVID-19 are black, even though black people make up only 29 percent of the city's population.

“The majority of the black COVID-19 patients who died had underlying health conditions including respiratory problems and diabetes. Eighty-one percent of them had hypertension, or high blood pressure, diabetes or both,” WBEZ in Chicago reports.

It's also possible that exposure to air pollutants can play a role. An epidemiology team from Harvard recently reported increased risk of dying from COVID-19 is also correlated with exposure to air pollution. Air pollution is known to harm the lungs and cardiovascular system, and a lifetime of exposure could make someone more vulnerable to damage from a respiratory virus.

The big picture here is that some demographics — who are more exposed to pollution, who suffer chronic diseases at higher rates, who have worse access to health care — may be more at risk from dying from COVID-19, and we should be mindful of this and seek to protect them.

There's so much more to learn

Scientists need to better understand these risk factors, so we can best protect the most vulnerable people. Higher-risk groups, for example, could be the first people to be vaccinated if a vaccine is approved and becomes available. The frustrating thing is, right now, this virus is still new.

It only came to the attention of the World Health Organization at the end of December. “We're still on the steep learning curve about the virus, and it could take a couple years to work out all these things,” Peter Hotez, dean of the National School of Tropical Medicine at

Baylor College of Medicine, says.

Unfortunately, in not knowing who is most vulnerable to get severe COVID-19, we may have to assume anyone can be.