

Science

www.sciencemag.org
Science 9 March 2012:
 Vol. 335 no. 6073 pp. 1155-1156
 DOI: 10.1126/science.335.6073.1155

[Prev](#) | [Table of Contents](#) | [Next](#)
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• NEWS & ANALYSIS

AVIAN INFLUENZA

Surprising Twist in Debate Over Lab-Made H5N1

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For the past several months, the media, the public, scientific groups, and a key U.S. government advisory panel on biosecurity have wrestled with how to deal with two unpublished studies they thought described the creation of a bird flu virus capable of triggering an influenza pandemic with the potential to kill millions of people. *The New York Times* even billed it as a “doomsday virus.” But now, a researcher who created one of the H5N1 mutants and a leading U.S. health official say the threat has been blown out of proportion, offering what they said were clarifications and “new data” to better gauge the risk it presents. Contrary to widespread reports, the researcher, Ron Fouchier of Erasmus MC in Rotterdam, the Netherlands, revealed that the virus made in his lab does not kill ferrets infected by the aerosol route. And it is more difficult to transmit the virus than Fouchier previously described.

These revelations promise to influence—although certainly not end—a contentious debate about whether to publish details about this virus and a second, related one that's less virulent. The wild-type H5N1 virus has decimated chicken flocks across Asia but has caused confirmed cases of disease in only about 600 humans, as it rarely spreads from person to person. Publishing the exact mutations the virus needs in order to spread among mammals could guide research on defensive measures and help derail an emerging pandemic, but many fear that the knowledge could help bioterrorists start one. To date, this debate has taken place largely in an information vacuum. Only a select group of people outside the two research groups involved have read drafts of papers describing the work, one of which was submitted to *Science* and the other to *Nature*. On 29 February, Fouchier attempted to partially fill that vacuum by offering glimpses of his group's data at a public meeting held by the American Society for Microbiology (ASM) in Washington, D.C. “There are a lot of misperceptions about what you can and cannot conclude from these studies,” Fouchier said at a panel discussion on the topic.

Fouchier sparked the controversy in September 2011 when he revealed at an influenza conference in Malta that his lab had engineered H5N1 to transmit readily in mammals for the first time. Fouchier's group used the popular ferret model, and as reported in the conference newspaper, *The Influenza Times*, a mere five mutations made the virus transmissible. “This is very bad news, indeed,” said Fouchier in *The Influenza Times* account of his presentation. “This virus is airborne and as efficiently transmitted as the seasonal virus.” He made similar statements to *Science* in November, calling the mutant “probably one of the most dangerous viruses you can



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Clarifying agents. Ron Fouchier (*left*) and Anthony Fauci urged people to rethink threat posed by engineered bird flu at a recent meeting in Washington, D.C.

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make.”

In December, the U.S. government's National Science Advisory Board for Biosecurity (NSABB) recommended that the researchers and the journals redact key information from the papers. The diverse panel—which includes scientists from several disciplines, veterinarians, and biosecurity experts—also questioned whether the teams should have used more stringent biocontainment measures to safeguard against these viruses escaping from the lab. An uproar followed. Some said the experiments never should have been performed. Fouchier and the researcher who led the second team, Yoshihiro Kawaoka of the University of Wisconsin, Madison, and the University of Tokyo, criticized the call for redaction and the attempts to control the free flow of scientific communication, as did many other scientists. Kawaoka also stressed in a *Nature* comment in January 2012 that his mutant did not kill ferrets and was no more dangerous than the strain that caused the relatively mild 2009 pandemic.

But the researchers and the journals agreed to follow NSABB's recommendation, and the influenza community called for a voluntary 2-month moratorium on research with such mutant viruses. Then in February, an expert group consisting mainly of influenza researchers met with Fouchier and Kawaoka for 2 days at the World Health Organization (WHO) in Geneva and came to a conclusion that directly contradicted that of NSABB: Redaction did not make sense, they said, for both scientific and practical reasons.

At the ASM meeting, NSABB acting chair Paul Keim of Northern Arizona University in Flagstaff led the discussion with Fouchier; fellow NSABB member Michael Osterholm of the University of Minnesota, Twin Cities; Science Editor-in-Chief Bruce Alberts; and Anthony Fauci, who heads the U.S. National Institute of Allergy and Infectious Diseases, which funded both experiments. Fouchier reported that his team swabbed the noses of four ferrets with the mutant virus, which then spread to three of four ferrets in a neighboring cage by the aerosol route. The researchers reisolated the virus from one of these animals, swabbed the noses of two uninfected ferrets, and found that they spread it to two of two animals in a neighboring cage.

Fouchier criticized press accounts that suggested, as he put it, that “this virus would spread like wildfire if it would come out of our facility.” Not only did the mutant fail to spread 100% of the time, he said, animals infected via the aerosol route were not as likely to transmit the virus as ferrets infected with seasonal influenza strains that routinely spread between humans: They made copies of the virus more slowly, and the peak levels of virus were much lower. “We have to conclude that this virus does not spread yet like a pandemic or seasonal influenza virus,” Fouchier said, in contrast to what he reportedly said in Malta. He did not respond to *Science's* request to discuss this discrepancy.

As for lethality, Fouchier presented data from a second set of experiments, which found that only one of eight ferrets infected with the mutant virus through nasal swabs developed severe disease, and none died. He noted that when they put “very, very high doses” into the lungs of six ferrets, “yes, the animals will drop dead.” In the aerosolized transmissions of the virus, he stressed, “we actually see no severe disease at all.” This is in stark contrast to what Fauci said was the widely held perception that one ferret sneezes and all the ferrets in adjoining cages die; he singled out a report by ABC News on 18 February that said aerosol transmission killed “all 40 of the exposed animals” in neighboring cages. “These viruses do not kill ferrets if they're sneezed on,” Fouchier said.

Fouchier further contended that if H5N1 does acquire mutations that make it more transmissible in humans, it likely will not cause severe disease in most people. To date, H5N1 has killed nearly 60% of the confirmed cases, but he said he did not think this fatality rate was accurate, because many cases that do not cause serious illness probably go undetected. He also pointed to an experiment he and his colleagues published in the *Journal of Virology* in March 2011, which showed that ferrets given seasonal flu virus before being exposed to wild-type H5N1 did not develop severe disease. “You all have been infected previously with seasonal flu,” Fouchier said. “It would be unlikely that you would have no cross-protection against a virus like H5N1.” (Osterholm later told *Science* that “there's absolutely no data to support that [assertion] beyond this animal model, and we have an abundance of data from real life that speak against it.”)


In another surprising twist, Fauci said he and other members of the WHO group had recommended that the researchers revise their manuscripts “to include new data and elicit clarifications of old data” and submit them to NSABB, which should reconvene and reconsider the issues. Given the secrecy surrounding the manuscripts and the reluctance of people who have read them to discuss details, it is difficult to determine what actually is new or being clarified. “This was overwhelmingly less about new data than making sure there was a clear understanding of the old data,” Fauci told *Science*.

Fauci said he was glad Fouchier had a chance to clarify that aerosol transmission of mutant H5N1 did not kill ferrets and that the virus, as some wilder news reports speculated, would not wipe out half the human population. “Thank goodness we had the opportunity today to clear the air,” Fauci said. But there are other fog banks on the

horizon.

Science contacted seven of the 23 NSABB members, and although several promised to review revised manuscripts with an open mind, they all said the new information and the clarifications presented at the ASM discussion, at first blush, did not change their views. "The issue is you have a virus generated in laboratory that's now transmissible [in mammals]," says NSABB member Arturo Casadevall, a microbiologist at the Albert Einstein College of Medicine in New York City. "This virus has the capacity to recombine, and we have no idea what will come out."

No date has been set for reconvening NSABB.

* With reporting by David Malakoff.

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