

ON THE TRAIL OF DISEASE IN SOUTHEAST ASIA

Infectious disease research is blossoming in cities like Bangkok, as local clinicians and scientists delve into the surrounding muddy tropics of Southeast Asia to learn about endemic pathogens.

By AMY MAXMEN

In 2000, an international team of doctors affiliated with the University of Oxford congregated in Laos to help tackle a devastating problem. Trembling, feverish villagers were being treated for malaria, whether they had the disease or not. With no accessible blood culture service, it was nearly impossible to determine the cause of fevers and other malaria-like symptoms. In the following years, the visiting doctors worked with Lao doctors to implement routine blood cultures for patients hospitalized with fevers. Malaria turned out to be relatively rare. Instead, many suffered from typhoid, *Staphylococcus*, and *Escherichia coli* infections (1). Just three days of antibiotics would have saved so many lives, reflects Nick Day, an infectious disease researcher in Thailand.

I take the train across Bangkok to meet Day, where he directs a collaborative center for disease research called MORU (Mahidol-Oxford Tropical Medicine Research Unit). By the time I reach downtown, torrential rain darkens the sky but does nothing to cool the air or slow the crowds that flow between animated vendors of mangoes, durians, donuts, fried chicken, and cheap socks. At 6 feet tall, Day sticks out above the masses. Raising a pink and white Hello Kitty umbrella, he shouts over the droning downpour and human murmurs, inviting me to tour their new laboratories.

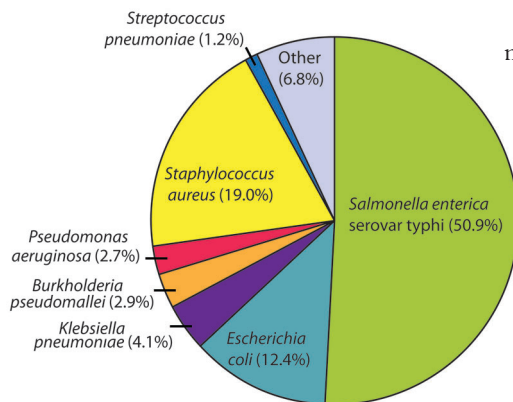
As we dodge puddles in the eroded pavement, I ask Day if he thinks rural areas are prepared to handle emerging outbreaks of virulent pathogens. He pauses and says in a hybrid drawl—part Oxbridge, part Ugandan—“First, we don’t even know what’s out there.” In poor rural regions, he says, “we still don’t know what is actually responsible for morbidity and mortality.”

Since Day’s arrival six years ago, funding from outside institutions has increased with the acknowledgment that epidemics arising in Asia won’t stay put. People travel and goods are shipped. Microbes move. A *Nature* study last January analyzed 335 infectious disease outbreaks between 1940 and 2004 and concluded that infectious diseases are,

indeed, on the rise (2). Bacteria accounted for more than half of the emerging infectious diseases in the study, and many of these were drug resistant. Poverty, population density, and changing agricultural practices conspire to make Southeast Asia a hot spot for outbreaks, according to the lead author on the study, parasitologist Peter Daszak.

Half of the world’s population lives in Asia, often in close quarters with pathogen-carrying animals like chickens and pigs. In impoverished regions of Cambodia, Myanmar, Indonesia, Laos, Vietnam, and Thailand, microbiology laboratories are rare and diseases go undiagnosed. And misuse of antimicrobials generates newer, stronger strains. The consequences of neglect are dire. People die needlessly. Outbreaks gain momentum.

“I’ve begun to worship good diagnostics,” laughs Sarah Dunstan, an Australian researcher at the Oxford University Clinical Research Unit in Ho Chi Minh City, Vietnam, who was in Bangkok for a recent Keystone symposium on emerging infectious diseases. The immensity of what is unknown about the pathogens underlying human mortality allows the epidemiologists of Southeast Asia to churn out data in the form of surveys and drug efficacy trials. “But these aren’t sexy studies,” Dunstan sighs, acknowledging disinterest



The microbes found in the first routine blood cultures taken at a hospital in Vientiane, Laos, 2000–2004.

ADAPTED FROM (1)

among many scientists and grant-making agencies in the industrialized world who often prefer fundamental research. Instead of, say, hypothesis-driven forays into T cell responses in mouse models of human disease, many researchers in Southeast Asia conduct fever studies. They ask why people die. It's highly relevant, but low in glory.

Although securing funds remains a challenge, new initiatives for disease surveillance and medical infrastructure offer hope. This past November, for example, the Bill and Melinda Gates Foundation donated more than \$22 million to the World Health Organization (WHO) for the control and monitoring of drug-resistant malaria in Southeast Asia. In 2007, the UK's Wellcome Trust put approximately \$19 million into disease research in Southeast Asia, much of it going to University of Oxford-affiliated institutions like MORU.



Nick Day directs a center for tropical disease research in Bangkok.

The effects of donations are beginning to show. Day beams as we cross the gleaming linoleum of MORU's laboratory floors. MORU's building in Bangkok has quadrupled in size since renovations began in 2002. Founded in 1979 as a collaboration between the University of Oxford and Mahidol University in Bangkok, MORU now forms a hub for ongoing studies in affiliated centers and hospitals around Thailand, Laos, Vietnam, Cambodia, Bangladesh, India, and Myanmar. The Wellcome Trust also recently granted Day's hopeful graduate student, Emma Nickerson, the funding she had been persistently begging for.

CHARTING TERRA INCOGNITA

Over beer and curry at a teakwood house with a towering gate and a sweeping garden, set back from the noise and exhaust of nearby Sukhumvit Road, Nickerson smiles. She mentions that she hadn't set foot in Southeast Asia before deciding to leave the comforts of the British hospital where she completed her medical residency. Since 2003, she's spent most of every year in Ubon Ratchathani, a province in northeastern Thailand bordered by Laos to the east and Cambodia to the south. There, farmers who till rice paddies commonly fall ill with melioidosis, a life-threatening infection caused by *Burkholderia pseudomallei*. Oddly enough, people also appeared to be dying from *Staphylococcus aureus*, a bacterium known to plague American hospitals but not generally considered problematic in the developing world. Nickerson's work is beginning to change that misperception.

"I'm still trying to dispel the myth that staph isn't a tropical disease," Nickerson remarks. In a letter published in *Lancet* in 2006, she reported that 9% of bloodstream bacterial infections at Sappasithiprasong Hospital in Ubon Ratchathani province are caused by *S. aureus* (3). Another recent survey in Laos found that *S. aureus* was the leading cause of bacterial infection in infants less than one year of age (1).

But many epidemiological trends like this one continue to go unnoticed in regions of the developing world where microbiology laboratories are in short supply and clinics struggle to handle emergency situations, never mind conduct long-term studies. To reach scattered hospitals, the ill must travel miles by foot, canoe, mule, truck, and inconsistent train. They come sweating and shivering with malaria, suffocating from tuberculosis, or dizzy from the pain of swollen abscesses. Full hospitals rarely turn them away. "There are only 1,000 beds at Sappasithiprasong Hospital," Nickerson says, "but they always make space."

Nickerson conducted the first study tracking disease progression in patients infected with *S. aureus* in Thailand in 2003. Before her arrival, overextended hospital staff members were unable to follow up with patients to check if their

infections cleared after they were discharged from the hospital. By collaborating with Thai clinicians, Nickerson learned the local lingo. To work out when bacteria most likely entered a patient's bloodstream, she no longer asks for exact dates. Instead she searches for landmarks; holidays or rice farming events that trigger memories about when the first fever hit.

"Just three days of antibiotics would have saved so many lives."

—Nick Day

S. aureus strains also vary considerably over homogenous terrain, says Nickerson. Siem Reap, Cambodia, is just 140 km south of Ubon Ratchathani, and though similar palms and rice paddies dominate the landscape, the microfauna varies. *S. aureus* strains acquired there can be reliably killed with oral antibiotics, whereas strains from northern Thailand are often drug resistant. At Sappasithiprasong Hospital, Nickerson found that 23–27% of staph infections were a potentially lethal variety of drug-resistant *S. aureus* (3).

Nickerson continues to profile strains from hospitals across 10 Asian countries. This is important information to have because delays in proper treatment lower the chance of survival. "People think you can just take data from wealthy countries and assume it's true for all countries," she says. "Asia is a patchwork; that's particularly relevant in terms of resistance. There's so little data, actually. We've hardly scratched the surface."

CONSEQUENCES OF NEGLECT

The emerging infections of highest priority are drug-resistant strains of well-known diseases like tuberculosis and malaria. Resistance has been fueled in part by unregulated sales of real and counterfeit medicine. Overuse of over-the-counter antibiotics speeds up bacterial evolution by selecting for strains that have acquired resistance. And counterfeits, which contain just enough medicine to foil screening tests, kill off only the most sensitive microbes.

To investigate the extent of the counterfeit problem, a local researcher dressed as a Burmese migrant worker visited shops in 16 villages around the Thai-



A hospital ward in Chittagong, Bangladesh.

Myanmar border in 2000. He purchased 50 packets of “yaa chud,” a medicine widely taken to battle malaria around rural parts of Southeast Asia. In the seven packets that actually contained effective malaria medicine, the active ingredient was at low levels (4).

Recent studies estimate that 38–52% of the drugs supposedly containing artesunate—the cornerstone drug against the deadliest of malaria parasites, *Plasmodium falciparum*—are counterfeit. “We make no apology for the use of the term manslaughter to describe this criminal lethal trade,” said researchers in a 2006 *PLoS Medicine* report (5).

In October 2008, cases of artesunate-resistant malaria caused by *P. falciparum* were noted along the Thai–Cambodia border—a volatile area that had already proven ripe for the development of resistance to other antimalarial drugs. *P. falciparum* attacks not only the blood and liver but also the brain, often leading to seizures, organ failure, and death. It accounts for most of the approximately one million malaria-related deaths each year, according to the WHO. In Southeast Asia, approximately 90–160 million people are infected with malaria each year, and 120,000 die.

Borderland health care is notoriously poor. Most doctors in the area request transfers because of political unrest. And the counterfeit drug industry thrives. An estimated 918,000 migrants, including refugees in camps, dwell or pass through the Thai–Cambodia border each year, possibly carrying resistant bugs with them. In the early 1970s, the region spawned *P. falciparum* strains resistant to the antimalarial drug chloroquine. Resistance spread like wildfire. Now the drug is almost totally ineffective in Southeast Asia, Africa, and most other parts of the world. Resistance to replacement drugs—first sulfadoxine-pyrimethamine, and then mefloquine—occurred in the region a few years after they replaced chloroquine.

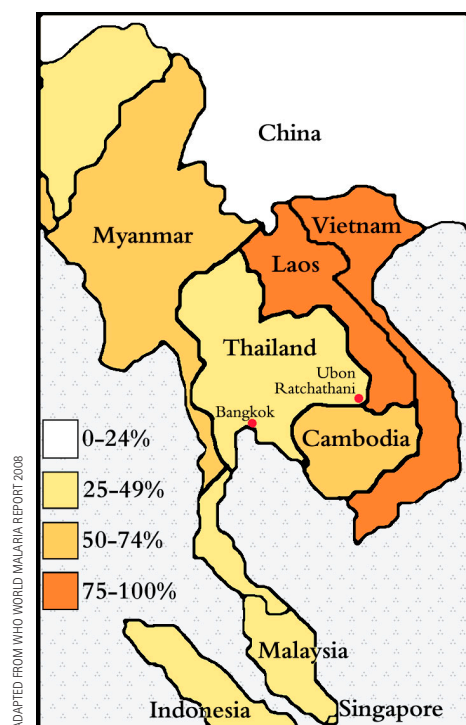
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With no alternative treatments for severe malaria caused by *P. falciparum*, the consequences of widespread artesunate resistance would be disastrous, says Day. Six UN agencies, including the WHO, and more than a dozen international nongovernmental organizations currently work along the border to improve health

care. Groups at Mahidol University and the Armed Forces Research Institute of Medical Sciences (AFRIMS) in Bangkok, the Cambodian National Malaria Control Program, the Sanger Institute in the UK, the Southwest Foundation for Biomedical Research in San Antonio, Texas, and Nanyang Technological University in Singapore are furiously studying artesunate profiles, parasite transcripts, and patient microarrays. “This is very collaborative since we’ve got to nail it,” Day says. “We can’t worry about who’s first author on the paper.”

LOCALS RESPOND

Photographs of human suffering lined the walls of the conference hall in Bangkok where the Keystone symposium on emerging infectious diseases took place between October 22 and 27. Scientists from around the world milled about beside the morose exhibit, sipping tea and nibbling mini-muffins. Those working in developing countries do not need the humanitarian reminder. They have seen the frightened faces of patients dying from diseases that are rarely seen, or are quickly cured, in industrialized nations. During the poster session, Vasanthi Ramachandran from AstraZeneca India in Bangalore and Ladaporn Bodhidatta from AFRIMS



Percent of malaria cases caused by *P. falciparum*.

in Bangkok heatedly discuss the bacterium *Shigella sonnei* and the different ways that children from their respective countries respond to infection and to the drug treatments for the accompanying diarrhea, fever, and stomach cramps.

"Everything we do goes back to the people," explains Jane Cardosa from the University of Malaysia in Sarawak. First of all, people need to be informed about how an outbreak spreads. "At the end of the day, we can't rely on outside help," Cardosa says. "The bird flu taught us that we need to build capacity locally so that we can respond quickly."

Global health rests on the shoulders of people who work where outbreaks first occur—clinicians, academics, and people like Yongyuth Yuthavong, who do a little of both and also help create infrastructure for medical research on a local level. "Are we only the hands and feet?" he asks. "Why not the brain?"

Yuthavong was the first president of Thailand's National Science and Technology Development Agency and, between 2006 and 2008, the country's Minister of Science and Technology. He is the type of man who mentions these positions as casually as someone might say they used to work the fryer at McDonald's.

When I see him at the Keystone symposium and ask when we might schedule a time to talk, he warmly replies, "Let's find a quiet place now."

TRANSFORMING MEDICAL RESEARCH IN THAILAND

Science was not a career one could survive on when Yuthavong first began research in the mid-1960s. Professors held other jobs during the day or in the evening. Yuthavong's first grant, for the equivalent of \$200, was handed to him in banknotes. "Do you know the word, 'moonlight'?" he asks.

Like many bright young Thais, Yuthavong completed college in London. "When I got back," he says, "all my colleagues had left to dig gold in the US." In the 1970s, to counteract a shortage of doctors, the Thai government instituted a rule that continues today: Citizens who receive government scholarships must return home to work for twice as long as they studied abroad. Simultaneously, nonprofit organizations like the Rockefeller Foundation started supplementing the income of local researchers in underdeveloped nations. Yuthavong credits the Foundation with helping to establish modern medical education in Thailand. Moonlighting scientists, for the most part, became obsolete.

By the end of the 1970s, a number of outside organizations had set up institutions using local researchers and clinicians. AFRIMS, a collaboration of the US Army and the Royal Thai Army, was established in Bangkok in 1977 to investigate infectious diseases like scrub typhoid that have plagued troops for centuries. Soon after, the Wellcome Trust funded MORU. These institutions now employ mainly Thai researchers. In 1983, the Thai government financed a research institute and funding agency named BIOTEC, which is now the third largest of Thailand's 15 disease laboratories. There, Yuthavong's group focuses on the molecular biology of malaria.

Over the last three decades, commitments from the private sector have enabled the government to make the marginal investments required to establish scientific research. Still, government investments for research and education do not reflect economic gains by the country, says Yuthavong.

Only 0.26% of gross domestic product in Thailand was spent on science in 2007, and less than half of that went to medical research. Most countries in Western Europe, the United States, and Japan spent 10 times that amount on research and development, between 2.5 and 3%.

The fruits of economic development have also not reached all regions of the country equally. While less than 2% of people living in Bangkok were below the poverty line in 2006, as many as 23% were living in poverty in surrounding regions, according to the WHO. In particular, the southern provinces near the Thai-Cambodia border remain vulnerable to the unrecognized disease outbreaks characteristic of poorer nations.

As news of the plummeting US economy sweeps headlines in Bangkok, many fear that the depression will infect Southeast Asia. If the Thai economy suffers, Yuthavong worries that the government will cut funding for science. It would be a setback for the work he has done to encourage Thai students to stay in research rather than pursue more lucrative fields. He sighs, "People cut from knowledge first, they cut funding for education and research."

"We need to build capacity locally so that we can respond quickly."

—Jane Cardosa

Meanwhile, back at MORU, the rain outside of Day's laboratory subsides. Day glances toward the window at the fading late afternoon light and says he ought to go polish off a grant. A train passes through the view on elevated tracks, cutting between concrete buildings and passing out of sight. The railway stretches for miles beyond the city, through interminable rice paddies, remote villages, overgrown jungles, swamps. Here, an epidemiologist can be engrossed for a lifetime.

1. Phetsouvanh, R., et al. 2006. *Am. J. Trop. Med. Hyg.* 75:978–985.
2. Jones, K.E., et al. 2008. *Nature*. 451:990–994.
3. Nickerson, E. 2006. *Lancet*. 6:70–71.
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5. Newton, P. 2006. *PLoS Med.* 3:e32–43.