CREDIT: GREGORY GRAY/DEPARTMENT OF ENVIRONMENTAL AND GLOBAL HEALTH, COLLEGE OF PUBLIC HEALTH AND HEALTH PROFESSIONS

Hog-tied research. Pork producers in many locales resist active surveillance for flu.

BIRD FLU CONTROVERSY

Does Forewarned = Forearmed With Lab-Made Avian Influenza Strains?

Behind the increasingly contentious debate over whether journals should publish the full details of how two labs engineered the deadly avian influenza strain H5N1 so that it spreads more easily among ferrets, and presumably humans, lies a conundrum: Knowledge cuts both ways.

No one at the front of this protracted battle wants to stifle free scientific exchange. But two camps have formed that view risks and benefits through different lenses. Proponents of full disclosure, including the researchers who conducted the work, contend that knowing the genetic signatures of these potentially devastating viruses might prove pivotal to shoring up surveillance measures and controlling an emerging threat.

Maybe, say opponents in the other camp, but they stress that in the predominantly poor countries where H5N1 circulates, surveillance and control systems are too rudimentary, or nonexistent, to take advantage of the new knowledge. They worry that if published, that data could provide a recipe for bioterrorists to unleash a doomsday scenario.

Ideally, a robust surveillance system will detect novel flu viruses in animals when they arise, which in turn will aid control efforts with vaccines and culling, preventing economic loss to farmers and the introduction of dangerous strains to humans. Early detection of new strains in humans can similarly give public health officials a jump on fashioning an effective response. Ideally.

The reality is far messier—a point that both camps agree is troubling.

When avian influenza viruses infect and adapt to humans, they have the potential to cause devastating pandemics because we have little, if any, immunity to them. Although public health officials have documented fewer than 600 cases of H5N1 infections since it surfaced in humans in 1997, H5N1 has received intense attention because more than half of the people who had symptomatic disease died (see sidebar, p. 786). The saving grace is that it has not spread easily among people. But two labs have made the virus transmit readily among ferrets by introducing mutations or creating a "reassortant" of H5N1 and the H1N1 virus that caused the 2009 flu pandemic. Papers about the studies, stuck in limbo at *Science* and *Nature,* remain unpublished while scientists, journal editors, and public health officials weigh the benefits and risks of full disclosure.

Influenza specialists often stress that surveillance *has* improved since H5N1's emergence in Hong Kong 15 years ago. They particularly praise virologist Malik Peiris at the University of Hong Kong and colleagues, who worked on the 1997 outbreak and then began to hunt for flu viruses in birds at markets and pigs at slaughterhouses. (Peiris makes the case online in *Science* that the new experiments will help surveillance, http://scim.ag/_h5n1.) "The folks in Hong Kong are a model of what should happen in the world," says Robert Webster, who studies influenza at St. Jude Children's Research Hospital in Memphis, Tennessee, and helped Peiris launch the program.

But Hong Kong remains the exception. At a debate held 2 February by the New York Academy of Sciences about the mutant H5N1s, the state of the world's surveillance efforts received a drubbing from a member of the U.S. National Science Advisory Board for Biosecurity, which made the controversial recommendation to remove from the papers details of the genetic changes that made the virus transmissible as well as the methods the scientists used to produce those mutations. "Surveillance out there right now is like a whole lot of broken smoke alarms," said flu expert Michael Osterholm of the University of Minnesota, Twin Cities.

Veterinary microbiologist Jürgen Richt of Kansas State University, Manhattan, agrees that surveillance is wanting but says the details could indeed be put to good use. Although H5N1 primarily circulates in poor countries that have limited access to sophisticated laboratories, they widely use inexpensive and relatively simple PCR tests that could hunt for the mutations linked to transmission. "We can design surveillance screens for transmissible versus nontransmissible H5N1," Richt says. Countries that find transmissible H5N1 in animals could ramp up programs to "immediately stamp it out," he says. "We would be weeks ahead."

But having the tools only helps if countries use them properly. "We don't have the surveillance or reaction system, so how is this really going to help?" asks veterinarian Ilaria Capua, who runs an influenza reference lab for Italy at the Istituto Zooprofilattico Sperimentale delle Venezie in Padua. Capua notes that influenza programs in developing countries depend heavily on funding from the wealthy world. "There's less surveillance going on than 3 or 4 years ago, because donors have changed their priorities," she says. (Despite her surveillance concerns, Capua, who in 2006 persuaded reluctant colleagues to share H5N1 sequences in the name of spurring scientific progress, supports full publication of the new data.)

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Capua works closely with Egypt, which has had more cases of human H5N1 than any country other than Indonesia. When it comes to culling H5N1-infected flocks, the primary control strategy, she notes that's easier said than done, too. "Egypt is a very poor country, they have social unrest, and they don't have the infrastructure and just cannot afford to cull the birds," she says.

Animal vaccination campaigns in poor countries, which complement surveillance and culling, similarly face huge obstacles. To combat H5N1, several countries launched massive vaccination campaigns in poultry, using more than 100 billion doses between 2002 and 2010, according to a recent review in a journal published by the World Organization for Animal Health. But birds have short life spans, and campaign success often waxes and wanes, largely dependent on how widely the vaccines are used.

Delays in moving animal samples from field to lab can also undermine the benefit of detecting dangerous strains. Several months often pass before samples from Egypt reach her lab, Capua says. Sample delays have compromised efforts in wealthy countries, too. In the United States, researchers have pushed for monitoring slaughtered pigs—the type of "active" surveillance Hong Kong does—but have met resistance from the pork industry, which took a financial beating during the 2009 pandemic and fears another backlash if the public learns that novel influenza strains infected their pigs. Hog producers wait until 3 months

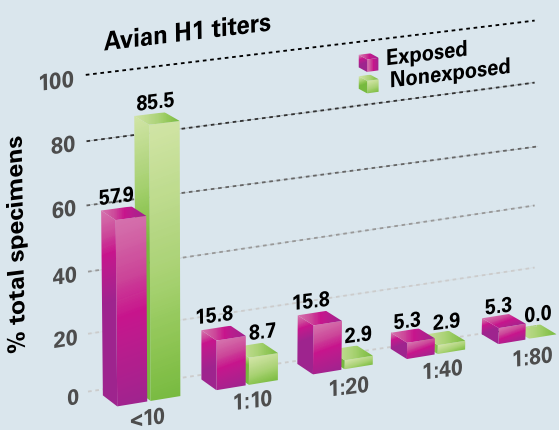
Dead Reckoning the Lethality of Bird Flu

"Peter, you know there's science and there are facts, and you know you can't have your own facts."

Those fighting words came from Michael Osterholm on 2 February at the New York Academy of Sciences, where he and Peter Palese, both prominent influenza researchers, debated just how deadly the avian virus known as H5N1 is to humans. That question bears directly on the current fracas over H5N1 variants created by two labs that spread easily among ferrets, a model for human transmission (see main text). Palese, a virologist at Mount Sinai Medical Center in New York City, thinks official figures overstate the lethality of H5N1 to humans, exaggerating the risk of the new experiments. Osterholm, an epidemiologist at the University of Minnesota, Twin Cities, asserts that Palese cherry-picks studies to discount the threat. "You misrepresented the data, and that's propaganda," Osterholm charged.

The fact is, the facts aren't clear.

Without question, H5N1 kills many of those it sickens but does not spread readily among people. As of 8 February, the World Health Organization (WHO) says, H5N1 had killed 59% of the 584 confirmed cases in humans since 2003. If H5N1 artificially or naturally acquired the ability to transmit easily among mammals, jumped into humans, and remained highly pathogenic, it could trigger what Osterholm called the "worst pandemic" ever seen. Osterholm is a member of the U.S. National Science Advisory Board for Biosecurity (NSABB), which made the contentious recommendation that journals redact key details before publishing the studies to prevent aiding bioterrorists.



Bird's-eye view. Poultry vets (purple) had significantly higher antibodies to avian H1 strains when several dilutions were combined.

Palese says making the details freely available poses little risk and will advance the field. In a 25 January online perspective he co-authored in the *Proceedings of the National Academy of Sciences* (*PNAS*), Palese notes that WHO ignores subclinical cases of H5N1, which one recently published study suggested occurred in 45 of 800 people (5.6%) tested in rural Thailand. "Even if only a low percentage of the rural population is asymptomatically/subclinically infected, the case fatality rate that is offered by the WHO—and that is driving this controversy—is likely orders of magnitude too high," Palese's *PNAS* perspective argued.

Osterholm noted that several studies contradict the Thai report, published in the 15 October 2011 issue of *Clinical Infectious Diseases*, which he called "by far the worst one of all." Epidemiologist Gregory Gray of the University of Florida, Gainesville, who led that study, counters that it's one of the largest and most carefully done serology surveys yet published. "Is it perfect? No," Gray says. "But it's the best we can do."

Osterholm focused on the antibody assay used by Gray's group to assess exposure to H5N1. The researchers performed a "serial dilution" that mixes antibody-containing sera with inert liquid at various concentrations and then tests whether they can prevent infections in culture. More dilute solutions can stop virus only if the starting sera contain higher titers of H5N1 antibodies, so "neutralizing" titers of 1:80 are more compelling than 1:10. WHO only ascribes symptomatic cases to H5N1 if they have titers of 1:80; combining published studies of asymptomatic infection with that cutoff, prevalence is 0.48%, Osterholm says. Gray's study used a 1:10 cutoff and found an 11-fold higher prevalence.

Gray says the 1:80 cutoff makes sense in the clinic, when people have acute infections, but not in a retrospective epidemiology study. He notes that he and his colleagues analyzed villagers 2 years after H5N1 was last detected in Thailand, at which point antibody levels likely would have waned. And 1:10 was simply the minimum requirement used to define a person as positive: Titers went as high as 1:40. Their final analysis combined the various titers using a statistical technique called proportional odds modeling, validated in an earlier study of avian viruses (see graph).

Osterholm told the New York audience, "I could find a number of you in this room positive using that study design." Not so, Gray says. "We've done thousands of these, and very few people have 1:10," he says. "I'm sure there are some false positives, but it's not an egregious thing." To more precisely determine subclinical infection rates, Gray says the field needs prospective studies—which he has under way—that capture antibodies from people during and immediately after exposure.

Osterholm says NSABB didn't debate H5N1's actual lethality. "If this virus was 20-fold lower in mortality, it would still be a very, very catastrophic pandemic," he says.

But what if H5N1 is 1000-fold less lethal than WHO estimates and Palese has a valid point? Osterholm agrees that's possible but contends scientists must err on the side of caution. As he said at the debate, "We can't afford to be wrong." **–J.C.**

GRAPHIC SOURCE: ANA CAPUANO AND GREGORY GRAY/UNIVERSITY OF FLORIDA, ADAPTED FROM MYERS *ET AL.*, *CID* 45:4 (2007)

after slaughter to give samples to Webster's colleagues at St. Jude's, a compromise he says is actually a step forward. The U.S. Department of Agriculture has no mandatory active surveillance of commercial swine or poultry, but many producers have joined voluntary programs that offer financial incentives or agree to not specify the location of infected farms.

Virologist Yi Guan, who works with Peiris in Hong Kong, agrees that knowing the signatures of transmission might help but says there's often a disconnect between the influenza surveillance and control efforts in animals and humans. Vaccination makes it difficult to track the virus in poultry, so mainland China is "using humans as sentinels," he says. "First they have a human case, then they start looking for bird flu."

Cull of duty. If surveillance detects H5N1 early, killing flocks can contain it, as the United Kingdom did in 2007.

As for surveillance in humans, the benefits of the new experiments are murkier. "Once a new influenza virus begins to be transmitted between humans, whether as a result of a Mother Nature–made pandemic virus or an intentional or unintentional release of a manmade virus, it's like having a screen door on your submarine; you'll never contain it," Osterholm says.

Whether the new experimental data will help protect humans, the debate has already spotlighted the inadequacies of surveillance and control, Richt says. "This whole discussion stimulates organizations and governments to review their emergency plans if an H5N1 epidemic arises, and that's a critical point," Richt says. "These people have to rethink."

–JON COHEN

With reporting by Dennis Normile.

SOCIAL SCIENCE

Marriage Decision Highlights Same-Sex Studies

As a rookie professor in the mid-1970s, social psychologist Letitia Anne Peplau would tell students about her studies of heterosexual dating. But "when gay and lesbian students asked why I didn't talk about their same-sex relationships, I explained that there really wasn't any good research," she recalls. She set out to change that. The University of California, Los Angeles (UCLA), academic hung posters and made personal appeals to recruit gay and lesbian couples for studies. Sometimes it wasn't easy because "it hadn't been that long since many psychologists viewed homosexuality as a mental illness." Peplau never imagined, however, that her work would ultimately land her in the middle of a landmark legal battle over same-sex marriage—or as a character in an unusual movie.

"In the '70s, marriage equality simply wasn't an issue," says Peplau, who is part of a small group of social scientists who provided expert testimony in the legal jousting over California's Proposition 8, a 2008 ballot initiative that banned same-sex marriage in the state. Last week, that battle took a major turn when a three-judge federal appeals court panel voted 2-1 to find the same-sex marriage ban unconstitutional, upholding a lower court ruling. Proposition 8 "serves no purpose, and has no effect, other than to lessen the status and dignity of gays and lesbians in California," the majority wrote. The decision in *Perry* v. *Schwarzenegger*, which applies only to California, could end up as a precedent-setting case before the U.S. Supreme Court.

Even if the case doesn't go that far, it has helped highlight a growing body of research on the psychological and socioeconomic aspects of same-sex relationships. Just a few decades ago, "there were a lot of myths out there but not much research," says Lee Badgett, a labor economist at the University of Massachusetts, Amherst, who served as an expert witness in support of overturning Proposition 8. Even into the 1990s, for instance, Badgett says stereotypes suggested that gay and lesbian workers tended to earn more than heterosexuals. "There was this image of the affluent gay male couple with no kids," she says. But after combing a trove of national survey data, Badgett and others concluded that gay men actually earned less on average than their straight colleagues, while lesbians typically "earned about the same or maybe a bit more." Such results ultimately led Badgett to examine the economic costs and benefits of marriage. One intriguing finding: Couples with legal ties, same or opposite sex, tend to use less government assistance, in part because the partners can turn to each other for help in hard times, and in part because state welfare agencies tend to be stingier with couples. The bottom line, Badgett says, "is that marriage can save taxpayers money."

On the stand. Peplau's studies of same-sex couples were the subject of extensive court testimony.

Over the past decade, same-sex marriage advocates have seized on such findings to bolster their arguments. And when the conflict moved into the courts, Badgett and other academics on both sides of the issue suddenly faced requests to trade the classroom for the courtroom. But perhaps no case placed them in the spotlight like *Perry* v. *Schwarzenegger,* which kicked off in 2010 with 12 days of public testimony in the San Francisco courtroom of federal district judge Vaughn Walker. In all, opponents of Proposition 8 put nine social scientists on the stand, including psychologists, economists, and political scientists who testified about everything from the political power of homosexuals to the impact of same-sex partnerships on child rearing.

Supporters of the measure called two experts, a historian and a political scientist, who argued in part that voters had a right to promote the "optimal" family structure for bearing and raising children. Judge Walker, however, ultimately rejected much of their tes-

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