Mission Possible

HSPH alum tracks clues to pandemics before they erupt.

All Photography ©Tom Clynes

In 1998—the year he earned his doctorate from the Harvard School of Public Health—Nathan Wolfe published a scholarly article entitled "Wild Primate Populations in Emerging Infectious Disease Research: The Missing Link?" Its tone was unreservedly optimistic. "Perhaps by learning from primates in their natural environments," he wrote, "we may better prepare ourselves for ... disease threats to humans."

In the 12 years since, Wolfe has set out to prove that his doctoral-era mission is not Mission Impossible. SARS, Ebola, and, most tragically, HIV/AIDS: Could scientists have detected these animal infections before they leapt species to become human plagues? If so, could timely public health measures have changed their deadly trajectories?

"When you go through the School, you can't miss the importance of prevention relative to treatment in individual medicine," Wolfe says. "I remember thinking to myself: Why doesn't this apply on a population level with pandemics?"

Now Lorry I. Lokey Visiting Professor at Stanford University, Wolfe has trained his career on that question. With arduous fieldwork in Africa, genetic analyses in America's top labs, and an innovative frontline surveillance system, he is hoping to prove that pandemic prediction—and maybe prevention—is within our grasp.

A woman in southeastern Cameroon prepares monkey for dinner.

SPECIES JUMPING

About three-quarters of emerging infectious diseases—from H1N1 flu to West Nile virus—are produced by disease-causing organisms (mostly viruses) in animals. Emerging infections are those that have newly appeared in a population, or are rapidly increasing in numbers or expanding in geographic range. How they vault from animals to take hold in people is one of the great puzzles in public health, Wolfe says. On a macro level, it's known that ecological change—from intensive pig farming to the clearing of rain forests to the growth of crowded megacities—ushers new germs into our lives. But on a real-time micro level, how and where and when do these border crossings take place?

For ten years in the tropical central African country of Cameroon, Wolfe worked with "bushmeat hunters" who slaughter wild animals for food. These men face a high risk of contracting a cross-species infection because of their close and bloody proximity to wild primates. Wolfe collected blood samples from the hunters and from other people in their community who did not have close encounters with raw meat. He gave the hunters pieces of filter paper to obtain blood samples from their animal prey. By testing all the samples for unfamiliar viruses, Wolfe identified microorganisms inhabiting both the animals' and the hunters' blood—prime candidates for emergence in humans. As Wolfe told *The New York Times* in 2008, "The main things we look for are: Does a particular virus cause disease, and is it transmissible?"

Scientifically, the approach bore fruit. Wolfe and his colleagues found two previously unknown human retroviruses—dubbed HTLV-3 and HTLV-4—that are in the same family as the human AIDS virus; though

continued

THIS IS PUBLIC HEALTH.

Pandemic infections such as AIDS and SARS have long been considered unavoidable—part of the natural emergence of disease caused by animal microorganisms jumping into humans. Scientists believe, however, that by studying the circumstances of these cross-species transmissions, they can prevent deadly pandemics from even happening.

their origins aren't clear, they appear to have jumped from monkeys. He found another retrovirus, known as simian foamy virus (SFV), as well; that virus seems to be native to a wide range of primates, including guenon monkeys, mandrills, and gorillas.

What's the significance of these discoveries? "We do not yet know whether SFV or the new HTLVs cause illness in people," Wolfe wrote in April 2009 in *Scientific American*. "Viruses do not necessarily make their hosts sick, and viruses that do sicken people and even spread from person to person do not always cause pandemics; often they retreat spontaneously. But the fact that SFV and HTLV are in the same family as HIV, which did spawn a global epidemic, means that epidemiologists must keep a close eye on them."

EAVESDROPPING ON "VIRAL CHATTER"

Buoyed by these findings, Wolfe in 2008 founded the Global Viral Forecasting Initiative (GVFI), a network that listens in on what he calls "viral chatter": the seemingly commonplace transmission of animal viruses to humans. GVFI enlists epidemiologists, public health workers, and conservation biologists around the globe to identify viruses, bacteria, and parasites in the animals where they naturally live, and to monitor those organisms as they move from animals into people—with the potential of later radiating through human populations. In most cases, the organisms that make it across the species barrier into people hit a dead end and do not trigger subsequent person-to-person spread of infection. But Wolfe suspects that in places where lots of species and strains of animal viruses intersect with humans, chances rise that one of the vagabond viruses will adapt to its new host and become a human contagion.

GVFI has about 100 scientists following at-risk populations not only in Cameroon but also in China, the Democratic Republic of the Congo, Laos, Madagascar, and Malaysia—all known hot spots where deadly emerging infections have appeared in the past few decades. Though many of the people it monitors are hunters, the organization also screens other populations apt to contract diseases from wildlife, such as workers in Asia's "wet markets," where live animals are sold for food—and where the lethal virus that causes SARS was launched in 2003. "If you had been studying the right populations earlier," Wolfe says, "you might have seen some SARS chatter."

The blood of captured monkeys may provide clues to emerging diseases that may pass from animals to humans.

SEPARATING SIGNAL FROM NOISE

As with any high-tech surveillance, separating signal from noise—or in this case, potential pandemic pathogens from harmless vagabond viruses—is tricky. Some public health experts insist that smoldering pandemics simply can't be seen until people start getting sick, because the process is so unpredictable. After all, who would have thought of looking for pandemic flu viruses in Mexico, or West Nile virus in Queens, New York?

But Wolfe argues that certain clues suggest pandemics in the making. Among these prognostic signs: animal die-offs (chimpanzees and gorillas often perish in clusters before

A nurse draws blood from a villager in southeastern Cameroon, adding to a collection of thousands of samples that will be analyzed for the presence of new diseases.

human outbreaks of Ebola) and large numbers of infections among people highly exposed to wild animals. Even with these facts in place, however, the potential pathogen must also prove capable of causing human disease, spreading readily from person to person, and finding its way to an urban center, where the high density of residents could fuel its spread.

had set in motion today's effective behavioral interventions, such as condom use, he adds, they might have limited the course of the epidemic.

TOPPLING THE CONVENTIONAL WISDOM

Last August, in the *Proceedings of the National Academy of Sciences*, Wolfe published another finding that quickly made headlines. He proposed that the parasite that causes the most common and severe form of malaria—a disease that every year claims more than 1 million lives—had jumped from chimpanzees to humans some time between 10,000 and 3 million years ago. By showing that the form of the parasite that infects chimpanzees—*Plasmodium reichenowi*—is far more genetically diverse and therefore older than the form of the parasite that strikes humans—*P. falciparum*—the study dismantled the long-held belief that malaria parasites in humans and chimps had descended from a common ancestor. Malaria, in other words—like SARS, like West Nile virus, like H1N1 flu—was a classic example of an infection that hopped from animals to humans and just kept going.

HIV/AIDS actually claimed lives in the early 20th century—but was not reported until 1981 because "we weren't listening," says Wolfe

Lawrence Madoff—attending infectious disease physician at the University of Massachusetts Memorial Medical Center, and editor of ProMED, an Internet-based system dedicated to rapid global reporting on outbreaks of infectious diseases—praises Wolfe's approach. "It's innovative and aggressive. I'm all for it," Madoff says. "Trying to devote resources to where you think things are going to happen and catch them early is a good idea."

Armed with such evidence, could public health officials actually stop a pandemic in its tracks? "Whether or not you prevent the pandemic, you have the potential to change the course of it," Wolfe contends. Though HIV/AIDS was first reported in 1981, studies of preserved blood and tissue samples prove that it had actually entered the human population and started claiming victims in the early twentieth century. "It was a 'silent epidemic' because we weren't listening," says Wolfe. If public health officials had known of the deaths before HIV had spread globally, and

Looking back over this still-evolving career, one can't help but notice that Wolfe gravitates toward knotty problems and surprising solutions, all of which may have been foretold at HSPH. Back in 1998, Wolfe's doctorate year, a leading scientist in the study of emerging infections—Frederick Murphy, at the University of California, Davis—wrote of novel animal-to-human infections: "In general, there is no way to predict when or where the next important new zoonotic pathogen will emerge or what its ultimate importance might be." Wolfe has spent his career disproving that assertion. "Sometimes," he says, "life is about being ignorant of—or ignoring—what other people say is impossible."

Madeline Drexler is guest editor of this issue of the Review. *Her book* Emerging Epidemics: The Menace of New Infections—*an updated and revised edition of an earlier volume—will be published by Penguin in January 2010.*

Scholarships Launched This Alum's Career

Critical funding from HSPH fellowship programs helped Nathan Wolfe launch his groundbreaking work while a doctoral student at the School. In 1995, he received support from the John F. and Virginia B. Taplin Fellowship Fund, an endowment fund that provides two years of partial tuition to students of exceptional merit. "The Taplin Fellowship provided critical support at a pivotal time in my developing research career," says Wolfe, who was in the first class of Taplin Fellows. He also received two traveling fellowships from HSPH: the Uwe Brinkmann Traveling Fellowship in 1996, and the Frederick Sheldon Fellowship in 1997.