BETTER THAN TEA LEAVES

Will mathematical models that consider climate change, disease agents, and human immunity—as a start—offer a reliable way to anticipate the next outbreak of cholera or malaria?

by Charles Schmidt | photography by Brian Ulrich | illustration by Darren Booth

The notion that a changing climate can trigger outbreaks of infectious disease has been around since the dawn of medicine. Ancient Romans knew this. Every summer, the wealthy escaped to hill resorts to avoid malaria—"mal'aria," or bad air in Italian.

But while the climate–disease link has been long appreciated, the nature of that link has been shrouded in mystery. Just as the weather is complicated, so too are the innumerable factors that dictate who gets sick from an infectious agent as well as when and why. Combining climate and disease variables into a predictive model—one that might offer early warning of a pending, weather-driven epidemic—is no easy task.

Enter HHMI investigator Mercedes Pascual at the University of Michigan. A marine and theoretical ecologist by training, with a gift for computational analysis, Pascual bridges the worlds of climate and infectious disease research. Her quantitative models—developed with collaborators in meteorology, epidemiology, and other fields—have generated convincing evidence that complex climate patterns influence infectious disease epidemics and their distribution.

Pascual's research has shown that cholera epidemics in Bangladesh vary in accordance with sea-surface temperatures 10,000 miles away in the Eastern Pacific Ocean. More recently, her models have revealed heightened risks for malaria in African highlands, accelerated by long-term warming trends that favor reproduction of the disease-carrying mosquitoes that were once less abundant in this region.

With global warming threatening major changes in how humans interact with infectious agents, Pascual's studies have taken on new urgency.

Looking for Patterns in Nature

Born in Uruguay, Pascual had a nomadic childhood, living in four Latin American countries while her father, a chemical engineer, moved from job to job. From an early age, she developed a love of the ocean that influenced her academic choices and career. An avid sailor, she was a crew member on yachts that traveled long-distance passages up and down the South American coast. And as an undergraduate at the University of Buenos Aires, she spent a summer studying dolphin ecology in Tierra del Fuego, just 600 miles from Antarctica.

Pascual's early interests revolved around marine ecology, but, as her academic career evolved, she found mathematics increasingly appealing. She says she was captivated by how complex dynamics in nature could be described in mathematical terms. "I liked how you could reduce observable patterns in population dynamics to numbers and equations," she explains. "And I liked that even messy data sets had patterns that might give you clues to their behavior in the real world, even though they might not be obvious at first."

When her studies took her to the United States in 1985, a meeting with Simon Levin, a pioneer in theoretical ecology at Cornell University (now at Princeton), helped Pascual realize she could combine her interests in math and ecology. After completing a master's degree in mathematics from New Mexico State University in 1989, she migrated east for a Ph.D. at the Woods Hole Oceanographic Institute to study with theoretical ecologist Hal Caswell.

These were heady times in the field, Pascual says. Scientists in theoretical ecology, including Caswell, were pioneering mathematical studies of "nonlinear" dynamics, which describe how ecological systems change and respond to their environments over time. Because of internal feedback between their components, natural systems almost never exhibit linear or proportionate responses to environmental influences. Plankton populations, for instance—the subject of Pascual's doctoral research— don't grow twice as large if their food supplies double. Many factors play into

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those growth rates, including competition among individuals. Given that, plankton populations exhibit complex, nonlinear responses to food increases that can be challenging to quantify.

Nonlinear dynamics have been central to Pascual's work ever since. But her emphasis has gradually shifted from their role in marine ecology to their expression in patterns of infectious disease. The transformation toward human illness began when Pascual moved to Baltimore in 1997 to work at the Center of Marine Biotechnology at the University of Maryland.

The Climate–Cholera Mystery

The Center for Marine Biology was headed by Rita Colwell (who later was director of the National Science Foundation from 1998 to 2004). Colwell had spent years studying cholera and was the first to propose that this water-borne illness—the result of *Vibrio cholerae* bacterial infections—could be linked to climatic factors. Her research had shown that the bacteria can survive in aquatic environments in association with plankton. When a massive cholera outbreak struck Peru in 1991, killing 10,000 people and sickening 1 million, Colwell proposed that a recent and remarkably strong El Niño was the underlying cause. In her view, unusually warm Pacific waters and heavy rains induced by the El Niño Southern Oscillation (ENSO) triggered a proliferation of cholera bacteria that fueled the epidemic.

In thinking about the epidemic, Pascual wondered if cholera's response to climate variability was nonlinear and governed not just by ENSO and its effects on the pathogen but also by an important limiting factor—i.e., the fraction of susceptible people in the at-risk population.

Infectious diseases need fuel to spread, Pascual explains, and that fuel comes in the form of susceptible individuals. Those who survive cholera develop temporary immunity to future exposure. When immunity predominates in a population, cholera outbreaks don't spread no matter how strong the environmental pressures. But when the pool of susceptible people rises—perhaps because of new births or human migration

Mercedes Pascual

A large fraction of the population of Dhaka, Bangladesh, has no access to clean water sources and can be exposed to the cholera pathogen through water bodies such as this pond, photographed during the city's dry season.

patterns—vulnerability to environmental pressures increases, making outbreaks more likely and intense.

Pascual wanted to study the interaction between ENSO and cholera outbreaks, but to do that she had to look beyond the Peruvian epidemic. El Niños occur every three to seven years, but before the 1991 event Peru hadn't experienced a cholera outbreak of any significance for more than a century. To model disease dynamics over multiyear timescales, Pascual needed to look at more than a single outbreak. She needed data from a country that faced cholera threats on a regular basis.

She turned to Bangladesh, where cholera is a fact of life. Bordered by India and the Bay of Bengal, Bangladesh is home to 150 million people, many of them forced by population pressure to the low-lying coast. Inundated by rivers that flow south from the Himalayas and perched on a landscape just a few feet above sea level,

Bangladeshis face routine flooding with water contaminated by fecal matter.

Cholera bacteria thrive in this setting; once ingested by a human, the microbes proliferate in the gut, doubling their numbers every eight minutes. Within hours, the disease produces an explosive, clear diarrhea, speckled with rice-like shreds of intestinal lining. Untreated, it can kill in a day.

Cholera cases in Bangladesh spike twice yearly, according to infectious disease specialist Gary Schoolnik at Stanford University School of Medicine. The first spike occurs just after the monsoon rains that pour torrentially from June to September, overwhelm sanitation systems, and liberate *V. cholerae* into water used for drinking and bathing. The second occurs during the hot, dry spring, when shrinking pools of standing water concentrate the bacteria, unleashing another round of infections. Yet, the intensity of these

seasonal outbreaks also varies on interannual timescales that, Pascual noticed, seemed to correspond to ENSO-generated escalations in ocean temperature.

Pascual had found valuable collaborators at the International Center for Diarrheal Disease Research (ICDDR) in the capital city, Dhaka, who had been monitoring cholera in different locations in Bangladesh since 1966. Their "time-series" data for Dhaka describing cases since 1980 was a crucial resource for Pascual's investigation. By considering those data against ENSO sea-surface temperature changes in a nonlinear model, she found what she was looking for: quantitative evidence tying ENSO to cholera dynamics. "In the end, we discovered a lag of 9 to 11 months between ENSO and an increase in cases," Pascual says.

The finding—reported by Pascual, Colwell, and colleagues in *Science* in 2000—made international headlines. By linking cholera to global climate cycles, Pascual had fueled hopes for an ENSO-driven warning system that might avert outbreaks in Bangladesh and elsewhere altogether. By that time, Pascual had received 10 years of research funding (in 1999) from the James S. McDonnell Foundation; in 2001, she moved to the University of Michigan to become an assistant professor of ecology and evolutionary biology.

The ability to forecast epidemics in advance would be an important breakthrough for public health, Colwell says. Cholera—a symptom of poverty that's been virtually extinguished from the developed world—is an imminently treatable disease. Most patients recover with antibiotics and an oral rehydration solution containing salts, sugar, and clean water. "Better outbreak prediction would make it possible to gather the needed treatments and resources more efficiently,"

Colwell says. "If you've got a few months to prepare, you can be more effective in dealing with the problem."

Better Predictions

From Michigan, Pascual continued her cholera studies, following up in 2005 with a paper in *Nature* that teased ENSO's role apart from the contributions of population immunity, which also cycles over multi-year time frames. "I wanted to approach the role of climate with a better understanding of what was happening with respect to the disease itself," Pascual says.

Doing that wouldn't be straightforward. To control for host immunity, Pascual had to know the fraction of susceptible people in the Bangladeshi population over time. Those data weren't available, so she used population data supplied by her collaborators at ICDDR. From 1966 to 2002, ICDDR staff had followed cases among roughly 200,000 people living in Matlab, a rural area just south of Dhaka. This defined population gave Pascual a denominator with which—by applying statistical wizardry—she could estimate the percentage of immune individuals living in the area from one year to the next. With that knowledge, Pascual was able to remove the influence of host immunity from her investigation of ENSO's effects on cholera transmission. She found that ENSO's effects still held up, meaning that the spike in cases couldn't be attributed solely to declines in immunity.

What those results didn't explain, however, was *how* ENSO held sway over cholera dynamics in Bangladesh. To answer that question, Pascual collaborated with scientists at the Climate Research Laboratory in Barcelona, Spain, and the Center for Ocean-Land-Atmosphere Studies (COLA) in Calverton, Maryland. Supported by the National Oceanic and Atmospheric Administration, the National Science Foundation, and the National Aeronautics and Space Administration, COLA scientists believe that the global climate—while chaotic—has predictable elements that allow for accurate forecasting on both short- and long-term timescales.

Crucial to their analyses is a 3,000-mile-long rectangular swath of Eastern and Central Pacific Ocean dubbed "Index 34."

Mercedes Pascual's computational models have generated evidence that complex climate patterns influence the incidence of infectious disease epidemics.
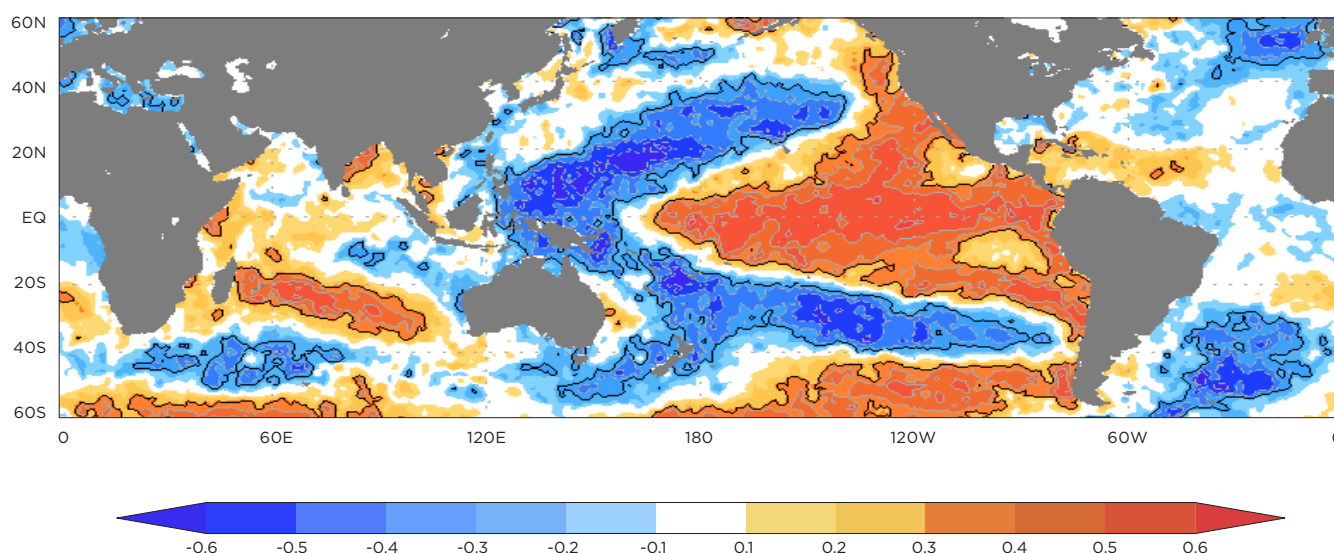
The world's ocean temperatures influence global climate variability and are important to infectious disease dynamics, according to Mercedes Pascual. This global ocean grid shows the correlation between sea surface temperature anomalies in January and cholera cases in September in Matlab, Bangladesh. The large orange area in the Pacific Ocean indicates a significant positive correlation between these variables (the color bar at bottom gives the values of the correlations). Interestingly, this is the same area in the Pacific that warms during El Niño events.

COLA research scientist Benjamin Cash says that during ENSO periods, sea-surface temperatures throughout Index 34 can rise by up to 2.5°C, producing a general warming of the tropical atmosphere. "And if that warming persists long enough to influence monsoon circulation patterns, you see increased rainfall over Bangladesh," he explains. "And Bangladesh is a low-lying country where floods lead to a breakdown in sanitation."

Pascual agrees that heightened rainfall may be the culprit behind the ENSO–cholera connection in Bangladesh. But, she adds, much about that connection remains unresolved. "ENSO produces high amounts of rainfall in some areas in Asia and lower amounts in others," Pascual explains. "Through our work with Ben Cash and Xavier Rodó (Barcelona) we're starting to get a better handle on what mediates the effect of ENSO on cholera in Bangladesh, but we're not in a position to make firm conclusions about the role of rainfall yet. We still need to know more about local climate drivers and how they mediate ENSO's influence. Whether we're better off predicting outbreaks on the basis of local or remote climate variables remains an open question that we're working on now."

Yet another factor to consider, Pascual says, is the role of "inapparent" or asymp-

tomatic cholera infections among the population and how they influence disease transmission. In a paper published in *Nature* in August 2008, University of Michigan's Aaron King, Pascual, and colleagues showed that the fraction of asymptomatic individuals can be greater than anticipated. These more mildly affected individuals have rapidly waning immunity, the scientists found, which could be crucial to interpreting patterns of disease outbreaks.

Climate Change Now

Ancient Romans experienced the impact of seasonal variation in temperatures on malaria transmission. But Pascual's research is supplying quantitative evidence that climate change—a trend of increasing temperatures—is having an important effect on malaria.

In 2006, she published a paper in *Proceedings of the National Academy of Sciences* suggesting that even small temperature increases in the East African highlands could amplify mosquito populations and boost human exposure to the malaria parasite.

Encompassing mountainous regions of Kenya, Tanzania, Rwanda, and Ethiopia, the East African highlands have traditionally avoided malaria. Mosquitoes don't

mind cool, high-altitude climates, but cooler temperatures slow the development of the malaria parasites, limiting disease transmission. Malaria incidence in several East African highland regions, however, has been rising since the late 1970s. What's more, time-series data generated by the Climatic Research Unit at the University of East Anglia in the United Kingdom show that ambient temperatures in the region climbed approximately 0.5°C from 1950 to 2002.

Experts argue about what's driving the rise in cases; some point to growing drug resistance among malaria parasites and changing demographics as probable causes. Pascual doesn't discount those possibilities. But she adds that her modeling results—which suggest that mosquito populations under current warming trends could have doubled in some regions—indicate that local climate change can't be ruled out as a contributing factor.

Andrew Dobson in the Department of Ecology and Evolutionary Biology at Princeton University concurs. He adds that it's difficult to validate Pascual's modeled findings, given the paucity of mosquito population data from the East African highlands and other areas in the developing world. "Scientists are only now

beginning to collect the data that allow us to make more predictive models," he says. "But you're starting to see the shadow on the wall—we've got more people with malaria in the highlands and it's my impression that this is the result of more transmission, which is in turn exacerbated by greater numbers of mosquitoes."

That conclusion, Pascual says, has implications for how scientists might consider the influence of global warming on infectious disease. Many current efforts on climate change and malaria focus on scenarios for spatial distribution of the disease in the future. But her ongoing work considers the recent past— the last three decades within her own lifetime—and shows that the effects of warming on disease transmission may already be under way in this highland region, providing an indication of what's to come in the years ahead.

But even as society absorbs information and predictions about the influence of warming on infectious disease, it must accept that modeled estimates are never perfect. Roberto Bertollini, director of the World Health Organization Department of Public Health and Environment, in Geneva, Switzerland, says that climate models need more development and systematic validation before they can be widely used as warning systems for disease outbreaks. "I see them as a very positive development for future applications in public health," he says. "For too long, our approach to public health has been reactionary—we need to become more proactive, more anticipatory when it comes to disease. We're not using these models now, but we encourage their development, we see them as useful tools to managing the effects of climate change."

"If we're going to understand the way global climate change modifies disease exposure conditions, we're going to have to bring a lot more mechanistic rigor into our modeling," says Jonathan Patz, professor of environmental studies and population health sciences at the University of Wisconsin–Madison and a leading expert on climate change and infectious disease. "That's what Mercedes brings to the table—an understanding of how to model climate change's influence on disease ecology and its impact on public health. And that's a component that we really need." ∎