AVIAN INFLUENZA

On Second Thought, Flu Papers Get Go-Ahead

Flu scare? Lab-created versions of the H5N1 avian influenza virus (*left*) turned out to be less frightening than a U.S. advisory panel first believed.

The end of an impassioned and often strident global debate over the proper balance between scientific openness and security began with 2 hours of mandatory, studious silence in a room protected by an armed guard.

When members of a U.S. government advisory panel gathered last week on the campus of the U.S. National Institutes of Health (NIH) near Washington, D.C., to reconsider their controversial December 2011 recommendation that two groups of scientists redact key details from papers describing how they made the H5N1 avian influenza virus more transmissible between mammals, one of the first items on the agenda was to read revised versions of the manuscripts. But government officials in the United States and the Netherlands, where the experiments had been conducted, didn't want the information falling into the wrong hands. One by one, the members of the National Science Advisory Board for Biosecurity (NSABB) and more than a dozen observers—including NIH head Francis Collins and Keiji Fukuda, the flu point person at the World Health Organization (WHO)—signed confidentiality agreements to receive their copies. "We were told to read them in silence," recalls NSABB member Arturo Casadevall, an immunologist at the Albert Einstein School of Medicine in New York City. "I felt like I was taking a graduate school exam," adds another biosafety expert, Joseph Kanabrocki of the University of Chicago, Illinois. When time was up, the readers turned in the manuscripts and their notes, which were ultimately destroyed.

Soon, the silence gave way to discussion—and decision. After an "exhausting" marathon that included hours of scientific presentations and a bus ride to a classified intelligence briefing (during which some board members wolfed down $16 boxed dinners), the NSABB met the next day and announced its new recommendation to the U.S. government: What one member called "the two most famous scientific papers that have never been published" should be made public, in full. The studies still include information that might someday be useful to evildoers, the NSABB said in a 30 March statement, but "additional information changed the Board's risk/benefit calculation." The potential public health benefits of publishing, they had decided, now outweighed the potential harm. A WHO panel reached a similar conclusion in February (*Science*, 24 February, p. 899).

Relieved. Yoshihiro Kawaoka (*left*) and Ron Fouchier (*right*) waited 5 months to find out whether their controversial papers would see the light of day.

The NSABB's recommendation isn't binding, and the U.S. government—which funded the studies through NIH—may take several weeks to decide whether it will endorse the advice. Still, both journals and the research teams welcomed the news and said they planned to move ahead.

Unlike NSABB's earlier recommendation, however, this one was not unanimous. Without exception, the panelists at the meeting agreed that a study under review at *Nature* led by Yoshihiro Kawaoka—who has a joint appointment at the University of Tokyo and the University of Wisconsin, Madison—should be "communicated in full." But six of the 18 NSABB members who voted opposed the full publication in *Science* of a study led by Ron Fouchier of the Erasmus Medical Center in Rotterdam, the Netherlands.

In interviews with *Science* and in public statements, 9 NSABB members discussed how the group reached those decisions. All stressed that they were speaking for themselves and, in keeping with the complexity of the debate, offered no single—or simple—explanation for their final positions. Still, there was wide agreement that this NSABB review differed from the first in important ways—and that the new recommendation was not necessarily a repudiation of the original. "We have not, not, not reversed ourselves, because these were revised manuscripts that we reviewed, not a reconsideration of the original ones," insists NSABB member Susan Ehrlich, a retired appellate judge with training in biotechnology. And Ehrlich and others stress that during the 5 months since NSABB first considered the two papers, much had changed—including the amount of information and the number of practical options available to the board. The issues that helped shape the outcome, they say, included:

Misunderstandings created by the brevity and tone of the original manuscripts. "The original papers were typical *Science* and *Nature* papers: very brief, short on detailed discussion, little to no information on biosafety/biosecurity/mitigation, and perhaps even a little sensational," says NSABB member Lynn Enquist, a molecular biologist at Princeton University. Fouchier's original paper, in particular, was somewhat misleading, several NSABB members told *Science*. And one, virologist David Relman of Stanford

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University in California, is harsher: "Data Ron Fouchier presented to us were confusing, contradictory, and poorly done." That helped sow confusion about the actual lethality of Fouchier's virus and its transmissibility, members say (*Science*, 9 March, p. 1155).

Fouchier agrees that his original 2500-word *Science* manuscript was "not as clear and as explicit as it could have been if we had been given another couple of hundred words." And NSABB acting chair Paul Keim, a microbiologist at Northern Arizona University in Flagstaff, says that he suspects "Ron will write papers differently for the rest of his life."

All parties agree that the longer, revised paper presented last week was clearer. It presents the data "in a more rational manner," says NSABB member Michael Imperiale of the University of Michigan Medical School in Ann Arbor. *Science* Editor-in-Chief Bruce Alberts, who attended the meeting, confirms that the journal has "agreed to give Fouchier extra space, and this was reflected in the revised manuscript that NSABB read." (He also noted that, because of Dutch export control rules, the silent session marked the first time *Science* editors had seen the revised manuscript.)

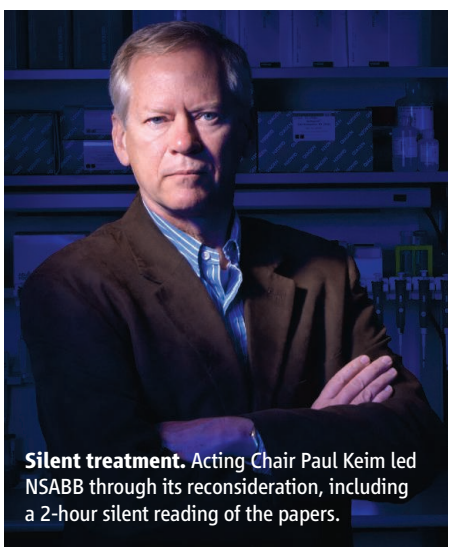
The second NSABB review also gave Fouchier and Kawaoka more time to clarify matters, in person. At last week's meeting, Fouchier "took the stage for more than 2 hours, and he answered many questions," Keim notes. "I almost felt a little sorry for him." In contrast, Fouchier spoke by phone with NSABB for about 45 minutes during the first review.

The lengthier discussions helped persuade several NSABB members to lift their objections to publishing both papers. But the give-and-take also confirmed that revealing Kawaoka's research presented less risk than publishing Fouchier's. In large part, that's because Kawaoka stitched the hemagglutinin gene (the H5) from the bird virus into a pandemic H1N1 virus that rarely kills humans and then manipulated his construct to make it less virulent. "There was a deliberate effort to reduce the risk of the thing [Kawaoka] was making," says Stanford's Relman. Fouchier's group took no such steps, Relman notes, one reason he became one of the six votes against fully publishing that paper.

Recognition that the mutations identified by the studies could be useful for H5N1 surveillance.

Science has learned that what the NSABB statement vaguely referred to as the emergence of "new evidence" that could aid surveillance referred to the putative discovery in birds of H5N1s that look more like the lab-created strains that move between mammals than any found before, suggesting that H5N1 in nature may be on its way to becoming transmissible in humans. "What it came down to for me … [is that there] might be a risk to *not* publishing," Imperiale says. "As you're surveying, you might start picking up those mutations and … make more effort to cull those flocks. That's really what carried the day." Sharing the information, he adds, might also help persuade countries that the economic costs of culling are worth the future global health benefits.

Along similar lines, the Einstein School's Casadevall says he changed his mind in part because the data might prod the world to improve H5N1 surveillance (*Science*, 17 February, p. 784): "I'm a believer that if the mutation information is available, this will drive the right type of surveillance." Part of the new epidemiological evidence was contained in a third paper, written jointly by Fouchier, Kawaoka, and a third researcher, which Fouchier says was presented at the meeting and has been submitted for publication.



Silent treatment. Acting Chair Paul Keim led NSABB through its reconsideration, including a 2-hour silent reading of the papers.

Doubts about the practicality of sharing the findings with only "responsible" scientists.

When NSABB first considered the two manuscripts, says board member and virologist Stanley Lemon of the University of North Carolina, Chapel Hill, it weighed three options: publish the entire manuscripts, redact information and share the full manuscripts only with those who have a need to know, or don't publish anything. This time, the possibility of sharing the manuscripts on a need-to-know basis had been taken off the table. NIH Director Collins explained that U.S. freedom of information laws and international export control rules posed seemingly insurmountable obstacles. "It was made abundantly clear that there's no way to do that in the current legal system," Lemon says.

Others noted that the need-to-know restrictions could particularly hurt developing countries that have endemic H5N1 and might benefit most from surveillance. "The risk of seriously alienating the international community and derailing influenza efforts" outweighed the risks of publishing, decided Lemon, who voted to fully publish both papers. Chicago's Kanabrocki came to the same conclusion: "The lack of a mechanism to communicate selectively changed the risk/benefit ratio for me."

Concerns about adequately regulating dual-use research.

Several NSABB members were heavily influenced by policy and process concerns. Ehrlich, for example, says one reason she voted against publishing the Fouchier paper was that he still planned to make changes to his manuscript. "I don't want to put the NSABB's imprimatur on a document that isn't the completed document," Ehrlich says.

NSABB member Randall Murch, a former FBI agent who is now a biosecurity scholar at Virginia Polytechnic Institute and State University in Alexandria, says he "could have gone either way." But his vote against publishing the Fouchier paper was partly intended to highlight the need to "find ways, both in the U.S. and globally, to develop better oversight of dual-use research; this process showed how far we have to go." One encouraging sign, he said, is that NSABB's original recommendation helped spur the U.S. government to release a long-delayed policy on screening certain biomedical research proposals for dual-use potential (see p. 21).

Relman says the latest NSABB meeting deserves scrutiny, too. "It was a very, very difficult environment in which to have thoughtful, deliberate, and in-depth discussions."

Many NSABB members say the sometimes painful arguments have been a worthwhile exercise. "When you think about the fact that your decision can affect a large number of individuals, it's humbling and frankly it's a little bit frightening," Casadevall says. "This whole process has been a learning curve for all of us," says Fouchier, who, along with many other players in the debate, attended another meeting on the debate at the Royal Society in London earlier this week. "But we just needed to take this time."

–JON COHEN AND DAVID MALAKOFF

With reporting by Martin Enserink.

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