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Odisha, in eastern India, has closed theatres, swimming pools, schools and other public spaces in order to stem the spread of coronavirus. Credit: STR/NurPhoto/Getty

Just how much has the coronavirus spread? More than 137,000 people in 117 countries and

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Based on conversations with three leaders in public health – at the WHO, the US Centers for Disease Control and Prevention (CDC) and at one of one of the largest research charities in the world – *Nature* explains how officials and researchers are attempting to estimate the size of individual outbreaks based on incomplete data.

Has the coronavirus that causes COVID-19 been spreading undetected in some populations?

“Yes, unequivocally,” says Jeremy Farrar, an infectious disease specialist and director of the research charity Wellcome, in London. A telltale sign of covert transmission in communities is finding a few confirmed but unrelated cases, with no recent history of international travel. That means these cases are connected through a hidden web of infections. The ideal way to know how many people in a community have had coronavirus infections, Farrar says, is to collect blood samples from people in every age group, looking for antibodies against the coronavirus, which show that someone has previously been infected. Data from such serology studies, as they are called, can then be used to accurately determine rates of fatality and transmission. But such studies take time. “We need to make policy decisions and clinical decisions now,” Farrar says. “You can’t say, ‘Let’s wait a month until we have the data.’”

Can scientists estimate the size of an outbreak without widespread testing?

Yes. Experts say that they compare various lines of evidence. One estimate begins with the number of deaths in an area. Farrar calls this a “guesstimate” because each of the variables researchers are using right now are subject to change, introducing uncertainty at each step in the calculation. However, it goes something like this: Data from China suggest that about three weeks passes between when a person feels sick and dies from COVID-19. And if you assume a

case fatality rate of roughly 1%, a back-of-the-envelope calculation suggests that each death represents about 100 cases in the first week. Right now, he adds, you can expect the epidemic to double each week if those cases aren't identified and isolated – bringing the estimate to 400 at the time of death. Because the error bars on each of these variables are large, epidemiologists check their figures against further information.

For example, experts have turned to analyses of coronavirus genomes. The best example is from Seattle, Washington, where on 29 February, Trevor Bedford, a computational biologist at the Fred Hutchinson Cancer Research Centre, and his colleagues reported that the genome of a virus collected from a teenager near the city closely matched that of one collected six weeks earlier, from an unrelated woman in her sixties who had returned to Seattle from China. The simplest explanation was that the virus had spread from the woman to other people, who spread it to yet others, eventually reaching the teenager. Bedford's team calculated that over the six weeks, several hundred people could have been infected.

Gregory Armstrong, deputy incident manager for the COVID-19 response at the CDC in Atlanta, Georgia, says that Bedford got in touch as soon as he finished the analysis. "I asked him to look at the probability of alternatives," Armstrong says. The teenager had not recently travelled internationally, so another possibility was that a second person had come to Seattle from the same region of China as the first traveller, with the same strain. But Bedford calculated that such a scenario was less likely than a single introduction.

So, how did the teenager acquire the infection without health officials noticing a huge uptick in cases? After the woman and her husband tested positive in mid- to late January, health officials monitored 347 people with whom they had come into contact¹. One possibility, Armstrong says, is that some of these contacts were infected, but showed few, if any, symptoms of COVID-19. If they didn't isolate themselves, they might have spread the virus in the community. When asked why the CDC didn't initially test more people in Seattle who complained of fevers and coughing in February, Armstrong says, "Resources, quite honestly."

In early March, academic laboratories ramped up screening for coronavirus, and have started to

reveal the extent of the outbreak. As of 12 March, King County health department, which covers Seattle, had reported 270 cases, with 27 deaths.

With so many cases undetected, how can the WHO make claims about how many countries have sustained transmission?

“We have to use the information we have,” says Maria Van Kerkhove, technical lead of the emergencies programme at the WHO in Geneva, Switzerland. Most of the WHO’s data come from surveillance and case detection, she says, but the organization also corresponds with scientists who conduct genome analyses and other studies. Understanding the extent of transmission in each province or state can help policymakers to tailor their responses.

Van Kerkhove says there is evidence that containment measures worked in China, which has reported just about 20 new cases per day, for the past week. (By comparison, Italy confirmed more than 2,000 cases in the past 24 hours.)

An early signal that China had begun to turn the tide on their epidemic was that most newly reported cases began to occur among known and quarantined contacts of cases, she says. In other words, the virus wasn’t spreading undetected – at least not as frequently as it once was.

“But while we are seeing a decline in cases across Asia, the big worry now is Europe,” says Van Kerkhove. “We know that with more aggressive containment, countries can hit a turning point. But in some countries it will get worse before it gets better.”

Armstrong worries that Europe's situation could foreshadow what's to come for the United States. “It’s hard to believe we won’t see that kind of spread here,” he says. “I hope we don’t, but health departments – every one of them – will tell you this is the most complex public health emergency we have dealt with.”

Is it time to ditch the idea of containing COVID-19?

Absolutely not, say Farrar, Armstrong and Van Kerkhove. Farrar explains that containment and

mitigation strategies overlap because measures that help to prevent an outbreak spreading also mitigate its effects on lives and hospitals. The most basic containment measure entails testing to identify infected people, finding their contacts and preventing them from infecting others. The WHO credits the curbing of China's outbreak to the country's meticulous identification of cases and contacts. Chinese authorities quarantined contacts – at home and in facilities where they were monitored for 14 days.

“Sometimes people have hundreds of contacts, so that is a very intensive effort,” says Farrar. “But it's absolutely critical to do it, because even though it probably won't completely contain the outbreak, it buys you time to make sure hospitals are ready, to think about the consequences of closing schools.”

China's mitigation measures, such as banning large gatherings, also seem to have slowed transmission. Armstrong uses an epidemiological measurement called the basic reproduction number, or R_0 , to describe the number of people whom an individual with COVID-19 might infect. “We are estimating an R_0 of around two or three,” he says. “If we can more than halve that with mitigation strategies, the outbreak will no longer grow.”

“Right now, we need to do anything that buys us one week, two weeks; anything to delay will have a dramatic impact,” says Farrar. “If London, Seattle or Paris goes through what northern Italy is going through at the moment, it will be devastating.”

Hospitals in northern Italy are running out of beds for patients, and around 250 health-care workers have been infected. If current rates of infection continue, an analysis in *The Lancet* predicts, intensive care units in Italy will be at maximum capacity at the end of next week². “I was on the phone with colleagues in critical care in Italy over the weekend, and it's desperate,” says Farrar. “Anything to dampen outbreaks will save an enormous number of lives.”

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