Controversial research on bird flu

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In a top-security lab in the Netherlands, scientists guard specimens of a super-killer influenza that slays half of those it infects and spreads easily from victim to victim.

It is a beast long feared by influenza experts, but it didn't come from nature. The scientists made it themselves.

Their noxious creation could help prevent catastrophe in the battle against the deadly H5N1 bird flu that has ravaged duck and chicken flocks across Asia and elsewhere since the mid-1990s but has mostly left our species alone - for one crucial reason. Though H5N1 kills with brutality when it takes hold in a human, it infects extremely rarely and doesn't go on to easily spread between people.

Public health officials have long fretted that the virus may one day find a way to do so.

Now, in engineering what nature has so far not unleashed, the Dutch team and another in the U.S. that also has conducted sensitive H5N1 research have rekindled a debate that has smoldered since the 2001 anthrax attacks that killed five people.

The questions: Is some research too dangerous to publish? How do you make sure the wrong people don't get the information and the right people do?

In an unprecedented move, a government biosafety advisory panel has

asked the Dutch and U.S. teams, as well as editors at two prestigious journals where their work has been accepted for publication, to omit crucial details about the research "that could enable replication of the experiments by those who would seek to do harm."

Experts said the events signaled a "new phase" for the U.S. National Science Advisory Board for Biosecurity, which was chartered in 2004 to help assess potential risks of biological research and has never before stepped in so aggressively.

"We'll have to see how it plays out," said Ronald Atlas, a biologist at the University of Louisville in Kentucky and former president of the American Society for Microbiology who has been involved in discussions about biosafety for more than a decade.

"How one decides who to share the information with - who do you trust, especially when you're not dealing with classified information and it's not just in the U.S. - is going to be hard to work out."

Ron Fouchier, the Dutch virologist whose lab created the new H5N1 that can readily spread between ferrets - animals that respond to influenza much as humans do - has no doubt that his research is worthwhile. Creating viruses like this one is the only way to study them and get out ahead of a pandemic, he said.

"It's all about predicting what will hit you next. We want to predict earthquakes and tsunamis; we also want to predict what will happen with the bird flu virus," he said. "This work needed to be done."

As far back as 1997, he wanted to figure out whether H5N1, which has killed nearly 60 percent of the roughly 600 people known to have contracted it, could evolve to spread efficiently from mammal to mammal. If it could, that might pose a catastrophic threat to humans.

"We would be in very deep trouble," he said.

The genetic path to such an outcome is unclear. Though scientists know that the key to stoking a flu pandemic comes from the virus gaining the ability to transmit through droplets from sneezes and coughs, they can't say just what changes in the virus bring that about.

And with H5N1, in any case, many scientists thought it was impossible. Strains carrying the H5 type of a key influenza protein that helps the virus bind to cells in a host had never evolved to travel through the air from person to person.

Even if H5N1 did evolve such an ability, some researchers reasoned that it might do so at the expense of its ability to take hold deep in the lung. And that would make it less lethal.

"They said it's never happened before, so it won't happen at all," Fouchier said. "To me, that was weak."

Over the course of a decade, Fouchier carefully began to test these assumptions about H5N1 by trying to create a version of the virus that could travel from ferret to ferret.

He got approvals from the necessary oversight groups. He secured funding from the U.S. National Institutes of Health. His workplace, the Erasmus Medical Center in Rotterdam, built a so-called Biosafety Level 3 Enhanced lab to house the experiments.

In such labs, all workers wear full-body suits and breathe through powered respirators, said Daniel Perez, a virologist at the University of Maryland in College Park who studies interspecies transmission of a different kind of bird flu, H9N2, in the same kind of facility. Air is purified coming in and out.

"There's no chance for the virus to escape," Perez said.

Fouchier and colleagues used a combination approach, engineering the virus and then stepping back to let nature take its course. They introduced key mutations into H5N1's genetic code and then infected the ferrets.

Typically, Perez said, this is done by placing the virus in ferret noses, waiting a few days, swabbing out some mucus, infecting another ferret with it, and repeating the process over and over. Throughout the process, infected and uninfected ferrets would be placed in adjacent cages to see whether the virus could pass from one animal to the other without them touching.

The Dutch team completed its experiment and made an alarming discovery.

According to published news reports from Fouchier's presentation at a September conference in Malta, just five tweaks in two genes, followed by just 10 passages of the virus between ferrets, created a pathogen that could travel through the air from animal to animal.

The virus remained lethal.

Fouchier said his work should prod countries where the virus is widespread, such as Indonesia and Egypt, to work more aggressively to prevent a pandemic.

"This research brings H5N1 viruses to the very top of the ones we should be concerned about," said Richard Webby, a virologist who studies flu pandemics at St. Jude Children's Research Hospital in Memphis, Tenn.

Further study of the mutations implicated in Fouchier's work - and new

research at the University of Wisconsin-Madison that was also reviewed by the National Science Advisory Board for Biosecurity - could help scientists improve vaccines and antiviral drugs, Perez said. Only by understanding how a dangerous version of H5N1 is likely to look genetically can scientists develop effective vaccines before it's too late.

The information would also help hone monitoring in the field, Webby said. Say, for example, samples of H5N1 collected in Egypt were found to share four of the five genetic changes that exist in Fouchier's killer strain.

"Knowing that information tells us we're only one step away" from a pandemic, Webby said. "That would increase surveillance and eradication programs."

But just because this deadly combination of mutations is in the cross hairs doesn't mean different combinations couldn't arise in the wild and be just as lethal, scientists said.

"Flu always does things we don't expect," Webby said.

Northern Arizona University geneticist Paul S. Keim, acting chairman of the biosecurity board, said that the debate over what to do about so-called dual-use biological research - work that can be applied to good or evil ends - had been simmering at least since the 2001 anthrax attacks, when spores believed to be taken from a laboratory were sent through the mail, killing five people and sickening 17.

Since its 2004 creation, the biosecurity board has been asked by the Department of Health and Human Services to review about half a dozen papers concerning potentially dangerous research results, Keim said. These included studies of smallpox and the 1918 Spanish flu, estimated to have killed at least 50 million people.

This is the first time the board has ever asked researchers to redact details.

Keim called the episode "a watershed moment" for the U.S. government that could change the way such dual-use work is conducted.

The board, which makes recommendations but doesn't set policy, will spend the next few weeks developing guidelines for scientists and governments around the world, he said.

The board might suggest a short-term moratorium on publishing or presenting further research on transmission of H5N1 flu while it ponders not only whether sensitive research is published but also what should be studied to begin with, and how.

"In the future, this area will be examined from start to finish," Keim said.

The immediate issue is what to do with the new H5N1 papers.

Editors at the journals Science and Nature, who had agreed to publish the Dutch and U.S. research, respectively, said last week that they were awaiting word that the U.S. government had devised a way to share the findings with scientists who have legitimate reasons to see them while keeping the data from becoming a how-to guide for would-be bioterrorists. The process could take months.

Fouchier said he was cooperating, but he thought the strategy was impractical. When he and his colleagues made a list of the people they thought should see the data, they came up with more than 100 international organizations - close to 1,000 individuals.

"As soon as you share information with more than 10 people, it's no

longer confidential," he said. "Our opinion is, and has been, that it would be best to publish the research, in a responsible way."

Richard Ebright, a molecular biologist at Rutgers University in Piscataway, N.J., who is a critic of the way the scientific community handles dual-use work, said the H5N1 debate highlighted a basic flaw in the system. Experiments like these should be more formally assessed for their risks and benefits before they're ever embarked on, he said.

"That's not done today, and that's what brought us to this situation," he said.

He said that at this late stage in the game, the H5N1 research should be published in its entirety because plans to limit access will be expensive, unwieldy and unworkable.

Besides, he said, labs could probably reproduce Fouchier's experiment already based on information that has been circulating for months.