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Down on the Farm**

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## AVIAN INFLUENZA

## Combating the Bird Flu Menace, Down on the Farm

A race is on to beef up avian influenza surveillance and train scientists in some of the poorest corners of Southeast Asia

**VIENTIANE AND PHNOM PENH**—According to Buddhist tradition, a pinch of salt repels evil spirits. For Maha Ouan, lime does the trick. On a farm 15 kilometers northeast of Vientiane, the capital of Laos, Ouan sprinkles the disinfectant on dirt tracks and around chicken enclosures to repel an evil not found in sacred Buddhist writings: the H5N1 avian influenza virus. In January 2004, the dreaded strain swept into this impoverished country, wiping out 45,000 chickens before a mass cull smothered the outbreak. Ouan got lucky: The avian reaper bypassed his 18,000 egg layers. He realizes that was a fluke, though, and isn't taking any chances. "Who knows whether bird flu will come back," he says.

Odds are it will. Few Laotian farmers share Ouan's zeal for hygiene and for keeping livestock penned. Chickens, ducks, and the occasional scruffy hog outnumber people along the road back into town, lined with rippling flags, always in pairs—Laos's full moon over a blue Mekong River and the Communist rulers' Soviet-esque hammer and sickle against a red background. Free-ranging animals "are a very serious concern" because they can fan the flames of an outbreak, says David Castellán, a poultry expert with the California Department of Food and Agriculture in Sacramento, who spent 6 weeks in Laos late last year.



**Paragon of poultry.** Maha Ouan is one of the few farmers in Laos taking measures to stem the spread of bird flu, such as keeping chickens caged (*inset*).

So far, Laos and neighboring Cambodia appear to have been spared the worst. Laos has not detected bird flu since 2004, and not one person has tested positive for H5N1. Cambodia has had only sporadic flare-ups among birds and just four human cases. Yet, the regional powers that sandwich them—Thailand and Vietnam—have grappled with frequent outbreaks and a large share of the global total of 91 human deaths attributed to H5N1 since 2003. This strain is more likely to rear up on large commercial poultry farms, which



**Basic training.** A technician in Phnom Penh's new avian diagnostics lab prepares to test samples of duck blood for bird flu antibodies.

are common in Thailand and Vietnam, experts say. But the quiet in Cambodia and Laos does not mean that health officials here can afford to be complacent. "Something could happen at any time," notes Somphanh Chanphengxay of Laos's Ministry of Agriculture and Forestry.

Thanks to a \$1.9 billion windfall, pledged by the United States, the European Union, the World Bank, and other donors in Beijing last month (*Science*, 27 January, p. 456), Laos, Cambodia, and other Southeast Asian nations are redoubling efforts to strengthen surveillance, both by training health workers on what to look out for and by equipping new labs. The cash infusion will help these countries transform their scientific corps, greatly bolstering their capacities to anticipate and track future disease threats. In some areas, they are starting from scratch: Laos, for example, plans to set up its first-ever faculty of veterinary science at National University in Vientiane.

The scientific buildup here is coming not a moment too soon. "Southeast Asia is the first line of defense" against a potential pandemic, should the H5N1 strain acquire the ability to pass easily among people, says Finn Reske-Nielsen, U.N. resident coordinator for Laos. "There has to be a minimum capacity to say, 'Something funny is going on here. This has to be reported.'" He

hopes to see adequate surveillance put in place over the next several months. "It's a huge, huge challenge."

### Extreme makeovers

In a modern lab in the heart of Phnom Penh, two technicians squeeze drops of duck blood from syringes into small plastic vials. The women, staff members of Cambodia's National Animal Health and Production Investigation Centre (NAHPIC), are going to spin the blood down and probe the serum for avian influenza antibodies. Outside, the squeals of children at play can be heard from a primary school next door. "We have to be very careful here," says NAHPIC's director, Sorn San.

A year ago, the Cambodian government was incapable of routine surveillance. Before H5N1 descended, the government had no facility to detect

any strain of bird flu and had few staff members qualified to work with infected specimens. “A lot has happened since then,” San says.

Over the past several months, Cambodian authorities have outfitted an avian influenza diagnostic lab at NAHPIC, using funds raised over the past 2 years by the U.N.’s Food and Agriculture Organization (FAO). The center now has 31 staff, most of whom have B.Sc. degrees from the Royal University of Agriculture. “They’re young and need more expertise,” says San, one of the few intellectuals who survived the brutal Khmer Rouge years before earning a veterinary degree in Cuba in the 1980s.

Nowadays, hundreds of Cambodians each year stream overseas to earn advanced degrees. “The problem is that few come back,” says a U.N. official. Laos, too, suffers an acute shortfall of young scientists. Most Laotian researchers are in their late 30s or older, having earned degrees in the East Bloc, says Chanphengxay, who trained in Hungary. When the Soviet Union collapsed, opportunities for training dried up. In Laos, says Reske-Nielsen, “basically there are five people in the Ministry of Health who are qualified” to deal with bird flu.

FAO is helping close the expertise gap, in part by sending young scientists from Cambodia and Laos abroad for training. And it has sent in a one-man cavalry: Huaguang Lu, an avian virologist at Pennsylvania State University, University Park, who in 2002 developed a cheap dot-ELISA (enzyme-linked immunosorbent assay) test for rapidly identifying the fast-mutating H5 and H7 subtypes of bird flu. Lu has assisted San in setting up NAHPIC’s lab, teaching staff how to handle avian influenza samples, isolate viruses in chicken embryos, run dot-ELISA to detect the H subtype, and use agar gel immunodiffusion to check for antibodies. A planned expansion later this year, paid for by funds raised in Beijing, will enable researchers to carry out the polymerase chain reaction (PCR) for rapid diagnosis of H5N1 and add a walk-in cooler and an incubator room. The NAHPIC lab “will be one of the most advanced avian diagnostic labs in the region,” says Lu.

Epidemiologist Wantanee Kalpravidh, FAO’s avian influenza coordinator for Southeast Asia, is impressed with how far Cambodia has come in such a short time. “Lu is very, very energetic,” she says. And he’s persuasive, too: “When he asks for something,” such as convincing officials to hire more technicians or provide more lab space, “people cannot resist,” she says.

Lu is helping establish a similar facility in Vientiane. When chickens began dying in droves in early 2004, Laos lacked the capacity to confirm H5N1 as the culprit; that was done in Thailand. “They never had a virology lab in their history,” Lu says.

The need for handling nasty pathogens was great, though, even before H5N1. Laos has struggled to stamp out foot-and-mouth disease, which prevents it from legally exporting beef and buffalo meat. Laos is also grappling with swine fever and hemolytic septicemia. To boost surveillance of these perennial foes, the Ministry of Agriculture and Forestry a few years ago began building a lab at the National Animal Health Centre (NAHC) in Vientiane. But Laos’s economy tanked just before avian influenza struck, halting construction.

On NAHC’s grounds overlooking the Mekong, the unfinished three-story lab center, a concrete frame with brick walls but no windows, sits behind a dilapidated corrugated steel fence. Center staff, some wearing Adidas tracksuits, toil in cramped quarters next door. The bird-flu lab was carved out of two tiny rooms in NAHC’s 75-year-old main complex. Funds channeled through FAO have enabled NAHC to install a biosafety hood for handling virus-laden blood, and Lu has trained staff to run the same virus-isolation, dot-ELISA, and antibody tests used in Phnom Penh. The Laos government is seeking about \$800,000 from foreign donors to complete construction of the new building.

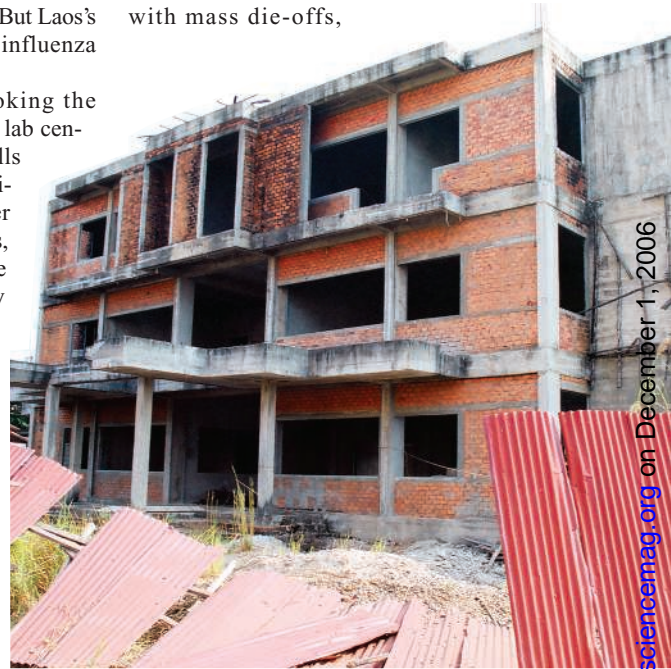
Like its counterpart in Cambodia, NAHC’s lab is strictly for animal samples. “We still don’t have the capacity to make diagnoses in humans,” says Sithat Insiengmay, a microbiologist at Laos’s Ministry of Health. He hopes to dispatch staff to the United States for training and at the same time upgrade biosafety in a health ministry lab to allow it to work with tainted human blood. Samples from five suspected cases since 2004 were sent to Tokyo for testing; none were positive for H5N1. Insiengmay hopes Laos will be able to do PCR on denatured human blood by the end of 2006.

#### Casting a wider net

The most urgent need is heightened vigilance. “We worry a lot about undetected outbreaks in small backyards,” says Chanphengxay. This blind spot isn’t restricted to Cambodia and Laos. Myanmar hasn’t reported a single bird flu case in poultry or people. Given its brittle relations with the country, FAO cannot judge whether Myanmar’s surveillance is up to snuff.

A lucky find in Cambodia illustrates how easy it is to miss an outbreak. Last August, a team from NAHPIC and the Pasteur Institute in Phnom Penh, on a routine surveillance mission, drew blood from a couple of dozen young ducks from a domestic flock in Prey Vêng province, about 80 kilometers east of the capital. Some samples had antibodies to H5,

prompting a closer look. When researchers followed up last October, they discovered that roughly 600 of 800 ducks in the flock had died the previous July. “I was shocked,” says the Pasteur’s Sirenda Vong. “When we were there in August, nobody had reported this to us.” They expanded the study, drawing blood from 41 flocks and interviewing farmers. More than half the flocks had been hit with mass die-offs,



**Sign of the times.** An economic downturn has prevented Laos from finishing construction of this animal-health laboratory.

and antibody tests nailed H5N1. “The virus was all over the place,” Vong says.

Detecting future H5N1 outbreaks in ducks and tracking the virus’s origins are top priorities, says Vong, a 41-year-old medical epidemiologist who returned to Phnom Penh in late 2004 after a 4-year stint at the U.S. Centers for Disease Control and Prevention in Atlanta, Georgia. In December, Vong’s Pasteur team, working with NAHPIC, deployed about 100 sentinel ducks at a lake near Kampong Cham, 100 kilometers northeast of Phnom Penh; they plan to swab cloacae and tracheas and draw blood from the tagged ducks twice a month. And Pasteur plans to work with the Wildlife Conservation Society to look for H5N1 in excrement of migratory birds that pass through Cambodia on their way to northern breeding grounds.

But although Pasteur has put a watch on Prey Vêng and Kampong Cham, it can’t keep tabs on all of rural Cambodia. “If people aren’t reporting bird deaths, we’re not going to detect anything,” Vong says. It’s unknown, he says, how often outbreaks in ducks flare up and die out on their own.

Hand in hand with better monitoring is the need to raise public awareness of the H5N1 threat. “We need to reach families,” says Insiengmay, who notes that in Laos alone, 85% of poultry is

kept in backyards. To disseminate bird-flu warnings more widely, the government is now translating data sheets in Lao into languages of ethnic minorities, including the Hmong and Khmu. Laos's diverse ethnic groups "pose a huge challenge for risk communication," says Castellán.

Last December, Castellán worked with FAO to train health workers in the Laotian hinterlands, including Champasack, a high-risk province bordering Thailand and Cambodia that was hit hard in 2004. "This is where the rubber hits the road,"

he says. Their messages were simple: Raise chickens, ducks, geese, and other poultry separately, sell live poultry separately from processed poultry products, and practice good personal hygiene.

However, "it's very difficult to change the minds of farmers," says San. For example, rural Cambodians have no fear of eating chickens that die of Newcastle disease. In unvaccinated flocks, this virus has a mortality rate exceeding 50%, rivaling that of H5N1. "It's hard to distinguish between Newcastle and avian influenza"—

even for a veterinarian, says San. The best strategy, he says, is to insist that chickens that succumb to disease are buried, not eaten. "We're trying to train the village health workers to put a stop to that," San says.

Transforming rural lifestyles "won't happen overnight," Castellán says. But on the front lines of Southeast Asia, the battle to stave off a pandemic flu strain is likely to be won or lost not in the cities, but down on the family farm.

—RICHARD STONE

## INTELLECTUAL PROPERTY

# What Good Is a Patent? Supreme Court May Suggest an Answer

Two cases raise fundamental questions about the scope of a patent and the right balance between protecting innovation and hindering commerce

Next month, the Supreme Court will hear two cases that could punch holes in a strong patent regime credited with fostering the remarkable growth of the U.S. biotechnology industry. Experts predict that the high court may rein in a specialized lower court that has shaped U.S. patent policies for the past 2 decades. At a minimum, the court's involvement reflects a world increasingly dependent on intellectual property.

The two cases pose key questions about what can be patented and the force a granted patent should have in the marketplace. In *Laboratory Corp. v. Metabolite*, a case involving two makers of diagnostic blood tests, the high court will probe the limits of patenting basic scientific principles. In *eBay v. MercExchange*, the court could rule on how much a patent holder can interfere with the activities of a company or organization infringing on its patent. (A third case up for review this spring would give the court a chance to decide how obvious a proposed invention must be to be denied a patent.) Together, the cases could have "major, major impacts" on existing patents and future applications in a range of disciplines, says former U.S. commissioner of patents Nicholas

Godici of Birch, Stewart, Kolasch & Birch LLP, based in Falls Church, Virginia.

The cases come amid calls for reforming a system bogged down by questionable patents and expensive lawsuits. Although a 2004

report by the National Research Council of the National Academies concluded that the system "does not require fundamental changes," it warned that further deterioration of patent quality could "impede research progress" and discourage innovators from "invent[ing] and disseminat[ing] technology." Last year, Congress took up the issue, but disagreements over patent quality and the appropriate use of injunctions against violators derailed proposed legislation (*Science*, 17 June 2005, p. 1725).

The framers of the U.S. Constitution included patents as a way "to promote the progress of science." For nearly 2 centuries, the United States has had some of the strongest patent rights of all nations. But since the founding of the specialized Federal Circuit appellate court in 1982, the system has struggled to find the best way to protect discoveries in biotechnology, information technology, and other emerging fields.

Because the Supreme Court rarely intrudes on the appellate court's turf on major issues, patent lawyers say its decision to accept the two cases suggests that the justices might want to step in and review how far the lower court has gone. But some patent lawyers turn queasy at the thought of having nine "outsiders" take on the system. "They think the [Federal Circuit] needs to be tightened down," says attorney Vern Norviel of Wilson, Sonsini, Goodrich & Rosati in Palo Alto, California. Under a worst-case scenario, says Kevin Noonan of McDonnell, Boehnen, Hulbert & Berghoff LLP in Chicago, Illinois, the court's upcoming rulings could imperil "thousands of [granted] patents" and "harm innovation."

### Can you patent nature?

The first case centers on defining what is a natural phenomenon and, therefore, not patentable. Metabolite has rights to a patent for measuring blood levels of the amino acid homocysteine, but the patent also covers use of the test to infer levels of vitamins B-12 and B-6, which help break down homocysteine. In 1999, Metabolite and another company sued Laboratory Corp.—called LabCorp—for patent infringement and breach of contract. A

