ON THE HUNT FOR THE NEXT DEADLY VIRUS

Searching for new viruses and tracking down the source of pandemics, scientists are laying the groundwork to defeat "spillover" diseases.

BY FRAN SMITH

The special packages arrived in January 2020 at the Bangkok laboratory of virus expert Supaporn Wacharapluesadee. They contained tubes of saliva and mucus from five people who had just landed at the city's main airport from Wuhan, China.

Days earlier, Chinese authorities had announced a cluster of mysterious pneumonia cases in Wuhan. Officials in Thailand, a top destination for Chinese tourists, rushed nurses to airports to screen arriving passengers for fevers or coughs. Health officials feared the culprit might be something nobody had ever seen.

"They asked me, could I detect the unknown or not?" says Wacharapluesadee.

There are as many as 1.6 million viruses we know nothing about lurking in mammals and birds, and as many as half might have the potential to jump to humans and infect us. That's an estimate, based on mathematical models, but the threat is clear. Six out of 10 infectious diseases that strike us come from animals. The list includes HIV/AIDS, Ebola, MERS, SARS, and in all probability COVID-19.

Scientists identified the pathogens responsible for most recent pandemics only after those pathogens started killing people. Researchers such as Wacharapluesadee say that's too late. She's part of a dogged international effort to find deadly

■ Before being released, a fruit bat gets a sip of nourishment after veterinarians took a blood sample. As part of the PREDICT project sponsored by the U.S. Agency for International Development, researchers sampled bats, pigs, and people in Chonburi, Thailand, seeking to identify dangerous viruses in animals before they can infect humans.

viruses before they find us, in hopes of stopping lethal outbreaks.

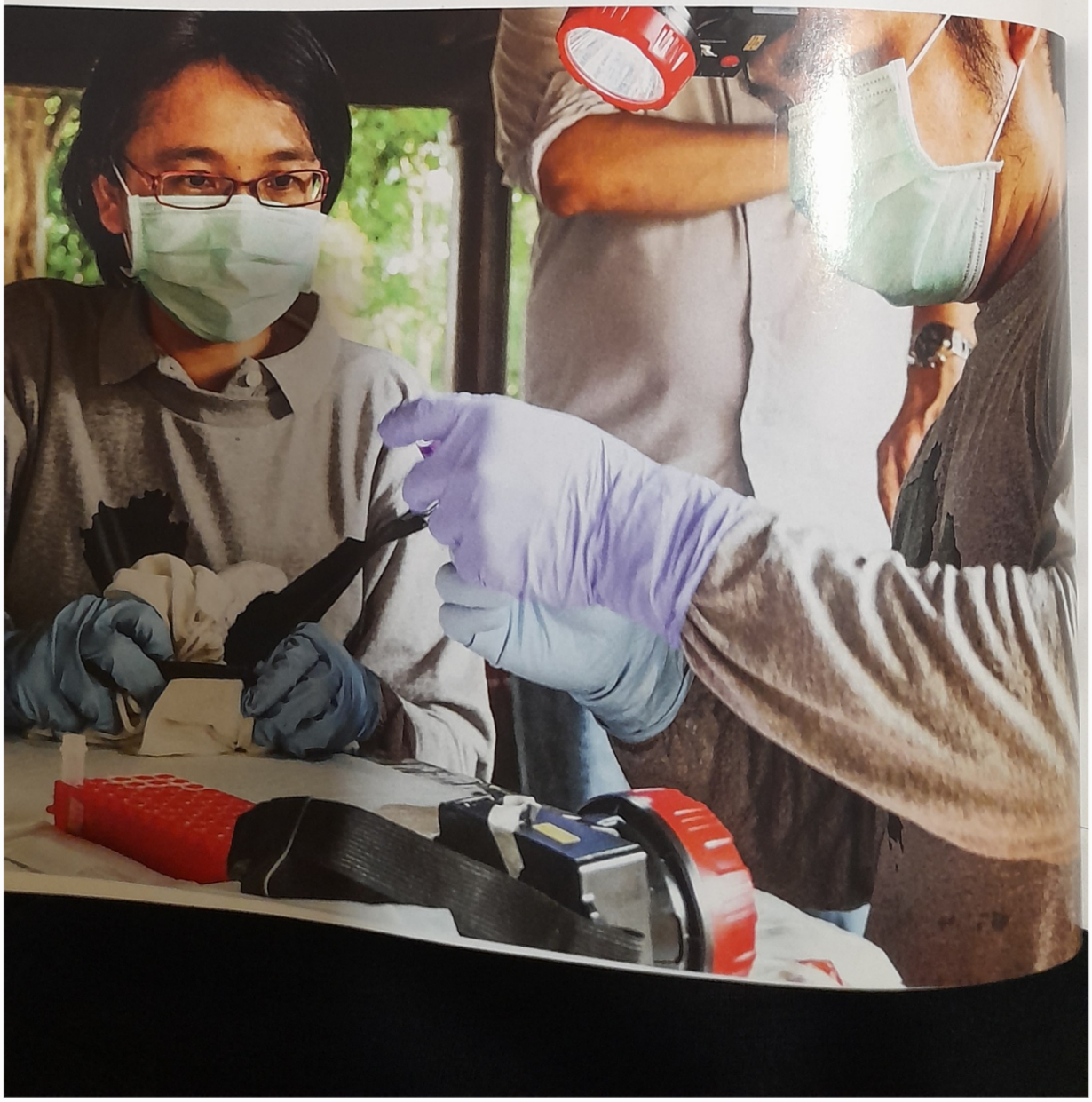
Those hopes have sent Wacharapluesadee into forests, remote villages, and musk-scented caves across Thailand. Wearing thick leather gloves and holding fine-mesh, long-handled nets, she and her colleagues captured 932 bats in the early 2000s, drew their blood, released the animals, and returned to the lab to test for rabies-causing lyssaviruses.

She then turned her attention to the deadly Nipah virus, which crossed from pigs to humans in Malaysia and Singapore in 1998. She tested thousands of samples of saliva, urine, and blood from 12 bat species and discovered worrisome signatures of Nipah infection in the sociable, pointy-eared Lyle's flying fox.

Most bats are protected in Thailand, but their fresh blood is treasured as an aphrodisiac. Wacharapluesadee's research led her to warn in a 2006 letter in a journal called *Clinical Infectious Diseases:* "Drinking bat blood may be hazardous to your health."

FOR THE PAST DECADE, Wacharapluesadee has collaborated with PREDICT, a U.S. Agency for International Development initiative to accelerate and coordinate global virus discovery and surveillance. The project has identified 949 novel viruses, created an extensive database of known viruses in wildlife, and trained nearly 7,000 scientists, lab technicians, and field workers

■ Supaporn Wacharapluesadee, a virus expert, and her team prepare to take blood samples from fruit bats. Her search for undiscovered viruses in the wild has taken her to forests, remote villages, and caves across Thailand. She was the first scientist to confirm the novel coronavirus had escaped Wuhan, China



through GenBank, a go-to DNA database for identifying novel pathogens. The virus looked much like a SARS virus found in the Chinese rufous horseshoe bat, but it was unlike anything previously detected in humans.

On January 9, she alerted Thai health officials that a new coronavirus was on the loose—two days before China reported to the World Health Organization that a new coronavirus had sickened 41 people in Wuhan, killing one. When China posted the virus genome online, Wacharapluesadee determined it was identical to the sequence she had found. It was the first confirmed case of the new coronavirus outside China.

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VIRUS HUNTERS are the swashbucklers of science, tromping through the wild and risking exposure to wretched diseases to unravel the mysteries of infectious nanoparticles. Picture the U.S. Army physicians who set up camp in a Cuban jungle during a yellow fever outbreak in the early 1900s. They hatched mosquito eggs, let the bugs suck the blood of the sick and then bite healthy volunteers, including the doctors themselves, to prove the disease was caused not by bacteria spread by poor sanitation, but by a virus carried by female Aedes aegypti mosquitoes.

Or imagine Beatrice Hahn, a German-born microbiologist now at the University of Pennsylvania whose years-long search for the source of HIV (human immunodeficiency virus) led her to chimpanzee colonies from Tanzania to the Congo River and southern Cameroon. She and her team would wake up early every morning, stand with collection baskets under the trees where chimps slumbered safely out of tigers' reach, catch the day's first urine shower, and then scoop feces off the jungle floor. Hahn's research confirmed suspicions that chimps are the natural reservoir of the closest viral relative to HIV. It likely passed to people through bushmeat, causing an ongoing pandemic that has killed 32 million people.

The risk of zoonotic diseases—infections transmitted from animals to humans—is increasing as we muscle in on the wild. The more we raze habitat for farmland and cities, hunt and trade wildlife, vacation in remote forests, and hike through once inaccessible caves, the greater the chances of "spillover," as scientists call a virus that vaults from a species it doesn't harm into one it does, such as ours.

Scientists have identified about 260 viruses that infect people—a tiny fraction of what's out there. Viruses are ubiquitous. Add them all up and they'd weigh more than all plants and animals, though they are tiny. About 100 million particles of the new coronavirus, SARS-CoV-2, can fit on a pinhead, virologist Peter Piot told a TEDMED interviewer in 2020.

A researcher in protective gear collects biological samples in Chonburi, Thailand. The PREDICT project has led to an extensive database of known viruses in wildlife.

An international collaboration of scientists has announced the formidable goal of finding, identifying, and mapping 99 percent of viral threats to human health and food security within 10 years. But their effort, the Global Virome Project, faces the equally formidable task of raising the estimated $3.7 billion it would need to reach such an ambitious goal.

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As Simon Anthony, an assistant professor of epidemiology at Columbia University, puts it, "Of all the viruses out there, which have the genetic prerequisites to be able to infect people?"

And if a virus can infect people—that is, if the virus can bind to receptors on a human cell and penetrate it—will that infection kill us, cause a mild ailment, or trigger no symptoms at all? Which potentially dangerous viruses are most likely to jump from their animal hosts to humans? And where in the world would it be most likely to happen?

These questions drive Anthony's research. In looking for answers, he has focused on two virus families: filoviruses, which include Ebola, and coronaviruses, which include several common viruses that cause sniffles or coughs. Nobody recognized the coronavirus family as a big problem until SARS (severe acute respiratory syndrome) emerged in southern China, infecting nearly 8,100 people across 26 countries and causing 774 deaths.

Anthony was part of a major study of coronaviruses in the wild, testing more than 19,000 animals—bats, macaques, bonobos, gorillas, mandrills, rats, mice, porcupines, squirrels, and more—in 20 countries over five years. The research, published in 2017, turned up 100 different coronaviruses, overwhelmingly found in bats, and helped the scientists begin to understand why some viruses can infect people and others cannot.

In 2018, he was part of a PREDICT team that identified a new Ebola virus, called Bombali, in free-tailed bats roosting inside people's homes in Sierra Leone. It is the sixth known Ebola virus and the first to be discovered before triggering a deadly outbreak. Another research group soon found the virus in bats in Kenya, and a PREDICT team isolated it from bats in Guinea. "That tells us this virus is widely distributed, and we need to be able to be prepared," said Tracey Goldstein, the PREDICT research leader, director of the One Health Institute at the University of California, Davis, and leader of the research in Sierra Leone and Guinea.

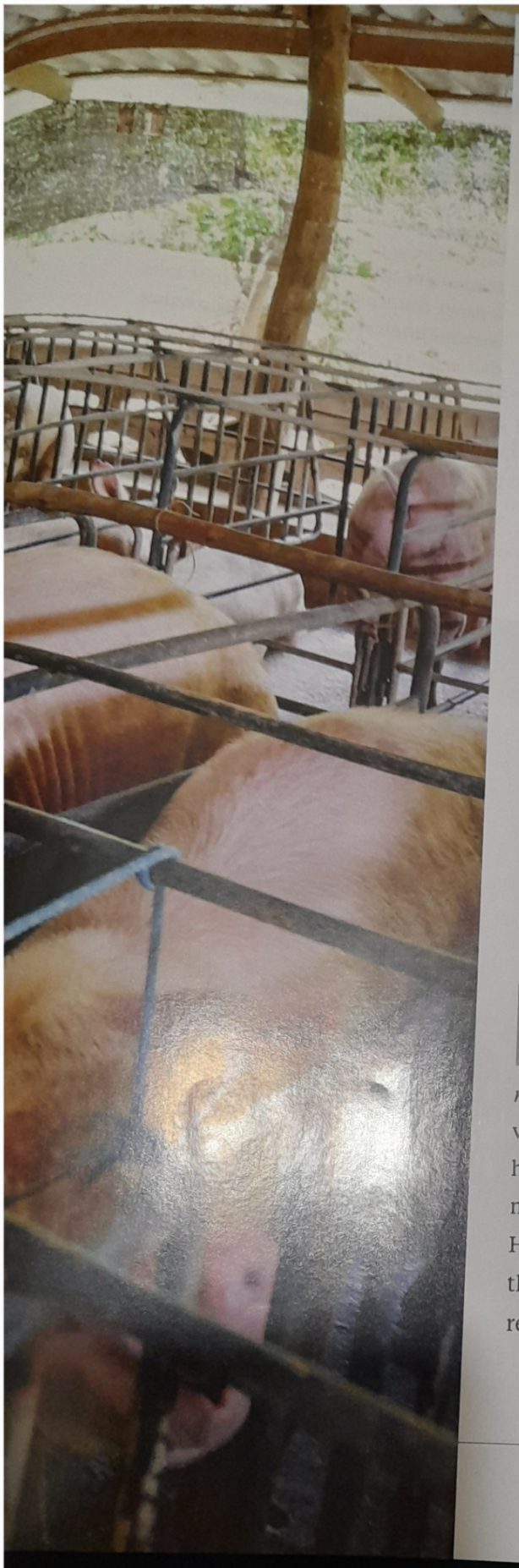
Spurred by the discoveries, EcoHealth Alliance, a PREDICT partner, created a picture book, *Living Safely With Bats*, in 12 languages. PREDICT field teams used the book in education campaigns in villages

A research team collects samples from livestock in Champasak, Laos, as part of the PREDICT project. The program worked with 31 countries to coordinate animal and human disease surveillance.

in Sierra Leone and the forest region of Guinea. The message: Don't eat the animals or fruit they may have contaminated. But don't exterminate them either, because they are important pollinators, they protect crops by eating beetles and other pests, and they can spread infection if they are disrupted. The Minister of Education in Sierra Leone brought the campaign into schools. The PREDICT effort reached thousands of people, but whether it changed behavior is unknown.

The Bombali discovery raised more scientific questions than it answered. "On one hand you think, OK, that's really scary. We have an Ebola virus living in such close proximity to people," Anthony recalled recently. "On the other hand, you think, well, if it's living in such close proximity to people, and Ebola virus is really, really bad, then why aren't we seeing outbreaks?"

In lab studies, Anthony demonstrated that the virus can infect human cells but less efficiently than the Zaire Ebola virus. That strain has been responsible for most Ebola outbreaks, including the devastating



epidemic in West Africa from 2014 to 2016. But three of the other four strains also can cause serious human disease, and the fourth is known to sicken pigs and nonhuman primates.

PREDICT was established in 2009 to strengthen and coordinate what had been a hit-or-miss approach to discovering viral threats and to improve the scientific and technical capabilities to monitor the danger in high-risk regions. The name suggested an early warning system, like an air-raid siren screeching at us to seek cover from incoming bombs, but that is a fanciful aspiration.

With $207 million in funding over a decade and an unimaginably vast universe of viruses to uncover, the project had to pick its shots. PREDICT focused on five of the 71 virus families, a few dozen hot-spot regions, and the basic drivers of spillover—the complex relationship among human activity, environmental degradation, animal behavior, and virus microbiology.

"We are literally only at the beginning of generating the foundational knowledge that we need to try to move the needle on getting better at prediction," Anthony said.

IN FEBRUARY 2019, a well-known virus hunter, Linfa Wang, published a virus watch list of sorts in the journal *Current Opinion in Virology*. It assessed the viruses most likely to jump from bats to humans, directly or through an intermediate host, and cause a pandemic. He ranked coronaviruses at the top of the list for several reasons. They spread readily, generally through coughing and

sneezing. They adapt to a wide variety of hosts, including pigs, rodents, cows, civet cats, and camels—any one of which could become the intermediary between bats and us. And coronaviruses often undergo mutations and other genetic changes that can transform a benign strain into a vicious pathogen.

Wang directs the Program in Emerging Infectious Diseases at Duke-NUS Medical School in Singapore. When I Skyped with him in 2020, as COVID-19 cases were swamping hospitals in the United States, I told him his assessment seemed eerily prescient. "I made a stronger, better prediction in 2013," he said jovially. "A local newspaper interviewed me." He promptly emailed me the article from the *Straits Times* with his quote: "I am almost certain that in the next 10 years, a new killer virus spread by bats will emerge."

Wang was in the news at the time because he and Shi Zhengli of the Wuhan Institute of Virology had just published a paper confirming that horseshoe bats were the original carriers of the virus that had caused SARS a decade earlier. Masked palm civets, initially seen as the source, were only the intermediaries. Although camels were implicated in the outbreak of MERS (Middle East respiratory syndrome), Wang was pretty sure they'd turn out to be middlemen, and that virus, too, would trace back to bats.

A curious piglet watches as researchers take samples from pigs in a nearby pen. Surveillance of viruses in animals may help in predicting spillover disease from animals to humans.

"That really scared me because we knew for a fact there are hundreds of thousands of coronaviruses circulating in bats all over the world," he told me, "and now we had two major outbreaks in the space of nine years."

Wang and Shi—the scientist who first isolated the virus that causes COVID-19—followed up their research on SARS and bats by investigating an obvious question: How often do people get infected directly from bats? The researchers drew blood samples from 218 villagers living near bat caves in Yunnan Province. Six people had antibodies to SARS-like viruses—evidence of prior infection. None had ever been sick with SARS or had contact with SARS patients, but all had seen bats flying in their villages. The study, published in 2018, provided the first evidence that people probably could get SARS-like infections directly from bats.

I asked Wang how it feels to see his most dire forecasts come to pass.

"As a scientist I have very mixed feelings," he said. "I have been warning people and predicting what's going to happen. But now that was proved, I feel like I should not have predicted it."

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MORE THAN TWO MONTHS passed between the day Wacharapluesadee identified the new coronavirus and when Thailand's government announced one of the strictest national lockdowns. Officials came under criticism for not acting faster, but Thailand contained the virus more effectively than most countries, according to the Center for Strategic and International Studies. The center credited the country's model health care system and its investments in health security, including infectious-disease reporting and laboratory testing.

Wacharapluesadee doesn't know when she'll get back to the bat caves, but during the height of the pandemic, her lab ran nearly round the clock, testing specimens sent by hospitals. She's studying the biology and activity of the new coronavirus in hopes that the knowledge can fortify us against another, inevitable viral assault. "The next pandemic could not be predicted, but we can prepare and slow down the outbreak," she told me.

PREDICT ended in 2020, after more than a decade of work, and the U.S. government has kicked off its successor, STOP Spillover. The five-year, $100 million initiative is focused more narrowly on specific zoonotic viruses, such as Ebola, Nipah, and coronaviruses, in select high-risk countries in Asia and Africa.

Scientists who have dedicated their lives to discovering and understanding viruses say the knowledge is essential for reducing risk and averting the next pandemic. How can you persuade people to stop drinking bat blood or get governments to clamp down on wildlife trading if you can't tell them what viruses are out there and how likely they are to harm us?