

# Bird flu virus research awaits approval

1 March 2013, by Karen Herzog

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A bird flu virus at the center of an international debate sits in a padlocked freezer, deep inside a University of Wisconsin-Madison lab, waiting for new government guidelines that will allow researchers to continue unlocking its secrets.

The virus is protected by alarms.

It isn't deadly.

But government anti-terrorism rules dictate tight security around any biological agent that poses a potentially severe [health threat](#).

Similar H5N1 avian [influenza viruses](#) circulating in nature don't follow anyone's rules.

They may be mutating into deadly threats capable of causing great loss of life, UW-Madison scientist Yoshihiro Kawaoka says, as he leads a hand-picked group of scientists, FBI agents and journalists on a rare tour of the \$12.5 million Influenza Research Institute built exclusively for his research.

Some scientists believe the risks of accidental release or misuse of experimental viruses in labs such as this one outweigh the benefits of the research.

But a subset of mutations identified by Kawaoka's team already has been detected in viruses circulating in poultry flocks in Egypt and parts of Southeast Asia, he says.

If those viruses gain the ability to jump from birds to people, scientists will need stockpiles of the right vaccines and [antiviral drugs](#) to stop a deadly pandemic, says Kawaoka, a professor of pathobiological sciences in the UW-Madison School of Veterinary Medicine.

While the research is on hold in the United States and several other countries, Kawaoka is losing valuable time.

"Not just me. The entire world," the scientist says matter-of-factly.

Kawaoka's research has been voluntarily on hold for more than a year while the government develops new guidelines for scientists to study how many mutations - and which ones - could give the virus the ability to efficiently spread between humans and cause a pandemic.

His research must follow strict regulations that govern select agents - any [biological agent](#) or toxin the government deemed, after 9-11, could pose a severe threat if it fell into the wrong hands.

The government inspects all research facilities that work with such "select agents" every three years. Inspectors also can make surprise visits.

UW-Madison has the second largest academic select-agent program in the country, said Research Compliance Specialist Rebecca Moritz. The largest is at the University of Texas Medical Branch.

Nearly 200 registered support staff and scientists work directly with select agents in various UW-Madison labs, Moritz said.

"We have to document every single thing we do," she said. "The federal government stance is, if you don't document it, it didn't happen."

The UW Influenza Research Institute, which opened in 2009, is a nondescript building in a residential neighborhood, miles from the main Madison campus.

The 2,000-square-foot lab is designated as a BSL-3Ag research facility. That's a half-step below BSL-4, the highest level of lab biosafety and biosecurity, which the University of Texas Medical Branch has for its select-agent research.

Both types of lab are constructed the same: Walls 12 to 18 inches thick of continuously poured concrete with steel reinforcement, said UW-

Madison Facilities Engineer Darren Berger.

But workers in BSL-4 labs must take chemical showers and wear positive pressure suits.

Researches in a BSL-3Ag lab wear protective suits with double gloves and air purifying respirators that provide a constant whoosh of clean air. They're required to take five-minute showers with soap and shampoo.

"The influenza virus is sensitive to detergent," Kawaoka explained. "They die."

As an added safety measure, all liquid from the facility, such as water from showers and sinks, is sterilized before being released to the city's sewerage district, Berger says.

The rare tour of Kawaoka's lab was possible because it was decontaminated and shut down for routine maintenance.

When it's running, no one is allowed inside without FBI security clearance, extensive training, elaborate protective clothing and a personal air purifying respirator.

"One of the myths circulating the last year and a half was that there was a lack of oversight for this research; that no one was actually paying attention; that this research was done under the radar," Moritz said.

The public doesn't understand why the research is necessary, she said.

It boils down to the difference between [avian influenza](#) viruses and seasonal influenza viruses, Moritz said.

Seasonal influenza each winter can kill the most vulnerable - especially the elderly and very young - but most healthy people have some immunity.

There is no immunity to avian influenza viruses, which rapidly kill both the vulnerable and the healthy, Moritz said.

It's been 16 years since the H5N1 virus was first

identified in China.

While it hasn't caused a pandemic, H5N1 does have a deadly track record.

Of the more than 500 people around the world it has infected, 300 have died. The virus is generally passed among birds.

Hundreds of millions of birds in [poultry flocks](#) have been culled in Southeast Asia and the Middle East because scientists detected potentially dangerous mutations in circulating H5N1 viruses, and tried to wipe them out before they could potentially jump to people.

Kawaoka is ready to tackle new questions about how avian influenza virus evolves in nature.

He never expected to be thrust into the international spotlight in November 2011, when his research was lumped together with a scientist's research in the Netherlands that - unlike Kawaoka's work - created a deadly H5N1 virus strain.

Kawaoka does research only with influenza viruses that are sensitive to antiviral drugs, Moritz said.

Making a virus that's resistant to countermeasures would be a major violation of U.S. government guidelines, she said.

To determine whether H5N1 viruses could be spread among humans, Kawaoka's team generated viruses that combine a gene of avian influenza with genes from a human pandemic 2009 H1N1 influenza virus.

The team used ferrets because the mammals sneeze and cough like humans when infected with a virus. That's how flu viruses are spread among people.

The freezer holding the viruses in the Madison lab is accessible to only a handful of approved personnel. It's kept at -80 degrees Celsius (-112 Fahrenheit), and the virus inventory is checked monthly.

The facility has two of everything vital: air compressors, boilers, chillers, HEPA filters for air quality, power feeds and waste systems.

It has an emergency power generator.

"We want to reduce the probability to almost a point of no probability of ever having the facility go down when we're doing research," Berger said.

Alarms also are attached to data collection points: temperature, room pressure, humidity and fans.

Every square inch of the lab's interior is soap bubble tested to make sure there are no leaks or cracks. A pinhole is too large a leak to pass the test, Berger says.

Moritz describes each isolator cage where ferrets live during experiments as a box within a box, within another box of biosafety.

The same is true for the biosafety cabinets that researchers reach inside to work with vials of virus, she said. The researchers are protected by "a curtain" of clean air.

Researchers enter the suite of labs through a locker room, where they remove all clothing and jewelry, and put on scrubs and garden clogs with shoe covers. As they work their way into the laboratory labyrinth, they exchange the scrubs for protective suits, double gloves and air purifying respirators.

The security barriers include airtight submarine doors with double rubber seals to control air flow.

Air in the labs is constantly filtered. And it's double HEPA filtered before being released into the environment, Berger says.

Anyone who works in the containment lab is required to get a seasonal flu shot. A clinical H5N1 vaccination may be added as an extra precaution.

Those who work directly with the virus also are subject to five-day quarantines after they've been in the lab.

During that time, they can't go to a petting zoo or poultry facility, where potential hosts for avian influenza live. They aren't allowed to have pet birds.

Ferrets used in experiments with the virus are euthanized, sterilized to inactivate any virus that might remain in the carcass, and incinerated.

UW police monitor multiple levels of security and respond to any type of threat to the building.

But in a medical emergency, firefighters and police officers wouldn't be allowed inside the lab because they lack security clearance.

Lab personnel are trained how to get a co-worker out of restricted areas in a medical emergency.

Some question H5N1's potential to cause a pandemic, and whether stockpiling H5N1 vaccines is a waste of taxpayer money, Kawaoka tells his guests on the tour.

But only a few genetic changes may make an H5N1 virus transmissible among mammals, possibly including people, Kawaoka says.

Kawaoka's research is funded by the National Institutes of Health.

UW-Madison's position is that H5N1 can be safely researched under current regulations.

So far, the list of Tier 1 agents includes such well-known agents as the Ebola virus, anthrax, the plague and smallpox.

If the government were to take an even more drastic measure, requiring research with transmissible avian influenza be done in a BSL-4 lab with the highest biosafety, Kawaoka would have to move his research from Madison.

That's not expected to happen.

Based on the Madison research, and that of scientist Ron Fouchier in the Netherlands, Kawaoka says they now know the type of avian influenza viruses that may transmit among mammals.

So they can look at viruses circulating in nature, and identify those with high pandemic potential.

That information would allow scientists to produce vaccines that match viruses that pose the likeliest threat, Kawaoka said.

As scientists around the world debate the wisdom of creating viruses in labs that could pose serious health threats if accidentally released, or intentionally misused, UW-Madison scientists continue to defend the safety and security surrounding their work.

How would UW researchers know if the virus escaped into the lab?

"That's why we have multiple layers of protection," Moritz said.

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