The Bioterrorist Next Door

Man-made killer bird flu is here. Can -- should -- governments try to stop it?

BY LAURIE GARRETT | DECEMBER 15, 2011

In September, an amiable Dutchman stepped up to the podium at a scientific meeting convened on the island of Malta and announced that he had created a form of influenza that could well be the deadliest contagious disease humanity has ever faced. The bombshell announcement, by virologist Ron Fouchier of Erasmus Medical Center, sparked weeks of vigorous debate among the world's experts on bioterrorism, influenza, virology, and national security over whether the research should have been performed or announced and whether it should ever be published.

Meanwhile, a joint Japanese-American research team led by the University of Wisconsin's Yoshihiro Kawaoka says that it, too, has manufactured a superflu. Additionally, a team at the U.S. Centers for Disease Control and Prevention (CDC) in Atlanta has acknowledged doing similar research, without successfully making the über flu. The U.S. National Science Advisory Board for Biosecurity is now deliberating whether to censor publication of the Fouchier and Kawaoka papers, though it lacks any actual power to do so: It could so advise scientific journals, but editors would still decide. The advisory board is expected to release its decision on Dec. 15.

The interest in this brave new world of biology is not limited to the scientific community. U.S. Secretary of State
Hillary Clinton made a surprise visit to Geneva on Dec. 7, addressing the Biological Weapons Convention review conference. The highest-ranking U.S. official to speak to the biological weapons group in decades, Clinton warned, "The emerging gene-synthesis industry is making genetic material widely available. This obviously has many benefits for research, but it could also potentially be used to assemble the components of a deadly organism."

"A crude but effective terrorist weapon can be made by using a small sample of any number of widely available pathogens, inexpensive equipment, and college-level chemistry and biology," Clinton also stated. "Less than a year ago, al Qaeda in the Arabian Peninsula made a call to arms for, and I quote, 'brothers with degrees in microbiology or chemistry to develop a weapon of mass destruction.'"

Noting that "It is not possible, in our opinion, to create a verification regime" for biological weapons compliance under the convention, Clinton called for voluntary transparency on biological experimentation among the 165 countries that have signed the agreement.

Officials throughout the U.S. government are declining to comment on the influenza experiments or elaborate on Clinton's comments and appearance in Geneva. The influenza scientists were politely but firmly instructed recently by U.S. officials to keep their mouths shut and provide no data or details regarding their experiments to anybody. Sources inside the Dutch, German, and French governments say that discreet agreement was reached among Western leaders to greet the influenza pronouncements with a wall of silence, pending the advisory board's decision and detailed analysis of the experiments by classified intelligence and scientific bodies.

Should we worry? If these scientists have indeed used the techniques that they have verbally described (but not yet published) to produce a highly contagious and virulent form of the so-called "bird flu," the feat can at least theoretically be performed by lesser-skilled individuals with nefarious intentions. Perhaps more significantly, the evolutionary leaps might be made naturally, via flu-infected birds, pigs, even humans. In other words, the research has implications for both terrorism and a catastrophic pandemic. Moreover, several experimental antecedents involving smallpox-like viruses and polio lend credence to the idea that concocting or radically altering viruses to create more lethal or transmissible germs is becoming an easier feat and an accidental byproduct of legitimate research.

The advisory board is debating whether the work, as well as details on how the flu viruses were deliberately mutated, should be published. That is the wrong question. As a practical matter, experimental results are now shared with lightning speed between laboratories, and I know that several leading scientists outside Fouchier's and Kawaoka's labs already recognize exactly how these experiments were executed. The genie is out of the bottle: Eager graduate students in virology departments from Boston to Bangkok have convened journal-review debates reckoning exactly how these viral Frankenstein efforts were carried out.

The list of attempts by governments to stifle scientific information is lengthy and marked by failure. I was at a 1982 optical engineering meeting in San Diego that was disrupted by a censorship order handed down by the Ronald Reagan administration's security chief, Adm. Bobby Ray Inman, compelling seizure of about 100
papers. The administration claimed the findings in those mathematics papers would, in Soviet hands, pose an existential threat to the United States -- an assertion that proved laughable when the studies soon saw the light of day. In 2006, George W. Bush’s administration tried to block climate change–related presentations by NASA scientist James Hansen; every single one of Hansen's data points swiftly appeared on the Internet.

Rather than trying to censor research because its inevitable release might be harmful, we ought to be having a frank, open discussion about its implications. The correct questions that scientists, national security and political leaders, and the public ought to be asking are: How difficult was it to perform these experiments? Could they be replicated in the hands of criminals or would-be terrorists? What have these experiments shown us about the likelihood that the H5N1 "bird flu" virus will naturally evolve into this terrifying form? Are we safer, or less secure, today due to the post-2001 anthrax-inspired proliferation of high-security biological laboratories?

What Genie Has Popped from Which Bottle?

In 1997, the form of influenza now dubbed H5N1, or avian flu, emerged in Hong Kong, killing six people and forcing the destruction of every chicken in the protectorate. The virus had been circulating in aquatic migratory birds and domestic poultry flocks within mainland China for at least two years, but it was not recognized as a unique entity until the Hong Kong outbreak. The spread of H5N1 was temporarily halted by Hong Kong health official Margaret Chan, who ordered the mass culling of the area's poultry. Chan now serves as director general of the World Health Organization (WHO).

The virus reappeared in Thailand in 2003, killing flocks of chickens and ducks that November and infecting humans in January 2004 in Thailand and Vietnam. The H5N1 virus mutated in 2005 as it spread among various species of birds migrating through northern China, giving avian flu the capacity to infect a far greater range of bird species, as well as mammals -- including human beings. That year, human and animal outbreaks of H5N1 appeared across a vast expanse of the globe, from the southernmost Indonesian islands, up to central Siberia, and as far west as Germany.

By mid-2011, H5N1 had become a seasonal occurrence in a swath of the world spanning 63 countries of Asia, the Pacific Islands, Eastern and Western Europe, the Middle East, and North and West Africa. Since its 2004 reappearance, H5N1 has sickened at least 565 people, killing 331, for an overall mortality rate of 59 percent. The Ebola virus can be more lethal -- as high as 90 percent -- but is not terribly contagious. Rabies, in the absence of vaccination, is 100 percent lethal, but it can only be transmitted through the bite of an animal. It is estimated that in pre-vaccine days, the smallpox virus killed about a third of the people it infected.

Only influenza holds the potential of both severe contagion and, in the case of H5N1, astounding mortality rates, ranging from about 35 percent in Egypt (where the virus circulates widely) to more than 80 percent in parts of Indonesia (where 178 confirmed cases have resulted in 146 deaths). The virulence of H5N1 is far higher than that seen with any other influenza, including the notorious 1918 flu that killed an estimated 62 million people in less than two years. (Some reckonings of 1918 death tolls in poor countries that lacked epidemic reporting systems, such as China, India, and all of Africa, put the final mortality at 100 million, when the world
population was just 1.8 billion and commercial air travel did not exist.) Six years ago, the spread of H5N1 sparked concern in the Executive Office of the Secretary-General of the United Nations, the White House, and many of its counterpart centers of government worldwide. Tremendous efforts ensued to kill infected domestic poultry, rapidly identify outbreaks, and pool scientific resources to track and scrutinize various H5N1 strains as they emerged. Some 400 million domestic birds were killed between 2004 and 2010, at an estimated global cost of $20 billion. It all seemed to work: By the end of 2008 the annual number of poultry outbreaks of H5N1 had shrunk from 4,000 down to 300.

In fearful anticipation, health and virus experts also watched for signs that the virus was spreading from one person to another. Although there were clusters of victims, infected families, and isolated person-to-person possible infections, the dreaded emergence of a form of humanly contagious H5N1 never occurred. By 2010, many leading virologists concluded that H5N1 was a terrifying germ -- for birds. The confident consensus, however, was that the mutations that avian flu would have to undergo to be able to spread easily from one human lung to another's were so complex as to approach evolutionary impossibility.

By mid-2011 the global response to avian flu had grown lethargic and complacent. Predictably, in the absence of vigilant bird-culling and vaccination efforts, trouble emerged as outbreaks mounted across Asia. Between January 2010 and the spring of 2011 more than 800 outbreaks were dutifully logged by government officials worldwide. In late July, a 4-year-old girl died of H5N1 in Cambodia, making her the seventh avian flu mortality in a country that had been free of the microbe for a long time.

On Aug. 29, the Food and Agriculture Organization sounded a mutation alarm, noting a new strain of the virus, dubbed H5N1-2.3.2.1, had surfaced in wild and domestic bird populations in Vietnam. Vietnam was one of six countries (including Bangladesh, Egypt, Indonesia, China, and India) in which avian flu had become endemic, meaning it permanently circulated among local and migratory birds. A week later, a Boston biotech company called Replikins announced the discovery of a mutant combination of the avian H5N1 flu and the so-called "swine flu" that spread swiftly among people during the 2009 global pandemic. Replikins's claim implied that the highly virulent bird flu could gain the capacity to spread rapidly between people by absorbing infection genes from the contagious-but-wimpy H1N1 swine influenza.

Although these announcements sparked a minor panic in Asia, further scrutiny of both the 2.3.2.1 and Replikins's claim left the WHO convinced that no new human threat loomed. In early September, a collective sigh of public-health relief was expelled.

Three days later, the conference of the European Scientists Fighting Influenza (ESWI, the Romance-language acronym) convened in Malta, opening with scientific evidence of current pandemic potentials. The stage was set by renowned University of Hong Kong flu scientist Malik Peiris, who described with exquisite precision which genetic factors made the "swine flu," H1N1, highly contagious between pigs, ferrets, humans, and other mammals. Peiris offered evidence that the 2009 H1N1 pandemic started among American pigs but had been circulating in swine populations throughout North America and China for decades before making the
mutational steps that sparked global spread.

Fouchier, the Dutch scientist, who has tracked H5N1 avian flu outbreaks in Indonesia for years, then suggested that vaccines used for years on chicken farms are now failing. Perhaps under selective evolutionary pressure, forms of vaccine-resistant H5N1 have appeared, Fouchier told the Malta meeting, adding, "We discovered that only one to three substitutions are sufficient to cause large changes in antigenic drift." In other words, naturally occurring, infinitesimal changes in the flu's genetic material are sufficient to render vaccines useless.

Fouchier went on to describe what he dubbed his "stupid" experiment of infecting ferrets in his lab sequentially with H5N1. One set of the animals would be infected, and then Fouchier would withdraw nasal fluid from the ferrets and use it to inoculation-infect a second set of animals. After 10 repeats, the superkiller H5N1 emerged, spreading through the air rapidly, killing 75 percent of the exposed animals. (Because Fouchier's work has not been published, accounts of the experiment vary, based on reporting from those who were present to hear his Malta speech. In some accounts the superlethal bird flu resulted from only five serial passages in ferrets -- a number far more likely to occur randomly in nature.)

"This virus is airborne and as efficiently transmitted as the seasonal virus," Fouchier told the Malta crowd, adding that he had identified which specific five mutations were necessary. Only five minute switches in RNA nucleotides -- the most basic elements of genetics -- were needed.

"This is very bad news, indeed," a sober Fouchier concluded.

The five dire mutations (technically, single nucleotide changes occurring inside two genes) have been separately found in influenza viruses circulating in the world. The actual mutations are not, therefore, unique. Fouchier's only innovation was in making all five occur inside the same virus at once. The more famous flu researcher from Erasmus, Albert Osterhaus, told reporters that what is done in the lab can happen in nature, adding, "Expect the unexpected.... The mutations are out there, but they have not gotten together yet."

Under questioning in Malta, Fouchier said his ferret form of H5N1 would certainly spread among humans and is "one of the most dangerous viruses you can make."

Shortly after Fouchier's announcement, Kawaoka, the University of Wisconsin scientist, let it be known that he, too, has made an airborne-transmissible H5N1 that readily spreads among mammals. Kawaoka's efforts were jointly executed by teams he heads at the University of Wisconsin and the University of Tokyo. No further details regarding this effort are publicly available, though Kawaoka has submitted a paper detailing his techniques and discoveries for review by the U.S. National Science Advisory Board for Biosecurity, as has Fouchier. Both scientists wish to publish their work in major scientific journals.

Scientists are deeply divided regarding publication. "If I were a journal editor and I received an article that said how to make a bioweapon, I'd never publish it, but that would be based on self-regulation, not any government restriction," anthrax expert and retired Harvard University professor Matt Meselson told an interviewer. "I've
never heard of a case where the government has restricted publication. I don't think it would work." But fellow anthrax researcher Paul Keim, who chairs the advisory board, told reporters, "I can't think of another pathogenic organism that is as scary as this one. I don't think anthrax is scary at all compared to this."

Perhaps the most intriguing comments came from Australian scientist Ian Ramshaw, who suggested that the Fouchier or Kawaoka papers could serve as bioterrorism blueprints: "As a researcher you do the good thing, but in the wrong hands it could be used for evil. In this case I'm not so worried about bioterrorism. It's the disgruntled researcher who is dangerous -- the rogue scientist," Ramshaw warned, according to the Canberra Times. Ten years ago Ramshaw accidentally made a superkiller form of mousepox, the rodent version of smallpox, in his Australian National University laboratory. He injected lab mice with the pox virus to test out a completely unrelated contraceptive vaccine, but the experiment transformed the virus into a deadly monster with a 100 percent fatality rate. In 2001 Ramshaw's work spurred high-level concern about the use of genetically modified smallpox by a rogue nation or terrorist group, launching the vigorous, multibillion-dollar post-9/11 American smallpox vaccine effort, as detailed in my new book, I Heard the Sirens Scream.

Within two years of Ramshaw's accidental mousepox creation, separate labs deliberately created viruses. In 2002, researchers at the State University of New York in Stony Brook built a polio virus from its genetic blueprint. This constituted a proof of principle, demonstrating that in a sufficiently skilled laboratory, all that is required to make a deadly virus is its nucleotide sequence -- details of which are now routinely published for everything from anthrax to the Ebola virus. At the time, Eckard Wimmer, the lead scientist on the project, warned: "The world had better be prepared. This shows you can re-create a virus from written information."

The following year another scientific team deliberately mimicked Ramshaw's mousepox accident, not only with the rodent form of pox but also with pox viruses that infect rabbits and cows. And in 2005 the CDC famously joined fragments of RNA from thawed tissue of victims of the 1918 flu, re-creating the original superkiller.

The Genie Is Out of the Bioterrorism and Pandemic Bottles: How Scared Should We Be?

This April, a team of CDC scientists published word that it had tried to manipulate H5N1 genes to render the avian virus a human-to-human spreader, but could not make it work. The team used a different method from the one apparently deployed by Fouchier and Kawaoka's team: The CDC group directly altered the genes of viruses, rather than sequentially infecting ferret after ferret. The CDC concluded, "An improvement in transmission efficiency was not observed with any of the mutants compared to the parental viruses, indicating that alternative molecular changes are required for H5N1 viruses to fully adapt to humans and to acquire pandemic capability."

That seemed comforting.

But in 2007 a different CDC team did to the SARS virus what Fouchier apparently has done to H5N1, with lethal results. Just as Fouchier produced highly infectious bird flu in ferrets by sequentially infecting one group of animals after another, the CDC group passed the SARS virus through one group of mice after another. Mice
are normally harmlessly infected by SARS, which cannot cause disease in the rodents. But after 15 such passages, the team got a 100 percent fatal form of the virus. Moreover, it was an airborne killer, sniffed out the air. (SARS, or severe acute respiratory syndrome, killed more than 900 people worldwide in 2002 and 2003, mostly in China.)

The University of Minnesota's Michael Osterholm, an expert on both bioterrorism and pandemics, thinks that understanding how animals might pass a virus like SARS or H5N1 among themselves, in a fashion in nature that mimics the laboratory experiments, may hold a vital key to predicting future epidemics. "We don't want to give bad guys a road map on how to make bad bugs really bad," he recently told Science reporter Martin Enserink. Health experts, however, do applaud the controversial research because it shows which mutations are necessary and at least one way they might arise.

There is no way to put a number on the probability of such natural mutational events. Are the odds 50-50 that a deadly, contagious form of H5N1 will wreak havoc across the world in the next 10 years? Anybody who claims to answer such a question, or pooh-pooh the asking of it, is a fool or a charlatan. It is an unknown.

What About the Proliferation of High-Security Biology Labs: Good or Dangerous?

Before the anthrax mailings terrorized America in 2001, there were only a handful of top security Biosafety Level 4 (BSL-4) labs in the world and a few dozen of the next-level BSL-3 facilities. The CDC and U.S. Army had the two largest pre-2001 BSL-4 labs, which nested like matryoshka dolls, with one layer of security inside another and another. The innermost labs required identity clearance, scientists wore protective space suits, and all air and water were specially cleansed and filtered to prevent accidental escape of Ebola, smallpox, and dozens of other superlethal organisms. The world's most dangerous known microbes were carefully kept under lock and key in a clearly identified handful of BSL-4 labs.

Even the less-secure BSL-3 labs required that scientists undergo security checks, wear spacesuits, and breathe through special respirators. Their numbers were finite and known, and researchers working on influenza, anthrax, or other deadly-but-treatable microbes represented a fairly small pool of scientists.

Since the 9/11 terrorist attacks, however, the number of such laboratories has proliferated spectacularly, not only inside the United States, but all over the world. In 2001 the United States had five "centers of excellence," as they were called, devoted to bioterrorism. By the end of 2002, more than 100 such centers were named, amid a record-breaking expansion in the numbers of laboratories and scientists studying anthrax, smallpox, Ebola, botulism, and every other germ somebody thought could be weaponized. After 9/11, the European Union saw the number of BSL-4 labs grow from six to 15. In the United States: from seven to 13. Canada built a BSL-4 complex in Winnipeg. Just as possession of rockets in the 1950s or nuclear power plants in the 1960s seemed the marks of a serious state power, so having BSL-3 and BSL-4 labs suddenly became a mark of national significance in the world -- an achievement to which countries should aspire. This year India opened its first BSL-4 facility, and it is rumored that Pakistan is now building one.
The proliferation of high-security labs means a great deal more than the mere construction of physical buildings. Where 10 years ago a finite pool of predominantly senior scientists toiled in such facilities, today thousands of graduate students, postdoctoral fellows, technicians, and senior researchers work in facilities stocked with humankind's worst microbial foes. Accidents have occurred with alarming regularity since the lab proliferation commenced, as I have detailed in my book. The facilities also constitute locations wherein individuals could theoretically execute experiments to produce supergerms without risking harm to themselves or others, regardless of whether the intent were noble, as appears to be the case for Fouchier and Kawaoka, or whether the intent were evil, as was the case with those responsible for the anthrax mailings.

Since 2005, several flu experiments conducted under BSL-3 conditions have raised eyebrows, as critics have charged the work should have been done inside the far more difficult but secure BSL-4 conditions. The original 1918 virus was "revived" from a long-frozen human body and grown inside a BSL-3 lab. Experiments were done on the 1918 virus in an effort to discover what genes made it so lethal. And the research that the CDC team, Fouchier, and Kawaoka performed on the H5N1 virus was all done in BSL-3 labs.

In September, when news of the Fouchier work started to appear in science magazines, Thomas Inglesby of the Center for Biosecurity at the University of Pittsburgh told New Scientist, "Small mistakes in biosafety could have terrible global consequences." His Pittsburgh colleague D.A. Henderson concurred: "The potential for escape of that virus is staggering."

According to the FBI, the culprit behind the 2001 anthrax mailings was Bruce Ivins, who worked in the U.S. Army's BSL-3 and BSL-4 labs in Maryland. Whether or not the FBI caught the right man -- a point of controversy among scientists -- it remains extraordinary that the response to what the agency calls "Amerithrax' is the creation of more such facilities in which more "Ivins" might toil.

The questions that arise from these H5N1 experiments have nothing to do with publication of the Fouchier and Kawaoka papers. We should be asking what we can do to ensure that such terrible man-made viruses never accidentally escape their laboratory confines or are deliberately released. And we should heed the question posed in the recently released Hollywood thriller Contagion when a Homeland Security character queries a CDC scientist:

"Is there any way someone could weaponize the bird flu? Is that what we're looking at?"

"Someone doesn't have to weaponize the bird flu," the CDC scientist responds, "The birds are doing that."
recipient of the 1996 Pulitzer Prize for her coverage of the Ebola epidemic in what was then Zaire, and author of I Heard the Sirens Scream: How Americans Responded to the 9/11 and Anthrax Attacks.