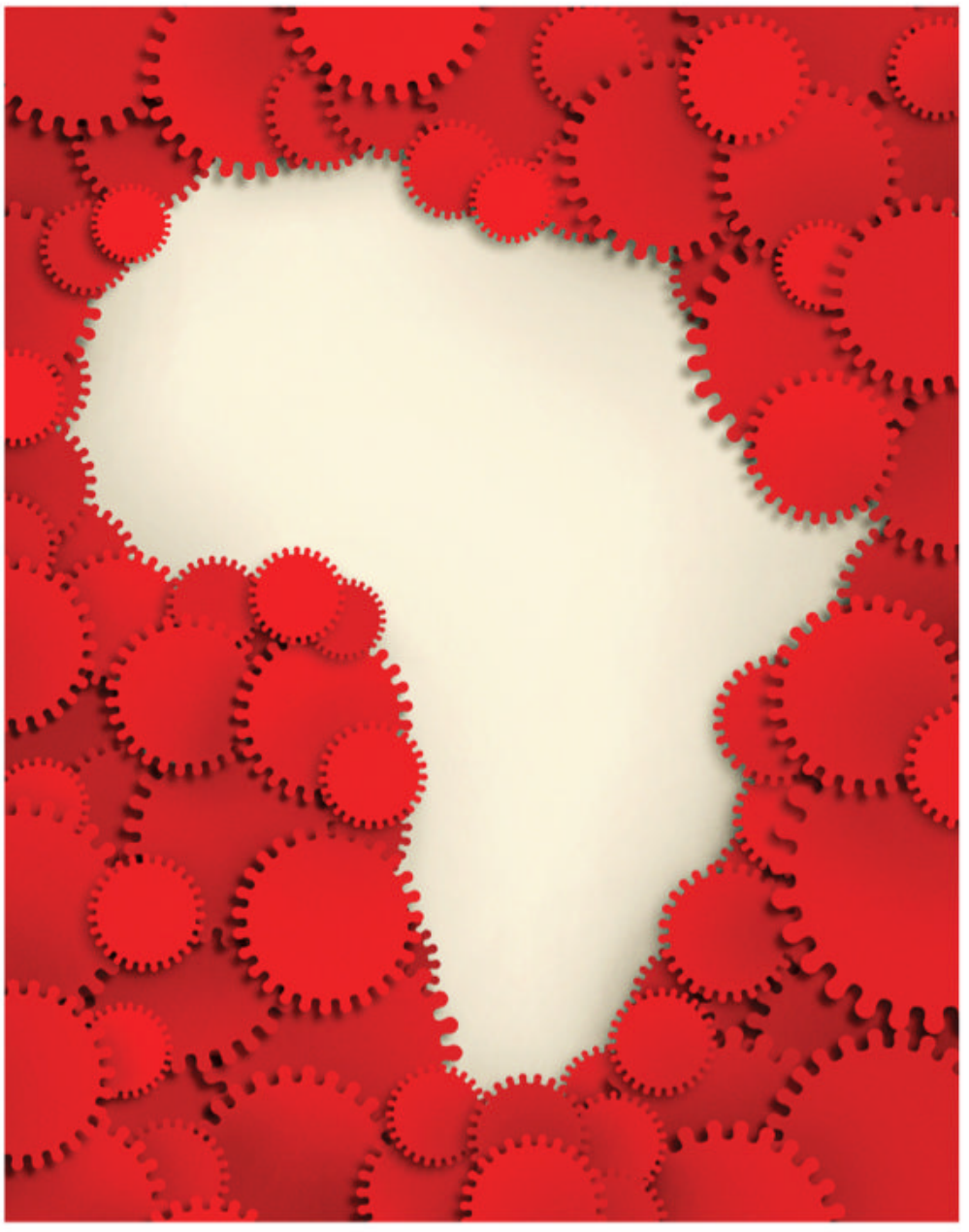
CORONAVIRUS CHRONICLES

THE COVID CONUNDRUM

Why does the pandemic seem far deadlier in some countries than in others?

BY SIDDHARTHA MUKHERJEE



On December 2nd, Mukul Ganguly, an eighty-three-year-old retired civil engineer in Kolkata, India, went to the Salt Lake Market to buy fish. The pandemic was surging around much of the world, and he wasn't oblivious of the risks of spending time at a wet market. His wife, a former forensic analyst, protested vehemently. But Mr. Ganguly wouldn't be deterred. He picked up his fabric shopping bag, tucked a doubled-up handkerchief in his pocket, and stepped out.

Mr. Ganguly lives in a modest, two-story, book-filled house a few blocks from the market. He tied his folded handkerchief into a makeshift mask, and spent about two hours buying groceries, choosing vegetables and sweets, and bargaining with the venders. (Give a man a fish and you feed him for a day; teach a man to haggle with a fishmonger and you'll feed him for a lifetime.) Two days later, he came down with a fever and a dry, incessant cough; he was barely able to walk to the bathroom. His daughter-in-law, in New Jersey—a cousin of mine—called me in a panic: he had tested positive for COVID-19.

We worked up a plan. He was to be isolated in a room with a pulse oximeter. His vitals were monitored twice daily. We arranged for a supplemental oxygen tank to be brought home in case his O_2 levels dipped too low. I called my doctor friends in Kolkata and asked them to stand by. For two days, Mr. Ganguly had a fever—100 degrees, 101 degrees—and then it subsided. By Christmas, he was pretty much back to normal. When I spoke to him in late December, he told me, in Bengali, that his experience had been typical. Various friends, all in their seventies and eighties, had contracted COVID-19. All had bounced back.

I called a friend in Mumbai, Shashank Joshi, who is a member of his state's COVID-19 task force. "Our I.C.U.s are nearly empty," he told me. Joshi is a doctor with seemingly infinite reserves of energy: a stethoscope perpetually dangling across his chest, he has spent the past several months carrouselling among slums, hospitals, and government offices, coördinating the state's response. Early last spring, when the first serious spread of COVID-19 was reported in India, Joshi jumped into action. Dharavi, in Mumbai, is Asia's largest slum: a million residents live in shanties, some packed so closely together that they can hear their neighbors' snores at night. When I visited it a few years ago, open drains were spilling water onto crowded lanes. (The next monsoon season, three young boys fell into the drains and died.) The tin roofs of the houses overlapped one another like fish scales; a roadside tap dripped a brown fluid that passed for potable water. When a toddler ran out from an open door onto the street, a neighbor caught him and lifted him up. Someone in the family—I counted six people in a single room, including an elderly couple—sent another child to retrieve him. In that episode alone, I later realized, I had witnessed at least nine one-on-one contacts.

After the pandemic was declared, last March, epidemiologists expected carnage in such areas. If the fatality rate from the "New York wave" of the pandemic were extrapolated, between three thousand and five thousand people would be expected to die in Dharavi. With Joshi's help, Mumbai's municipal government set up a field hospital with a couple of hundred beds, and doctors steeled themselves to working in shifts. Yet by mid-fall Dharavi had only a few hundred reported deaths—a tenth of what was expected—and the municipal government announced plans to pack up the field hospital there. By

Many regions report a COVID-19 death rate that's a hundredth of the U.S. rate.

ILLUSTRATION BY TYLER COMRIE

late December, reports of new deaths were infrequent.

I was struck by the contrast with my own hospital, in New York, where nurses and doctors were prepping I.C.U.s for a second wave of the pandemic. In Los Angeles, emergency rooms were filled with stretchers, the corridors crammed with patients straining to breathe, while ambulances carrying patients circled outside hospitals.

And there lies an epidemiological mystery. The usual trend of death from infectious diseases—malaria, typhoid, diphtheria, H.I.V.—follows a dismal pattern. Lower-income countries are hardest hit, with high-income countries the least affected. But if you look at the pattern of COVID-19 deaths reported per capita—deaths, not infections—Belgium, Italy, Spain, the United States, and the United Kingdom are among the worst off. The reported death rate in India, which has 1.3 billion people and a rickety, ad-hoc public-health infrastructure, is roughly a tenth of what it is in the United States. In Nigeria, with a population of some two hundred million, the reported death rate is less than a *hundredth* of the U.S. rate. Rich countries, with sophisticated health-care systems, seem to have suffered the worst ravages of the infection. Death rates in poorer countries—particularly in South Asia and large swaths of sub-Saharan Africa—appear curiously low. (South Africa, which accounts for most of sub-Saharan Africa's reported COVID-19 deaths, is an important exception.)

As the pandemic engulfed the world during the past several months, I kept returning to the question of what might explain these discrepancies. It was an epidemiological whodunnit. Was the "demographic structure" of a population the real factor? Were the disparities exaggerated by undercounting, with shoddy reporting systems hiding the real toll from public-health analysts? Was government response a critical variable? Or were other, less obvious factors at play? Perhaps any analysis would prove premature. If new viral strains, such as the South African variant of the virus, known as 501Y.V2, were to sweep through Africa, every prediction of mortality might be overturned. But as I started speaking with colleagues from around the world I found that my puzzlement was widely shared. For many statisticians, virologists, and public-health experts, the regional disparities in COVID-19 mortality represent the greatest conundrum of the pandemic.

"However you might think of it, the mystery remains," Mushfiq Mobarak, an economist at Yale who has helped research COVID-19 response strategies for developing nations, told me. "Tenfold differences, or one-hundredfold differences—these aren't minor. You have to account for other factors. You can't just wave the numbers off. It's going to be a lesson for this pandemic and for every future pandemic."

Mobarak, who grew up in Bangladesh (a hundred and sixty-three million people; eighty-three hundred reported COVID-19 deaths, or 3.5 per cent of America's, on a per-capita basis), studies populations and health. When I asked him about the puzzle, he began with what everyone accepts is the most potent variable for COVID-19 severity: age. The median age in India is twenty-eight. In Spain and Italy, it's forty-four and forty-seven, respectively. After the age of thirty, your chance of dying if you get COVID-19 doubles roughly every eight years.

So, if we were building a predictive model, we'd want to go beyond crude numbers, like median age, and get a more detailed picture of the so-called population pyramid. What's the proportion of people between seventy and eighty in Senegal versus Spain? How does the population pyramid of Pakistan compare with that of Italy? Even a carefully drawn pyramid can tell us only so much. Mexico has a median age similar to India's; the percentage of the population that's over sixty-five is within a point or two of India's. Yet India's reported rate of COVID-19 deaths per capita is less than a tenth of Mexico's.

So perhaps other populational features are significant. Take, for instance, the structure of an individual family and its living arrangements: who cohabitates with whom? Since the virus is often spread by close contact among family members—a grandchild infects a grandmother—we might want to know how often the elderly are found in multigenerational dwellings. As a rule, the higher a nation's per-capita G.D.P., the smaller the household size of the elderly. In the United Kingdom, where the per-capita G.D.P. in 2019 was forty-two thousand dollars, the average household size is 2.3. In Benin, where the per-capita G.D.P. is twelve hundred dollars, the average household size is 5.2, and nearly a fifth of these households have at least one member above sixty-five.

Mobarak suspects that, in places like the United States, "the spatial distribution of the elderly" probably also matters. Around a third of the deaths in the United States have occurred among residents and staff of long-term nursing homes. How do you assess the relative risks of the "warehoused elderly" in the developed world and the "homebound elderly" in the developing world, where seventy- and eighty-year-olds often live with a handful of younger family members? Is the grandfather of the Orou family in Benin, sharing a home with children and grandchildren who go out and about in the city, more vulnerable than the Smith couple, seventy-five and eighty-two years old, who reside in an assisted-living facility in Long Island with dozens of other elderly people, attended to by a rotating crew of visiting nurses?

Ideally, we'd also take account of the average level of contact among individuals. In densely populated, highly social contexts—urban environments, with wet markets, shantytowns, or subways—that number is high; in rural environments, it tends to be low. The virus spreads more easily in crowded spaces.

The task, then, is to factor in both intrinsic vulnerabilities (such as age or obesity) and extrinsic vulnerabilities (the structures of households, the levels of interpersonal contact). And here you start to get a sense of the challenges that our medical mathematicians must contend with. There are trade-offs battling trade-offs: are the risks greater for a younger country with a larger family size but with infrequent social contacts or for an older country with a smaller family size but frequent contacts?

The epidemiologists with whom I spoke agreed that these variables were the important ones to factor in. Accordingly, amid the spring surge, researchers at Imperial College London enlisted these variables in building models of COVID-19 mortality—with options for dialling up or down the level of interpersonal contact and viral contagiousness, and

generating a range of possible outcomes.

The models didn't always provide a time period when these deaths would occur; perhaps the worst is yet to come. Still, for rich countries, deaths predicted by the model weren't far from what we've seen, or, anyway, what we can now reasonably extrapolate. (The pandemic is far from over.) The surprise emerged when looking at South Asia and most of sub-Saharan Africa. The model—which, it should be emphasized, took age differences into account—appeared to be off, in most cases, by a staggering margin. Pakistan, with a population of two hundred and twenty million, was predicted to have as many as six hundred and fifty thousand deaths; it has so far reported twelve thousand. Côte d'Ivoire was predicted to have as many as fifty-two thousand deaths; by mid-February, a year after the pandemic reached the continent, it had reported under two hundred.

I called Abiola Fasina, an emergency-medicine physician in Lagos, Nigeria. In the early days of the pandemic, a prominent sponsor of public-health initiatives in Africa had envisaged "bodies out on the street" there. Between April and July, Fasina had run a field hospital and an isolation unit for COVID-19 patients. At first, she told me, "we were seventy or ninety per cent full. When I walked through those wards, I remember that the patients were mostly asymptomatic or mildly symptomatic. But as the pandemic continued patients mostly remained mildly symptomatic. It's all quite mild over here."

I asked Fasina, who is also a health-policy expert, to look out her office window at the street life below. "You know, life goes on pretty normally," she told me. "The markets are open. If you walk around the city, there are some people with masks and some without." Watching a video of street life in Lagos, I had a similar impression. In December, 2020, as London entered another stringent lockdown, the storefronts on Lagos's Nnamdi Azikiwe Street and Idumagbo Avenue were open. Carts shaded by brightly colored umbrellas were doing a brisk business. A woman carrying a basket on her head navigated gracefully past a man pushing a trolley full of gasoline cannisters.

A policeman pulled a motorist over—because he was unmasked? No, because he was smoking, and in Lagos State it's against the law to smoke while driving. Meanwhile, dozens of maskless people pushed past one another through shoulder-to-shoulder pedestrian traffic.

"Lagos is many things, and it's New York in Africa—activity on steroids," Olajide Bello, a lawyer there, told me. "We practically all live cheek by jowl, with almost no green spaces." The city, with fourteen million inhabitants, has returned to its usual chaos, Bello found. In late January, amid a new surge in COVID-19 infections, a national mask mandate was enacted, but enforcement has been spotty, and so has compliance.

Nigeria was predicted to have between two hundred thousand and four hundred and eighteen thousand COVID-19 deaths; the number reported in 2020 was under thirteen hundred. Ghana, with some thirty million residents, was predicted to see as many as seventy-five thousand deaths; the number reported in 2020 was a little more than three hundred. These numbers will grow as the pandemic continues. As was the case throughout much of sub-Saharan Africa, however, the statistical discrepancy was of two orders of magnitude: even amid the recent surge, the anticipated devastation still hasn't quite arrived. The field hospital that Fasina had helped set up in Lagos was packed up and shut down.

"Look, I don't come into your home office and tell you to get out of the tub."

Could the mortality gap be a mirage? Politicians may have an incentive to minimize the crisis (although the matter of incentives is complex: countries like Ghana and Nigeria sought and received billions of dollars in foreign assistance to help them combat the virus). At the same time, COVID-19 can be stigmatized in poorer countries, and, as Mobarak pointed out, that stigma, which he's seen in Bangladesh, "can lead to exclusion from economic life." The fishmonger has cause to keep his infection covert. And it's easy to imagine how such deaths might be underreported; a coroner's report might classify a COVID-19 death as "pneumonia" or "sepsis."

Oliver Watson, an epidemiologist at Imperial College London, who helped build the models, had a strong argument that systemic underreporting was a factor. He cited the example of malaria: "Only one in four deaths from malaria are estimated to be detected globally—in some low-income settings, it can be one in

twenty. And so a one-in-ten detection rate for COVID-19, an illness that carries far greater stigma, might well easily explain some of the discrepancy." Most of these undetected COVID-19 deaths occur at home, and hospitals routinely record COVID-19 deaths incorrectly.

Watson directed me to a study in Zambia, which recorded under four hundred COVID-19 deaths in 2020. (The model had predicted between twenty thousand and thirty thousand there for the entirety of the pandemic.) In Zambia's capital, Lusaka, researchers performed post-mortem tests of three hundred and sixty-four people who had been assigned various causes of death, and found that the coronavirus was present in seventy, or almost one in five. Forty-four of the seventy had manifested symptoms suggestive of COVID-19, including cough, fever, and shortness of breath, though only five had been tested for the virus while alive. The researchers carefully distinguished between "probable" and "possible" COVID-19 deaths, drawing from often scant clinical records, but, whatever the exact numbers were, it was obvious that the official records drastically shortchanged the reality. Lawrence Mwananyanda, a physician and global-health expert who helped lead the study, believes that Zambia's real death toll from COVID-19 might be as much as ten times as high as the official one. Any notion that the pandemic has bypassed Africa is, as Christopher Gill, an infectious-disease specialist at Boston University and another leader of the study, puts it, "a myth born of poor or absent data." Underreporting was plainly a serious issue.

The data problem could be worse in some countries, better in others. We'd expect that the amount of undercounting would vary from place to place because public-health resources vary, too. Westerners often think of sub-Saharan Africa as an undifferentiated landscape of underdevelopment, but that's far from the case. Zambia's per-capita G.D.P. is just sixty per cent of Ghana's or Nigeria's. Burkina Faso's is sixty per cent of Zambia's.

What to do when you can't take coroners' reports at face value, assuming that you even have a coroner's report? Public-health experts have a saying: "It's hard to hide bodies." So a surge of deaths under any description—"all-cause mortality"—might help us glimpse the true dimension of the problem.

What's the story in India? I turned to Ajay Shah, a soft-spoken economist from New Delhi, who has performed a notably detailed analysis of deaths in India during the pandemic. Rather than relying on hospital data, Shah and his co-author, Renuka Sane, have used a longitudinal household survey, in which each household is assessed three times a year, to examine the number and the pattern of deaths. They found that the total number of "all cause" deaths reported between May and August almost doubled in India compared with the same period in each of the past five years.

"Is that because the number of COVID deaths in the country has been vastly underestimated?" I asked.

"It's impossible to have a decisive answer," Shah told me. "But the pattern of the excess deaths doesn't really shout out COVID as the cause. It just doesn't." When his researchers analyzed the data by age, location, and gender, they found that excess deaths tended to be observed in younger cohorts, and in rural rather than in urban settings; nor was there evidence of the usual coronavirus skew toward greater lethality in men. "The telltale signatures of COVID just aren't there," he said. He won't venture any hypotheses about the cause of the excess deaths. But among the possible candidates are indirect consequences of the pandemic: wage loss, displacement, malnourishment, forced migration, and disruptions in health care—the skipped clinic visit for malaria, diabetes, TB, or hypertension. According to World Health Organization analyses, disruptions in medical care and prevention programs related to malaria, TB, and H.I.V. will have cost many more lives in sub-Saharan Africa in the past year than the coronavirus. In poorer regions, especially, infection isn't the only way that the pandemic can cost lives.

What if the storm simply hasn't yet arrived in the countries reporting oddly low death rates from COVID-19? Patrick Walker, another Imperial College epidemiologist and modeller, cautioned, "There's a time element that has not been built into the model. There have been waves after the first wave, and we still don't know how many deaths each wave might carry." It's certainly true that, in much of the Global South, reported COVID-19 deaths have risen substantially this season. To what extent have low-mortality regions simply avoided exposure to the pandemic?

In July and August, the health economist Manoj Mohanan and a team of researchers set out to estimate the number of people who had been infected with the new coronavirus in Karnataka, a state of sixty-four million people in southwest India. Random sampling revealed that seroprevalence—the rate of individuals who test positive for antibodies—was around forty-five per cent, indicating that nearly half the population had been infected at some point. Findings from a government survey last year showed that thirteen per cent of the population was actively infected in September. A large-scale survey in New Delhi, according to a recent government report, found a seroprevalence level of fifty-six per cent, suggesting that about ten million of its residents had been infected.

It's difficult to get seroprevalence numbers for Nigeria, say, but it's far from a secluded enclave; in 2019, it had an estimated twelve thousand Chinese workers, and, in a typical year, millions of people fly in and out of the country and within it. "Oh, there is probably a *lot* of endemic COVID transmission going on over here," Fasina, in Lagos, told me. "But we are just not seeing the extreme severity." (Most African deaths, the W.H.O. finds, are associated with such risk factors as hypertension and Type 2 diabetes.) In Niger State, which is the largest in Nigeria and is situated in the middle of the country, a seroprevalence study conducted in June found an infection rate of twenty-five per cent, comparable to the worst-hit areas in the United States. Fasina expects that the rate in Lagos and its surroundings will be higher. Nearly a year after Nigeria confirmed its first infections from the new coronavirus, Niger

State has reported fewer than twenty deaths. The country's numbers are climbing—but they'll need to grow exponentially in order to catch up with the models.

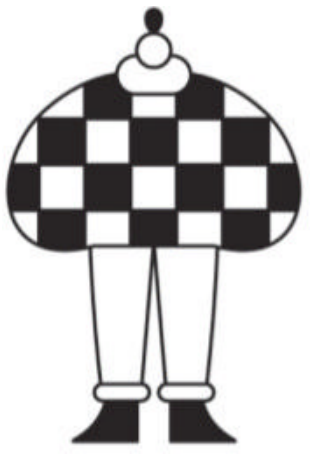
Some epidemiologists argue that an accurate account of geographical disparities must give due weight to another extrinsic factor: certain governments have responded more effectively to the crisis than others. Bethany Hedt, a statistician at Harvard Medical School, has worked in Rwanda for the past decade. She noted that in 2020 the low-income country reported only a hundred-some deaths from COVID-19, out of a population of thirteen million. "It's clear to me, at least," she said, "that it's because the government had very clear and decisive control measures." She went on, "When news of COVID hit, they imposed a strict curfew, and the Rwandan population really listened. There was limited travel outside the home without documentation. The police would stop you and check. Schools were closed. There were no weddings or funerals. And then, as the numbers decreased, the government played a very good game of whack-a-mole. They have a really strong data center, and anywhere they see an outbreak they do strict control at the local level."

Mohanan, the health economist who led the Karnataka study, agreed that, in some places, "decisive government action led to suppression of the pandemic." In Dharavi, health-care workers rightly take pride in their heroic efforts to track, trace, and contain infection. But the vigorous implementation of public-health measures was far from the norm in much of Africa and the Indian subcontinent. "If anything, India's response is a textbook case of what *not* to do in a pandemic—overly aggressive policy responses combined with communication strategies that undermined the importance of public-health prevention," Mohanan argued.

But what to make of the much discussed reports about how everyone in India started to wear masks this fall? My colleagues in India were doubtful about the reported level of compliance; they also noted that the recorded incidence of COVID-19 deaths in the country was creeping down almost as gradually as it had crept up, which didn't signal an abrupt change in behavior. My mother (who is under strict instructions to wear a mask and maintain social distance) routinely sends me pictures of gatherings in Delhi with dozens of maskless minglers.

Government actions in Ghana may have been better than in some of its neighbors, but mask-wearing in crowded urban centers remains intermittent. I was told of a bill-payment center in Accra, Ghana's capital, that, early in the pandemic, had mandated masks for entry. There weren't a lot of masks around, so the bill payers who had queued up took to wearing a mask to enter the building, and then handed their (used) mask to the next person in line when they exited, treating the mask mandate like the dress code at New York's Metropolitan Club—you put a "loaner" necktie on to get in, and hand it back for the next person to use when you leave. Yet New York City's official COVID-19 death toll in December was almost three times as high as Ghana's for all of 2020.

Other researchers are exploring whether acquired differences in human immunology might play a role. Acquired, or adaptive, immunity involves two principal kinds of cells: B cells make antibodies against pathogens, and T cells hunt for cells infected by a pathogen. B cells can be imagined as sharpshooters that target a virus with well-aimed bullets, while T cells are gumshoe detectives that go door to door, seeking viruses that are hidden inside cells.



Both B cells and T cells have an unusual capacity: after generating an immune response, some of them may become long-lived passengers in our blood, and carry the "memory" of an already encountered pathogen. These so-called memory cells are triggered when the pathogen reappears, and they can swiftly raise forces to fight it.

At the La Jolla Institute for Immunology, in California, researchers led by Shane Crotty and Alessandro Sette were studying the B- and T-cell responses to the coronavirus through samples of human blood plasma. To quantify the level of immunological activity against the virus, Crotty and Sette wanted a "negative control"—that is, samples of plasma that were collected before the pandemic.

But there was a peculiarity in the data: in more than forty per cent of pre-pandemic samples, the researchers found evidence that the new coronavirus was somehow triggering a T-cell response. These T cells were acting as if they'd recognized a virus they had assuredly never before encountered.

Sette, who was born in Italy, wears blue-rimmed spectacles, and rides his motorcycle to the lab where he works. "A negative control is supposed to be negative," he told me, stabbing his finger in the air. "We were totally surprised." He lifted his hands emphatically and waved them around, his ash-gray sweater stretching over his torso. "But the cross-reactivity is always there. We've repeated it. Other labs have confirmed the data. The number varies by geography and by the population—twenty per cent, forty per cent—but it's always there."

Why is that? Part of the answer may have to do with how T cells recognize pathogens. It's natural to think of our memory T cells as brandishing a criminal's mug shot. But what they "remember" is more like the curve of a nostril, the shape of an ear—distinctive snippets of a larger protein picture. Now, suppose a former intruder's much worse cousin shows up; it's a fresh face, but it shares a family trait—maybe those batwing ears—that could alert at least some of the memory T cells. Could the novel coronavirus share such traits with previously circulating pathogens?

He told me about an island in Italy, Isola del Giglio, that, he thought, might have been swept by a respiratory infection a few years ago. "But, when COVID-19 came and swept through Italy, the Giglio islanders were all spared," Sette said. "It may just be a story, but it makes you wonder whether one infection might protect you from another, perhaps via cross-reactive T cells."

Ben McFarland, a structural immunologist at Seattle Pacific University, had some thoughts about the possible origins of cross-reactive T cells. Last

spring, McFarland assigned his undergraduate students a project. "The university was under lockdown, so I had to think of something that the students could complete in their kitchens with the simplest of computer tools," he recalled. "And I thought, Why not line up the sequences of all the proteins from the different coronaviruses—both from the ones that cause common colds and from SARS-CoV-2—and look for fragments that they might share?"

It was akin to putting a bunch of closely related criminals in a lineup—some relatively harmless, some murderous—and asking the students to find closely matching features: a distinctive chin cleft or ear shape. The results were suggestive. "The students found a number of peptides"—the building blocks of a protein—"that could possibly induce T-cell cross-reactivity," McFarland told me. That novel coronavirus wasn't *entirely* novel. Even if the T-cell reaction wasn't strong enough to prevent an infection, he wondered whether it might diminish the severity of the disease.

Although the La Jolla researchers saw T cells in pre-pandemic blood samples which reacted to SARS-CoV-2, they didn't find antibodies that did so. This wasn't so surprising: they were looking only for a certain type of antibody, the "neutralizing" type that binds to a particular area of the spike protein. And, where T cells are guided by the equivalent of a flat snippet of a picture, antibodies typically attend to the full three-dimensional structure of a protein fragment. The antibodies are therefore more discriminating, less likely to fire in error—to be triggered by a criminal cousin.

Neither bench-lab work nor computer analyses, to be sure, tell us what happens with actual human beings. But researchers at Boston University tried to explore the hypothesis that prior common-cold coronavirus infections might affect the severity of COVID-19 by looking at patient outcomes. They identified a group of people who were found to have had any of four relatively harmless coronavirus variants—collectively termed eCoV—between May, 2015, and mid-March, 2020. When the tsunami of COVID-19 reached Boston, some of these people began to get infected with SARS-CoV-2. The researchers then compared the disease trajectory in eCoV-positive patients with that in a group of eCoV-negative ones. Among patients known to have had eCoV infections, there were lower rates of mechanical ventilation, fewer I.C.U. admissions, and significantly fewer deaths.

"Always an oil spill. Never a vodka spill."

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Unfortunately, the sample size was small in the Boston study; all the correlations could be accounted for by some as yet unidentified variable. A chastening recent study by a group of Philadelphia researchers didn't find that the presence of common-cold coronavirus antibodies correlated with clinical benefits. Cross-reactivity was seen, but not the kind that helped prevent or control infection. Meanwhile, German researchers have identified a surprising group of unrelated pathogens that share protein snippets—targets for antibodies and T cells—with the new coronavirus.

If it turns out that certain previously circulating pathogens can indeed induce a helpful level of immunity, then the specific geography of their reach—possibly in Lagos and not in Los Angeles—could show up in geographical disparities in death rates during the current pandemic. Shashank Joshi is among those who are inclined to credit the prior-immunity hypothesis, albeit tentatively. He told me that, in Mumbai, "there are plenty of infected older people living in crowded circumstances, such that we'd expect many hundreds or even thousands of deaths. But that's nowhere close to what happened." He made another observation: "In India, we've found that most people had really high levels of antibodies after an infection, and the levels don't decay, even among the older people. They stay on for a long period."

It reminded me of people who, having experienced chronic trauma, react to even the faintest trigger. Joshi was reluctant to speculate further about differences in immune reservoirs among populations: "It could be T cells, or it

could be some other aspect of the immune response. But we are definitely seeing signs of it in India."

It's tempting to think that Mr. Ganguly was one of those immunologically primed people, susceptible to infection but somewhat protected from the virus's worst effects. Maybe he was. Yet the prior-immunity hypothesis presents puzzles of its own. Why would some particularly protective viral strain, or strains, have reached South Asia, but not Latin America? Why Nigeria, but not South Africa, where the pandemic's death toll is so much higher than elsewhere in sub-Saharan Africa? Maybe there have been complex interactions between the intrinsic *and* the extrinsic.

Once you enter the zone of the plausible but unproven, other theories arise. Some researchers wonder whether the disparities are, in effect, dose-related. "I think one possible factor driving low deaths in India could be the low viral loads," Mohanan ventured. He and his lab-testing partners had found unusually low virus levels in infected patients. He went on, "One possible explanation for low viral loads is the open-air ventilation, which is more common in warmer parts of the world. This 'low-dose exposure' hypothesis is also consistent with the huge share of asymptomatic infections we've seen in India." Just as epidemiology calls for a truly detailed sense of a population's demographic structure, it might benefit, too, from a more intimate understanding of a population's immunological and socio-ecological profile.

William of Ockham was a fourteenth-century theologian who was educated at Oxford and wrote on a range of topics, from logic to theories of knowledge. But if his name is remembered today it's because of "Ockham's razor": the idea that, when seeking the cause of an event, we should favor the most parsimonious solution—the simplest one. Centuries before Ockham, and centuries after him, a host of thinkers argued for shaving away extraneous hypotheses to arrive at a straightforward and singular explanation for whatever they were puzzling over. It's among the strange ironies of intellectual history that if you ask "Who thought of Ockham's razor?" you'll wind up with not one but a plurality of answers.

The principle of parsimony has a special premium in the realm of science. We worship an elegant universe; we don't need to invoke multiple causes for why the planets move in geometrical orbits. Natural selection explains why the bones of human fingers look like those of a gorilla, just as it explains why new viral variants that have higher degrees of infectiousness can arise in the midst of a pandemic. Delving into mysteries, scientists are compelled by the logic of the classic mystery tale: one murder, one murderer, one weapon. In the pages of Agatha Christie, Hercule Poirot might unveil the solution with the flourish of a magician, and Miss Marple might murmur it into her pilled cardigan, but we finish such stories with a satisfying sense that all loose ends have been tied up, all oddities neatly accounted for.

Yet parsimony has its own perils, and the work that best helps me remember those perils, as it happens, isn't some meditation on the scientific method; it's Christie's "Murder on the Orient Express." A man has been found murdered on the train, his body perforated by multiple stab wounds. Poirot, on the train by happenstance, sets out to determine which of the passengers was the culprit. But the usual process of elimination fails him. Eventually, Poirot realizes that the murder is a long-planned act of collective revenge. There wasn't one murderer; there was a plurality of murderers.

What researchers have described to me as the pandemic's most perplexing feature may turn out to be the epidemiological version of that mystery on the Orient Express: there's no one culprit but many. With respect to the raw numbers, underreporting is an enormous problem; differences in age distribution, too, make a very deep cut, and perhaps the models must further calibrate their weightings here. Plainly, certain countries have benefitted from the strength of their public-health systems, fortified by a vigorous government response. (Our country has suffered grievously from corresponding weaknesses.) In New Zealand, raising the drawbridges and stringently enforcing quarantines made all the difference. But to come to grips with the larger global pattern we have to look at a great many contributing factors—some cutting deeper than others, but all deserving attention.

The COVID-19 pandemic will teach us many lessons—about virological surveillance, immunology, vaccine development, and social policy, among other topics. One of the lessons concerns not just epidemiology but also epistemology: the theory of how we know what we know. Epidemiology isn't physics. Human bodies are not Newtonian bodies. When it comes to a crisis that combines social and biological forces, we'll do well to acknowledge the causal patchwork. What's needed isn't Ockham's razor but Ockham's quilt.

Above all, what's needed is humility in the face of an intricately evolving body of evidence. The pandemic could well drift or shift into something that defies our best efforts to model and characterize it. As Patrick Walker, of Imperial College London, stressed, "New strains will change the numbers and infectiousness even further." That quilt itself may change its shape.

Today, in Britain, the National Health Service, like many of its patients, is fighting for its life, overwhelmed by a new influx of COVID-19 patients, many of whom have the highly contagious B.1.1.7 strain. In Nigeria, the reported per-capita mortality rate remains low by Western standards, but people remember that the President's chief of staff—a father of four—succumbed to COVID-19, and watch as the nation's health-care system continues to fray. Many officials are seeing a second wave decidedly worse than the first, as both the highly transmissible British variant and the South African one have started to crop up across the continent. Ghana recently suspended its parliament after an outbreak among members and staff. Throughout western, central, and eastern Africa, health officials hope that the mortality rates will stay relatively low, but know better than to assume that they will.

Dr. Joshi is still shuttling between hospitals and clinics in Mumbai, although, with a substantial proportion of the local population having already been infected, he expects that new cases will keep declining. In Kolkata, Mr. Ganguly has fully recovered. He plans to go to the fish market this week. ♦