Designing new ways to detect viral threats earlier to prevent another pandemic

April 21 2021, by Michael Penn

Guyani Tillekeratne, MD, and her team set up a molecular diagnostics lab at the University of Ruhuna in Sri Lanka (pictured here), where she and Sri Lankan partners work to identify the viruses that cause severe respiratory illnesses in children and establish surveillance screening. Credit: University of Ruhuna

To Linfa Wang, Ph.D., some of the most important unanswered questions about the COVID-19 pandemic lie within slick layers of guano, deep in a hole in the ground.

A virologist with the Duke-NUS Medical School in Singapore, Wang was part of a team of international scientists tasked by the World Health Organization (WHO) with unraveling the origins of the original SARS virus 17 years ago. Now he's attempting to do the same with the coronavirus that causes COVID-19, known as SARS-CoV-2. While the exact path the virus followed to begin infecting humans isn't yet known, it's almost certain to run through bats, which have been the focus of Wang's work for nearly three decades. And that means looking at a lot of bat poop.

Last year, Wang developed a test to detect antibodies to SARS-type coronaviruses in bat droppings and urine, allowing him to hunt for genetic relatives of SARS-CoV-2. While a study last spring identified similar viruses in bats in southern China, in February, Wang and collaborators also found closely related viruses in bats and pangolins in Thailand. These discoveries indicate that the animal ancestors of the virus responsible for the pandemic may have been circulating over a wider geographic area than previously thought.

And that means a big piece of the COVID-19 origin story is still missing: It's clear the first cluster of human infections arose in Wuhan, China, but did a human or an animal bring the virus there, and from where?

"Most likely the hotspot is in southern China and Southeast Asia," says Wang, who is also a professor in the Duke Global Health Institute, "but we have to be open-minded." He says it can take many years to pin down the exact source of animal-to-human transmission.

But unlike the political finger-pointing around the origins of COVID-19, this quiet, meticulous research into the roots of the pandemic is not geared toward assigning blame for the outbreak, which most infectious disease experts see as an inevitable part of the natural cycle of viral evolution. In fact, it's not really about this pandemic at all. It's about the next one.

Diving into the Animal Reservoir

Sixty to seventy percent of the infectious diseases that affect humans start in animals, a formidable lineup that includes plague, Ebola, West Nile, Lyme disease and many forms of influenza. According to the U.S. Centers for Disease Control and Prevention, these diseases are responsible for 2.7 million deaths around the world each year. And when a novel virus breaks loose in human populations, it can cause chaos.

Even before COVID-19, animal-borne viruses had triggered at least four global outbreaks in this century: SARS in 2002, H1N1 flu in 2009, the respiratory disease MERS in 2012 and Ebola in 2014. Yet despite such regular reminders, the world's public health systems aren't very good at anticipating or preventing such deadly episodes.

"We have a whack-a-mole policy right now," says Gregory Gray, MD, MPH, a professor of medicine, global health and environmental health at Duke. "We wait for a pathogen to cause a lot of morbidity, and then we respond. We have to figure out a better way to predict emerging infectious diseases and mitigate them before they cause a lot of harm."

Gray and Wang are among a community of scientists who say we could do a better job anticipating new viral threats by paying more attention to the animals that harbor them. An approach known as One Health seeks to bridge the worlds of human, animal and environmental health by studying them as one interconnected system. If viruses aren't constrained by the boundaries of the natural world, One Health argues, neither should our efforts to understand them.

Trained as a biologist, Wang comes at the issue from an animal-centric—or, more precisely, a bat-centric—perspective. The planet's only flying mammals, bats have evolved a remarkable ability to tolerate viruses that make other animals, and people, sick. But this also means they can carry around a toxic stew of pathogens that sometimes spill over to other species. Over the years, Wang has tracked several bat viruses that have made their way into humans, most notably as part of the WHO team that traced the source of the 2002 SARS epidemic to a colony of horseshoe bats in China's Yunnan province.

Predictably, this work has earned Wang the nickname "Batman," but that doesn't mean he's particularly fond of bats. Rather, like the winged avenger, he's in it to protect humans from unseen dangers.

His study of the 1998 outbreak of the Nipah virus in Malaysia is a good example. The virus was unknown when it began infecting pigs in the country's Nipah River region, and within weeks hundreds of farmers developed severe cases of encephalitis. It took six months to identify the cause, and by then, nearly half of those infected had died. One million pigs were slaughtered in attempts to control the outbreak.

Studying serum samples from infected pigs, Wang and his collaborators found a related virus in a species of the fruit bat called a flying fox. Investigating the farms at the epicenter of the outbreak, researchers saw that farmers had planted fruit trees near their livestock pens to provide shade for their pigs. Bats fed on the trees, dropping pieces of half-eaten fruit into the pens, where pigs ate them and were exposed to the virus. The virus then jumped to farm workers and people who ate infected meat.

The scenario, which was featured in the 2011 movie "Contagion," illustrates why it's important to understand the exact pathogenesis of novel viruses, says Wang. "(Planting fruit trees) sounds like a creative and productive idea, but when you investigate, you find there's a huge risk factor." Farmers were able to prevent future outbreaks just by moving their pigs out of the shade.

Studying the Interface

But with an estimated 1.6 million different viruses circulating in the animal kingdom, including several hundred types of coronavirus that may infect mammals, which ones do we keep an eye on? "We've attempted to predict these viral threats, but we've missed the specific virus in both 2009 (with H1N1) and 2019 (SARS-CoV-2)," notes Gray. Divining the opportunistic leaps of evolution is never likely to be a winning game.

Gray thinks we can do better by narrowing the field. His research focuses on what he calls the "human-animal interface," or places such as farms and livestock markets where humans and animals come into regular contact. In these environments, viruses can churn between species, potentially accelerating evolutionary changes that might allow a pathogen to become highly transmissible to humans. The goal of Gray's work is to see those changes happening in real time, creating an early warning system for pathogens on the move.

"We know it can take many years for a virus to adapt to humans and longer still to be transmitted from human to human," says Gray, "and so we think that if we look for novel viruses at the human-animal interface, we will have time to develop mitigation strategies."

Gray's team is trying this approach on industrial pig and poultry farms in China, Malaysia, Myanmar and Vietnam. Researchers go in periodically to take samples from animals and workers, which are then analyzed in the lab for novel pathogens or new sources of infection. They have also experimented with using bioaerosol sampling devices to detect viruses circulating in the air at live bird markets. Even though the experiments are small-scale, they have been able to detect a number of viral spillovers between species.

At the same time, Gray is working with Duke Global Health Institute colleague Gayani Tillekeratne, MD, to create a different kind of alarm bell. Together, they have launched a pilot project to help clinicians in viral hotspots diagnose unexplained cases of pneumonia, which are often the first signs of a new outbreak.

Tillekeratne, an assistant professor of medicine at Duke, has seen this play out firsthand. She has spent much of the past decade researching infectious diseases in Sri Lanka, where hospitals often only have equipment to identify a few known viruses. In 2018, she and her colleagues were called in to help investigate a spate of severe, and sometimes fatal, respiratory illnesses among children. The team shipped in equipment to set up a molecular diagnostics lab at the University of Ruhuna, which helped identify the cause of the illnesses (a mix of three viruses) and establish surveillance screening.

One goal of the pilot project is to bring that detection capacity in-house. "We're developing assays that we can conduct on site so that we can perform the testing in real time," she says. "That's something we have been trying to do in Sri Lanka for a while."

An equally important objective is to aid information sharing. Gray and Tillekeratne hope to knit together a network of virus watchers in multiple countries who can alert others to unusual cases and patterns. Gray's international partners have already surfaced a few cases worth further exploration, including a cluster of respiratory illnesses in Malaysia that appear to be caused by a canine coronavirus that had not previously been known to infect humans.

"100 Percent Likely"

Asked if we will see another virus capable of causing a pandemic emerge in humans, Gray gives a rueful chuckle. "I think many people would say it's 100 percent likely," he says.

Many factors may be conspiring to make our world more pandemic-friendly, from the ease of global travel to high-density animal agriculture to the farming and trade of exotic animals. While smart policy can reduce those risks, they aren't likely to go away entirely. Viruses are viral. We will undoubtedly be here again, confronting an outbreak somewhere that threatens to become an outbreak everywhere.

Wang, who has now been called on to investigate six different viral epidemics, hopes we meet that moment with global solidarity. Improving our ability to detect new viral threats and prevent pandemic spread won't just take biomedical innovation, but transparency and open cooperation among countries, something that has not always been evident in this pandemic.

"We have to treat viruses like a common enemy, politics aside, like fighting terrorists or fighting crime," says Wang. "Interpol is an international organization to fight crime; can we have something like that to fight future viruses?"

Bold ideas have been envisioned before, only to vanish as threats fade and complacency sets in. Wang hopes this time will be different, and the lingering scars of the worst pandemic in a century will compel more proactive measures. But whether that happens or not, he and Duke's virus detectives will have their eyes on the interface, ready to respond, no bat signal needed.