

The risks and benefits of publishing mutant flu studies

Research describing two mutant strains of H5N1 avian influenza that spread between mammals is likely to be published in its entirety. *Nature* examines the controversial decision.

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Two teams of scientists, led by Ron Fouchier of Erasmus Medical Center in Rotterdam, the Netherlands, and Yoshihiro Kawaoka of the University of Wisconsin-Madison, have created [mutant strains](#) of [H5N1 avian influenza](#). These laboratory strains could be passed between mammals more easily than wild strains of the virus.

[News of the research](#) sparked an intense debate about [whether the two teams' work should be published in full](#) to aid pandemic preparedness or redacted to prevent misuse by terrorists. A [meeting](#) convened by the World Health Organization two weeks ago in Geneva, Switzerland, concluded that the papers [should be published in full](#), despite [recommendations to the contrary from a US government advisory board](#). *Nature* takes a look at the debate and the science.

What is H5N1?

It is a subtype of the influenza A virus — the most virulent of the influenza viruses to affect humans. These viruses are classified according to the identity of two of their surface proteins — haemagglutinin (H5 in this subtype) and neuraminidase (N1). The subtype behind the 2009 'swine flu' pandemic is H1N1, which has the same version of neuraminidase as H5N1, but a different version of haemagglutinin. One particular strain of H5N1, called highly pathogenic avian influenza (HPAI), is responsible for the 'bird flu' scares. It circulates regularly among birds and has jumped to humans on occasion.

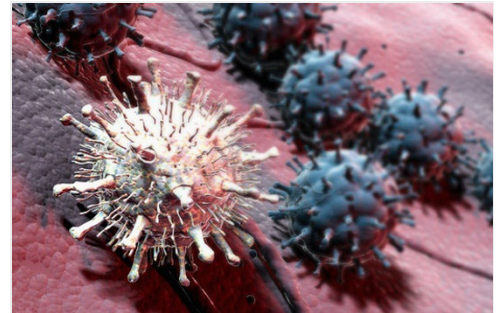
How dangerous is H5N1?

Since 2003, the wild virus has infected around 600 people; 59% died. However, [the true mortality rate will be lower](#) because there are probably some milder, unrecorded infections of H5N1. Even so, it seems likely that this virus has a greater mortality rate than either ordinary seasonal flu or possibly the [1918 pandemic](#) H1N1 strain.

So far, H5N1 has failed to spark a pandemic because it cannot effectively spread between people. [Wild H5N1 viruses cannot latch on](#) to the cells in a person's nose and throat, but the mutant strains created by Fouchier and Kawaoka can spread between ferrets, which are viewed as a good animal model of flu transmission between humans.

How was the virus mutated?

[Fouchier and his team initially](#) tweaked the virus's genome to create strains that could attach to mammalian nose and tracheal cells, but couldn't spread between individuals. He exposed ferrets to this strain, and used the animals' nasal fluids to infect others. After 10 rounds, the virus could spread through the air to infect ferrets in neighbouring cages. The genome of the airborne strain differed from



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Research into mutant strains of avian influenza (white) aims to reveal more about flu transmission mechanisms.



the original one by just five mutations, which have all been spotted individually in wild viruses. Fouchier's paper has been accepted for publication by *Science*.

Kawaoka and his team, whose work has been accepted by *Nature*, [created a chimeric virus](#) with the haemagglutinin protein from H5N1 and the genes from the 2009 pandemic strain of H1N1. It was an artificial version of the same process through which wild viruses shuffle their genes, known as reassortment. Both mutants spread easily among ferrets, but whereas Fouchier's strain reportedly killed all of the animals it infected, [Kawaoka's did not](#).

[Fouchier later added](#), however, that his mutant virus "does not spread yet like a pandemic or seasonal flu virus" and that the ferrets did not die when infected through aerosol transmission. Only when the virus was physically implanted into the trachea or nasal passages of ferrets did the infected animals die.

All work on mutant flu strains has been temporarily halted since 20 January 2012, when Fouchier, Kawaoka and 37 others called for a [60-day pause](#) to allow time for an [open debate](#) on the risks and benefits of such research. The moratorium has since been extended until a system to review the safety of such work and its consequences for security is put in place.

Why did they do the research?

The studies provide basic knowledge about the potential of H5N1 to mutate into a more transmissible form. [Kawaoka notes that](#) H5N1 viruses already circulate in nature, mutate constantly and could cause pandemics. "I believe that it would be irresponsible not to study the underlying mechanisms," he says. More practically, the research could allow public-health workers to monitor wild viruses for similar mutations that make H5N1 more dangerous to humans. In response, health agencies could then advise manufacturers of flu drugs and vaccines to ramp up production, or could instigate stricter public-health measures to prevent transmission.

Would that actually work?

For now, probably not. It seems unlikely that manufacturers will pre-emptively produce more vaccine on the basis of a potential threat. And the benefits of improved surveillance may be overplayed because [tracking flu mutations is logistically difficult](#). Surveillance is patchy, especially in poorer countries where H5N1 is most common. There are also many potential ways for H5N1 to become transmissible, and focusing on Fouchier's five mutations could lead to [a false sense of security](#). Nonetheless, Fouchier and others hope that the current controversy will stimulate more [funding of flu-surveillance systems](#).

Could the viruses be used in bioterrorism?

Unlike most other bioterror agents, H5N1 can be fought with vaccines and drugs, and cannot be targeted to a specific population. However, Paul Keim, acting chair of the US National Science Advisory Board for Biosecurity (NSABB) — which [recommended](#) that the mutant-flu work should not be published in full — cautions that there are not enough flu vaccines or drugs worldwide, and a rapid pandemic would overwhelm our ability to manufacture more. There are also signs that some wild strains of H5N1 have developed resistance to antiviral drugs.

Could the mutant viruses escape from laboratories?

Worries about escaping viruses are not unfounded. Accidental infections of SARS have affected staff at four biosafety level-3 (BSL-3) and BSL-4 labs in mainland China. The experiments that created the mutant H5N1 strains were done in [BSL-3 'enhanced'](#) labs. But some virologists believe that [research on the mutant strains should be confined to BSL-4 labs](#), where the most dangerous viruses, such as Ebola, are studied. Only a few dozen such facilities exist. They use extra safety protocols, including different suits, more rigorous decontamination and more security measures such as bomb-proofing and video surveillance.

Will the studies now be published in full?

At the recommendation of a US advisory board, *Nature* and *Science* [considered redacting both papers](#). However, attendees [at the WHO Geneva meeting](#) agreed that redaction would be ineffective, and that it would be impossible to [distribute full details to only selected researchers](#). Owing to the "substantial immediate risk" posed by wild H5N1 strains, which is greater than previously thought, the delegates concluded that both studies should be published in full. Meanwhile, the National Institutes of Health has asked the NSABB to [reconsider the fate of the two studies](#) in the light of unpublished data presented by both groups at the WHO meeting.

