



# Hong Kong Flu Still Poses Pandemic Threat

Brian Vastag

WASHINGTON—In December 1997, news watchers were confronted with sobering images of government workers in Hong Kong slaughtering 1.4 million chickens in a massive effort to prevent avian influenza from spreading through the densely populated city and, potentially, across the globe.

Earlier that year, what was later identified as a strain of influenza previously known to infect birds, but not people, had sent 18 patients to Hong Kong hospitals. The first case led to the death of a 3-year-old boy, followed by the deaths of five other patients.

Somehow the virus had jumped species. Working with the US Centers for Disease Control and Prevention (CDC), Hong Kong health officials began implementing a control plan designed to obviate such drastic measures in the future.

It didn't. In June 2001, and again in May 2002, a total of 4 million chickens in Hong Kong were destroyed to stanch potential pandemics. Both cullings were precipitated by detection of influenza virus in Hong Kong poultry, said John Siu-Lun Tam, PhD, a professor of microbiology at the Chinese University of Hong Kong, during a scientific session at the meeting of the World Medical Association held here in October.

And although angst over the specter posed by bioterrorism dominated the meeting, a CDC official warned that the threat of an influenza pandemic is still "very real." Such a worldwide outbreak would dwarf the influenza epi-

demics that sweep through the United States every winter, said Nancy Cox, PhD, chief of the influenza branch of the National Center for Infectious Diseases at the CDC.

While a typical flu season claims about 20 000 US lives annually, a pandemic could provoke 207 000 deaths, 734 000 hospitalizations, and 42 million outpatient visits, estimated Cox and

CDC colleagues Martin Meltzer, PhD, and Keiji Fukuda, MD (*Emerg Infect Dis.* 1999;5:659-671).

"It would be extremely overwhelming," said Cox.

## EMERGING STRAINS

The worst influenza pandemic of the 20th century (in 1918) spread so quickly that it claimed 20 million lives



Chickens—on their feet and on the rack—for sale at a shop in Hong Kong. In June 2001 and May 2002, a total of 4 million chickens were destroyed there to stanch the potential spread of influenza.



worldwide. The other two influenza pandemics of the past century, in 1957 and 1968, led to many fewer deaths, but still killed 70 000 and 34 000, respectively, in the United States alone. And while the winter flu preys mainly on the elderly and others with weakened immune systems, pandemics lead to a higher proportion of deaths among children and young adults, said Cox. Most of those killed in 1918 were working-age adults.

Methods to predict the where and when of a pandemic have not advanced appreciably since the 1918 pandemic. Cox warned that new strains can emerge suddenly and unpredictably—two factors that differentiate a pandemic (extensive emergence of a virulent new strain) from an epidemic (localized circulation of a known strain).

The 1997 Hong Kong outbreak caused such intense concern not only because the strain was new, but also because it apparently jumped directly from poultry to people. In the past, influenza watchers thought that to infect people, any new avian strain would first have to spread through herds of pigs. Susceptible to both bird and human influenza, the animals act as incubators of virulent strains, said Cox. As the porcine immune system fights infection, avian and human viruses shuffle genes in a sort of natural genetic engineering that can breed deadlier varieties.

But since people in Hong Kong prefer poultry to pork, pigs were not suspected in the 1997 “bird flu” cases. Instead, epidemiological investigations isolated domestic birds as the common link. The index case, a 3-year-old boy, often played with pet ducks. Twelve of the other 17 patients had handled poultry in the week prior to becoming ill. A recently published study confirmed the potential for chicken-to-human transmission, finding antibodies to the 1997 strain in 10% of 1523 Hong Kong poultry workers (*J Infect Dis.* 2002;185:1005-1010).

Conditions are ripe for nonoccupational exposure as well, said Tam. “There is a strong emphasis on freshness,” he

said, and customers like to pick up and inspect live chickens at the 930 poultry markets in the city. “They touch the neck and blow on the other end to see how good it is,” he said, holding up and turning his hands as if looking at the bird’s rear. Prior to 1997, Tam said, conditions at the markets were unsanitary, with feathers and feces abundant.

Since then, the city’s health department has mandated new hygiene and safety standards. Ducks and geese, which serve as the natural reservoir for the 15 known strains of influenza A, are now shipped and slaughtered separately from chickens—to interrupt the first link in the pandemic chain, said Tam.

New surveillance measures at the Chinese border, where 85% of the poultry consumed in Hong Kong originates, have also taken effect. Each arriving flock is quarantined, tested, and held for 2 days. Flocks with one or more sick birds are rejected while clean flocks move to a central wholesale warehouse, where they wait 2 days more.

“Four days is the time it takes a chicken to die” from influenza, said Tam. If a bird is still flapping at the retail market, it is probably not infected.

On the farms where the rest of Hong Kong’s chickens come from, any sign of infection—sick birds, positive antibody tests—leads to a quick slaughter and ring vaccination of birds at surrounding sites.

Despite these measures, which have gradually been phased in over the past 5 years, the health department again resorted to massive—although not massively publicized—cullings in 2001 and 2002. Questioned by a meeting attendee about this, Tam said that the prevalence of the virus type detected in 1997 is too widespread to eliminate completely. “We see this as a problem for the region, not just Hong Kong,” he said. “We tell people that we cannot eliminate [the virus], that we are trying to reduce the source to prevent human cases.”

#### INCREASED SURVEILLANCE

Fortunately, the 1997 virus apparently never acquired the ability to

spread from person to person, although a shred of evidence from a study of household contacts of patients suggests that such transmission is possible. Researchers found antibodies against the bird flu strain in a household member who had no contact with poultry (*J Infect Dis.* 1999;180:1763-1770). Concern that a mutation fostering airborne human transmissibility could arise, making the final link in the pandemic chain, has the Hong Kong health department, the CDC, and the World Health Organization constantly searching for methods to improve surveillance, detection, vaccination, and treatment.

The region that includes southern China and Hong Kong—a historical, although altogether not well understood, source of new influenza variants—is high on WHO’s hot list. With WHO’s support, the city’s surveillance system, widely credited for halting the 1997 outbreak, has been expanded and now includes 111 sentinel physicians.

In 1999, the sentinels and other local hospitals and clinics sent 17 351 specimens to a central laboratory for influenza testing. The health department collects and disseminates influenza information, including reports on extant subtypes, on a weekly basis.

#### BLIP ON SURVEILLANCE RADAR

In March 1999, the system flagged another new influenza strain found in samples from two sick children, although the source was never identified, said Cox. A cohort study found no evidence of person-to-person transmission, but an epidemiological investigation revealed that 23% of one group of poultry workers tested positive for exposure (*Emerg Infect Dis.* 2002;8:154-159). The strain was found in Asian poultry and pigs, but has not reappeared in Hong Kong’s clinics. This odd blip on the surveillance radar is a testament to influenza’s unpredictability.

That blip also prompted the CDC to develop vaccine for the strain; Cox said that three candidate vaccines are approaching human trials. But even while



the development of a vaccine targeting this novel strain is moving forward, vaccine production remains the “Achilles’ heel of pandemic preparation,” said Cox. With current technology, manufacturers need 8 months to produce 250 million doses of trivalent influenza vaccine, which typically comprises the three strains that experts believe (based on surveillance of strains circulating worldwide) constitute the most likely threat for the following winter.

Cox guaranteed that in the event of a pandemic, which could spread globally in a few months, “there won’t be

enough [vaccine] to go around.” She called for the development of “a library of candidate vaccines on the shelf, ready to go,” as well as expedited research into advanced production methods, such as cell-based cultures. In an age of sequenced genomes, influenza vaccine is still produced relatively crudely, inside incubated chicken eggs.

Until that method is replaced, then, Cox suggested an answer to the public health community’s version of the hoary chicken-and-egg riddle: stockpiles of egg vaccine first, before another outbreak of chicken virus. □

in risk of invasive breast cancer), exceeded benefits, which included a statistically significant decreased risk of colon cancer and osteoporotic fracture (*JAMA*. 2002;288:321-333). An estrogen-only arm of the study continues.

In the HERS II study, estrogen/progestin therapy did not significantly reduce CHD (*JAMA*. 2002;288:49-57), and it significantly increased rates of venous thromboembolism and biliary tract surgery (*JAMA*. 2002;288:58-66). Increases in breast cancer and hip fractures were not significant in HERS II.

Stanford University researcher Marcia Stefanick, PhD, a HERS and WHI investigator who served on the NAMS panel, said the recommendations are “one more step toward having the medical community accept these findings.”

## Questions About Hormone Therapy Remain Puzzling

Rebecca Voelker

CHICAGO—New clinical recommendations from the North American Menopause Society (NAMS) show that many physicians are left with more questions than answers following the recent release of data from two large clinical trials of hormone replacement therapy (HRT).

After the publication of follow-up findings from the Heart and Estrogen/progestin Replacement Study (HERS II) and a halted arm of the Women’s Health Initiative (WHI), the NAMS board faced two issues: whether to respond to the findings and, if so, how best to guide clinicians who prescribe HRT.

“Rather than come out with an acute, gut response, we decided to convene an expert panel to develop recommendations to deal with what we know and what we don’t know,” said NAMS Executive Director Wulf Utian, MD, PhD. Utian is the Arthur H. Bill professor emeritus of reproductive biology and obstetrics and gynecology at Case Western Reserve University School of Medicine, Cleveland.

### LACK OF CONSENSUS

The 10-member panel was cochaired by Utian and NAMS President Margery

Gass, MD, of the University of Cincinnati College of Medicine in Cincinnati, Ohio. Remaining members included investigators from HERS and the WHI, and experts in such fields as cardiovascular medicine, epidemiology, and obstetrics and gynecology. Utian noted that the panel could not reach consensus on a number of clinical questions the members discussed (see below).

Its report, he added, was not intended “to praise or bury the WHI—that debate will go on for years.” The WHI is considered the largest, most statistically valid study of HRT use in healthy postmenopausal women. But it has garnered criticism that the duration of follow-up of the combined therapy arm—an average of 5.2 years—is too short to precisely assess the effects of long-term treatment, and that regimens other than daily pills containing 0.625 mg of conjugated equine estrogens and 2.5 mg of medroxyprogesterone acetate were not included in the study.

The combined estrogen/progestin arm of the WHI study was stopped because overall health risks, particularly a statistically significant increased risk of coronary heart disease (CHD), stroke, and venous thromboembolism (there was a nonsignificant increase

### AREAS OF AGREEMENT

Based on findings from HERS, the WHI, and other published studies, issues on which the NAMS panel agreed include:

- The primary indication for estrogen/progestin therapy and estrogen alone is treatment of menopausal symptoms.
- Estrogen/progestin therapy should not be used for primary or secondary prevention of CHD. Without more conclusive evidence of its effect on CHD, neither should estrogen alone be used for primary or secondary CHD prevention.
- Because of the risks associated with this type of hormone therapy, alternatives for the prevention of postmenopausal osteoporosis should be considered.
- This type of hormone therapy should be used for the shortest time and in the lowest dose needed to meet treatment goals.
- Before patients start this hormone therapy, physicians should assess each woman’s individual risk profile and discuss it with her.
- Other forms of HRT, such as transdermal patches, may have advantages over daily pills. However, long-term risks and benefits of these alternatives have not been established.



In August, the American College of Obstetricians and Gynecologists also recommended that HRT not be used for CHD prevention, and that each woman's individual risk profile must be considered when physicians decide whether to prescribe HRT.

#### NOT ENOUGH DATA

Issues on which the NAMS panel could not agree were "the most frustrating part for everyone," said Gass. "There are not enough data to make strong recommendations in these areas."

Such issues included the determination of definitions for short- and long-term hormone therapy, the duration of therapy for symptom relief, and the best way to stop therapy. Current data do not indicate a point at which risks of therapy

outweigh benefits. Therapy lasting more than 3 to 5 years has often been considered long-term, but the panel thought the long- and short-term distinctions lacked usefulness and recommended that they be abandoned.

Gass noted that for many women menopausal symptoms subside gradually without HRT, but she said there is no way to know how long symptoms may persist past menopause. Gass said many of her patients who stopped the hormone therapy after the WHI findings were released are now calling her to discuss resuming therapy for symptom relief. The panel found only one published study on discontinuing this type of hormone therapy. The authors of that article concluded that women without symptoms before treatment

could stop therapy without having problems after they stop. Virtually no information in this regard exists involving women with severe symptoms.

Utian said the issues on which consensus is lacking point to the need for immediate research in several areas, including whether biological differences between women who have symptoms and those who do not may affect risk profiles, whether progestin is responsible for the apparently increased risk associated with combined hormone therapy, and whether this type of hormone therapy has long-term effects on cognitive function or the development of Alzheimer disease.

Further information on the issues in this article is available online at <http://www.menopause.org>. □

## MISCELLANEA MEDICA

• **Richard G. Pestell**, MD, PhD, has been appointed director of the Lombardi Cancer Center at Georgetown University Medical Center, Washington, DC. He was at the Albert Einstein College of Medicine of Yeshiva University, Bronx, NY, where he was chair of the Division of Endocrine-Dependent Tumor Biology.

• **George P. Taylor, Jr**, USAF, MC, a major general in the United States Air Force, has been confirmed as its new surgeon general. He succeeds **Paul K. Carlton, Jr**, USAF, MC, a lieutenant general, who retired in September.

• **Allen Gao**, MD, PhD, has been appointed an associate member in the Departments of Medicine and Pharmacology & Therapeutics at Roswell Park Cancer Institute, Buffalo, NY.

• **Toni Ferrario**, MD, general surgery attending and assistant manager of surgical services at the Veterans Affairs Western New York Healthcare System in Buffalo, has received the 2002 Humanitarian Award in Medicine from the Arnold P. Gold Foundation and the Healthcare Foundation of New Jersey.

• **Harold (Hackie) Reitman**, MD, an orthopedic surgeon and founder and

CEO of Orthopaedic Associates USA, Fort Lauderdale, Fla, has received the **Harold S. Strasser**, MD, Good Samaritan Award from the Florida Medical Association for his efforts "to help build brighter futures for the youth of Broward County."

• **Burton Grebin**, MD, president and CEO of St Mary's Health Care System for Children at New York Hospital Queens, has been honored at an event entitled "SummerFallWinterSpring The Children's Dance for All Seasons," which benefited the hospital's Department of Pediatrics.

• **Peter Kohler**, MD, president of Oregon Health and Science University, Portland, has received the Honored Citizen Award from the Architectural Foundation of Oregon for his role in "transforming the built environment around us."

• **Giles F. Whalen**, MD, has been appointed chief of the Division of Surgical Oncology at UMass Memorial Medical Center and a professor of surgery at the University of Massachusetts Medical School, Worcester.

• **Eric Henley**, MD, MPH, has been appointed associate professor and head of the Department of Family and Commu-

nity Medicine at the University of Illinois College of Medicine at Rockford.

• **Marc Allan Feldman**, MD, MHS., has been elected president of the the Ophthalmic Anesthesia Society. He is in the Department of General Anesthesiology at Cleveland Clinic Foundation, head of the Section of Anesthesia at Cole Eye Institute, and director of the Cole Eye Institute Operating Rooms at The Cleveland Clinic in Cleveland, Ohio.

• **C. Edward Coffey**, MD, vice president, Henry Ford Behavioral Health, and Kathleen and Earl Ward Chair of Psychiatry at the Henry Ford Health System, Detroit, Mich, has received the Administrative Psychiatry Award from the American Psychiatric Association.

• **Stephen Cannon**, MD, PhD, has been named chair of the Department of Neurology at the University of Texas Southwestern Medical Center at Dallas. He was a neurologist at Massachusetts General Hospital and neurobiologist at Harvard Medical School, Boston.

**Editor's Note:** Miscellanea Medica appears in the Medical News & Perspectives section occasionally. Items submitted for consideration should be directed to the attention of Marsha F. Goldsmith, Editor, *JAMA Medical News & Perspectives*.