



A terrace in Quedlinburg remained empty after Germany's new lockdown took effect on 2 November.

COVID-19

Europe is locking down again—but its strategy is unclear

Without a plan to eliminate the virus, countries may face shutdowns over and over, scientists warn

By **Kai Kupferschmidt**, in Berlin

Shortly before 11 p.m. on 1 November, a waitress passed out paper cups to the customers crowded around the tables outside Luzia, a bar in Berlin's lively Kreuzberg district. "I'm sorry, but you all have to leave," she said. "God, in 2 minutes it's going to be lockdown," a woman at one table said, as guests poured the remainder of their cocktails into the cups. The fun was over: For the second time this year, Luzia had to close on the German government's orders.

All restaurants, bars, gyms, and theaters in Europe's largest economy will remain shut until at least the end of the month in a new bid to halt the spread of COVID-19. Hotels are no longer allowed to host tourists. Residents have been asked to meet people from only one other household. Florent, the manager at Luzia, took some hope from the fact that Germany was locking down while cases were still lower than in neighboring countries. "Hopefully we'll reopen in a month," he said.

With COVID-19 cases mounting and threatening to overwhelm health care capacity, much of Europe has taken similar measures to curb human contacts. Two months ago, as numbers began to creep up after a

blissful summer lull, countries still held out hope that more limited, targeted measures could prevent a second wave (*Science*, 4 September, p. 1151). Now, that wave is here, with the force of a tsunami. Europe has surpassed the United States in cases per capita; last week, it accounted for half of the more than 3 million cases reported to the World Health Organization (WHO). "Europe is at the epicenter of this pandemic once again," WHO's regional director for Europe, Hans Kluge, said on 29 October.

Most countries are reacting without a long-term plan, simply trying to avoid the worst. Officials differ about the best way to bring the numbers down again, and how low a level they should strive for. And no one knows what comes next. Short of vaccines to save the day, countries may face an exhausting series of lockdowns—a sawtooth pattern, "up and down and up and down," that could wreck the economy, says Albert Osterhaus, a virologist at the University of Veterinary Medicine, Hanover. "There is no strategy in Europe," he concludes.

The lockdown seemed an almost shockingly blunt tool when China first applied it in Hubei province on 23 January. But it also proved remarkably effective, and countries around the world took the same approach in

the spring, with varying degrees of intensity.

Europe has had a more science-driven pandemic response than the United States, but unlike many Asian countries, it was unable to avert a resurgence. Instead of using the summer to drive cases down to practically zero, Europe celebrated the holiday season. People seemed to lose their fear of the virus, says Michael Meyer-Hermann, a modeler at the Helmholtz Centre for Infection Research who was involved in drawing up Germany's lockdown plans. They increasingly flouted rules on physical distancing, mask wearing, and avoiding large gatherings.

"The infectious seeds in the community have always remained above a certain threshold, where if you relax the physical distancing, it's all going to come back," says University of Hong Kong epidemiologist Gabriel Leung. Numbers crept up and overwhelmed the other pillar of virus control: testing, isolating cases, and tracing and quarantining their contacts. The fact that life has largely moved indoors in recent weeks likely aided the resurgence, and cooler air may also favor the virus. "I think winter does make things much harder," says Adam Kucharski of the London School of Hygiene & Tropical Medicine. "Countries have probably been doing control on 'easy' setting over the summer."

Not everyone is convinced lockdowns are the answer. On 28 October, the day Chancellor Angela Merkel announced the new measures, Germany's National Association of Statutory Health Insurance Physicians presented a strategy paper arguing against a lockdown. "We cannot put the entire country, or even a continent, into an induced coma for weeks or months," said Andreas Gassen, head of the association. Another co-author, virologist Jonas Schmidt-Chanasit of the Bernhard Nocht Institute for Tropical Medicine, is convinced Germany's prelockdown restrictions would be enough to keep the virus from resurging—if they were strictly followed. Instead of closing tens of thousands of public places and spending billions to keep them afloat, Germany should spend money on communicating the need to better follow the rules, enforcing them strictly, and even creating some opportunities for people to safely enjoy riskier things such as parties, he says.

But most scientists say lockdowns are now unavoidable, although they need not be as draconian as in the spring, Kucharski says. Back then, "Countries were just doing absolutely everything at the same time," he says. Now, they can skip measures that severely restrict people's lives but don't contribute much to virus control. "There's no reason we need to lock people in their home," for

instance, as long as they keep their distance outside, says Devi Sridhar, chair of global public health at the University of Edinburgh.

The biggest difference from the spring may be that many countries are keeping schools open. Karl Lauterbach, a health policy expert and member of the Bundestag for the Social-Democratic Party who helped design Germany's "lockdown light," says it's clear schools do contribute to the spread of the virus. "Merkel asked: 'Am I sure we can do this without closing schools?' I said no, but probably yes," Lauterbach says. But the harm of school closures was deemed too great, he says.

Calculations suggest Germany needs to reduce contacts between people by roughly 75% from the current level, Lauterbach says. "That is incredibly hard if you want to keep schools and most businesses open." But bars and restaurants account for many contacts while providing only about 1% of Germany's gross domestic product, making them "kind of the perfect target for pandemic measures."

The first wave of lockdowns provided other lessons. For one, framing the debate as a choice between public health and the economy is wrong, Sridhar says: "In the longer term, having uncontrolled spread is much worse for the economy. That's what we've seen across the world." Also, locking down later means locking down longer. "If you wait until your infection level is quite high, probably your 2-week lockdown is going to become a 3-month lockdown," Sridhar says.

Europe's bigger question, however, is what comes next. Osterhaus says the strategy should be to get cases to zero using a hard and long lockdown, combined with strict border controls and quarantines to keep the virus out. That strategy, applied successfully by China, Australia, and New Zealand, may be politically unpalatable, however, and would require intense coordination between countries. "I can understand why that didn't happen," Leung says. "But the virus couldn't care less whether there are good or not so good reasons." Others are urging governments to follow South Korea's example: Drive cases to low numbers while improving the system of testing, tracing, and case isolation enough to keep the virus from resurging.

For now, Europe appears to be stuck in a third scenario: intermittently locking down to prevent the health system from buckling. "These circuit breakers are almost kicking the problem down the road," Kucharski says. "The hope is that vaccines and treatments and better options will be available in the new year." Lauterbach says he favored a longer lockdown in summer to go for elimination. But that would be too hard in winter, he says. "All we can do now is break the wave," he says. "But the water level will remain high." ■

BIOLOGY

Growth spurt for height genetics

By tallying thousands of genetic variants, researchers account for height's remaining "missing heritability"

By **Jocelyn Kaiser**

For height, DNA is largely destiny. Studies of identical and fraternal twins suggest up to 80% of variation in height is genetic. But the genes responsible have largely eluded researchers. Now, by amassing genome data for 4 million people—the largest such study ever—geneticists have accounted for a major share of this "missing heritability," at least for people of European ancestry. In this group, they've identified nearly 10,000 DNA markers that appear to fully explain the influence of common genetic variants over height.

"This is a genuine landmark," says Daniel MacArthur of the Garvan Institute of Medical Research in Australia.

If the missing genetic contributors to other traits and diseases can be identified, and extended to other ancestries, the results could "inform new biology and contribute to personalized medicine," suggests Loïc Yengo of the University of Queensland in St. Lucia, Australia, whose team presented the work online this week at the annual meeting of the American Society of Human Genetics. For example, geneticists could more accurately assess people's risk of diseases from genome scans. But the study leaves some scientists dissatisfied because it identifies only markers linked to genes that sway height, not the genes.

The mystery of missing heritability dates back to the late 2000s, when researchers began to use new tools to scan human genomes for common markers linked to diseases and traits. They expected the results of these genomewide association (GWA) studies to match evidence from the genetics of twins and families, such as the overwhelming influence in wealthy countries of genes on height, rather than environmental factors such as diet or childhood infections.

But it turned out that each identified marker, which may be in or just near a relevant gene, only contributes slightly to a trait or disease risk, and tallying them up didn't solve the problem. For height, the first 40 DNA markers linked to the trait explained just 5% of its variation.

A number of possible explanations emerged, including rare gene variants missed

by the GWA studies, gene-gene interactions, and that the twin studies were wrong. But Peter Visscher, leader of Yengo's team, argued it was partly a matter of finding many more common variants with very small effects. He estimated that such variants should account for 40% to 50% of the genetic component of height. Picking out the faint signals would require studying the DNA of a huge number of people, however.

By 2018, Visscher's team and other members of a global consortium called GIANT had pooled DNA data for 700,000 people and found 3300 common markers that explained 25% of the variation in height. Now, by looking across DNA from 201 GWA studies with 4.1 million participants, GIANT has brought the total to roughly 9900 common markers, accounting for 40% of the variation. Other markers located

nearby and likely inherited together account for another 10% of height variability.

That's still short of the 80% predicted by twin studies. But last year, Visscher's group drew on whole-genome sequencing data of a smaller number of people to demonstrate that

rare variants—those carried by fewer than one in 100 people—should explain another 30% of height's variation. (The result was released in a March 2019 preprint that the team is revising.)

Some geneticists say they aren't surprised that heritability gaps can be filled once enough people had their DNA scanned. "It was expected," says Aravinda Chakravarti of New York University. The problem remains that few of the height-linked DNA markers have been tied to specific genes that clearly alter the trait. "It's mostly all still 'missing' in a biological sense," says David Goldstein of Columbia University.

The new findings brighten prospects for tracking down those genes, Yengo says. Instead of being scattered randomly across the entire genome, which would make it challenging to ever get a handle on the specific genes and their roles, the 9900 or so markers are confined to only about 30% of the genome. And many cluster in areas known to contain genes involved in growth. ■

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