Taking a break. Leading flu researchers will halt controversial studies involving H5N1 viruses (blue) for 2 months.

Flu Controversy Spurs Research Moratorium

Stung by a growing global controversy over the potential dangers of experiments involving the H5N1 avian influenza virus—and worried about possible government regulation—a group of leading influenza researchers last week agreed to a 60-day moratorium on some sensitive flu studies "to provide time" for international discussions.

"We recognize that we and the rest of the scientific community need to clearly explain the benefits of this important research and the measures taken to minimize its possible risks," the 39 researchers wrote in a statement published by *Science* and *Nature* (see p. 400). During the "voluntary pause," the scientists—who represent the world's major H5N1 research centers—have agreed to halt several types of studies, including experiments that could create H5N1 viruses that move more easily between mammals.

Flu experts are also helping to organize a summit on the issue, to be hosted by the World Health Organization (WHO) in Geneva on 16–17 February, which is expected to involve about 50 experts. But "it's not going to be a simple one-meeting process," says Keiji Fukuda, WHO's assistant director-general for health security and environment. "We don't want it to take forever, but [we] can't address all the issues at the same time."

"Governments and organizations need time to react," says virologist Ron Fouchier of Erasmus MC in Rotterdam, the Netherlands, who helped craft the agreement and is involved in the research that triggered the global debate (*Science*, 6 January, p. 20). Investigators on all sides of the controversy, meanwhile, welcomed the move, saying it will help ease tensions and clarify potential risks. But some question whether 2 months is enough time to resolve thorny conflicts between science and security or to institute national or international oversight. Biosecurity expert John Steinbruner of the University of Maryland, College Park, for instance, wonders whether governments can "do anything meaningful within the 60-day period. … What happens if they do not?" And one skeptic calls the moratorium "an empty gesture" designed to fend off stringent U.S. controls on research.

The announcement capped months of rising tension over two studies, in press at *Science* and *Nature*, which describe how researchers made the H5N1 virus more transmissible between ferrets, the animal model that most closely resembles humans in flu studies. The researchers say the work offers benefits for preventing flu pandemics, but others are worried that the studies could provide a blueprint for the creation of a bioweapon or lead to an accidental release of the virus. (Although H5N1 viruses readily kill entire chicken flocks and occasionally infect humans, they have not until now transmitted efficiently between mammals.)

In late December 2011, the U.S. National Science Advisory Board for Biosecurity (NSABB) announced that it had taken the unprecedented step of asking Fouchier, the lead author of the *Science* paper, and *Nature* lead author Yoshihiro Kawaoka of the University of Wisconsin, Madison, and the University of Tokyo to omit key details. The researchers and the journals reluctantly agreed, provided that the U.S. government, which funded the studies, came up with a way of sharing the details with "responsible" scientists and public health experts.

The deal sparked extensive criticism—with some scientists saying that redaction went too far, and others arguing that researchers should not have conducted the studies in the first place. It also set off shock waves in policymaking circles. In Washington, U.S. officials rapidly restarted a long-stalled process aimed at tightening oversight of so-called dual-use biological research. WHO, meanwhile, warned that the redactions could imperil a nascent global agreement to share flu viruses and the benefits of research on them. On 8 January, *The New York Times* weighed in with an editorial headlined "An Engineered Doomsday" that questioned the studies and called on scientists to destroy the new H5N1 variants in the name of safety.

Such high-profile attention prompted senior scientists at the U.S. National Institutes of Health (NIH) and elsewhere to warn flu researchers that the controversy could prompt government officials and lawmakers to impose onerous new rules on research. Others argued that the episode exposed the need to address troubling gaps in U.S. and global efforts to oversee research that could be used for good and evil. To give such issues a full hearing, a number of key players in the debate, including NSABB Chair Paul Keim, a microbiologist at Northern Arizona University in Flagstaff, floated the idea of a moratorium. But Keim advocated a stop only on publishing the results; flu scientists have gone much further by halting research. The pause is modeled in part on a landmark 1975 pact reached by scientists in the then-new field of recombinant DNA, who were also facing questions about safety. That moratorium led to a meeting in Asilomar, California, where scientists proposed safety guidelines for genetic engineering.

"I thought it would be a good idea for the investigators themselves to call for a time-

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More H5N1 coverage is at http://scim.ag/_H5N1.

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Ron Fouchier: In the Eye of the Storm

In a statement posted on the Web sites of *Nature* and *Science* last week and published on page 400 of this issue, a group of leading influenza researchers announced a 2-month moratorium on studies that make the avian influenza strain H5N1 more transmissible between mammals. The moratorium is intended to allow time for an international debate about this type of research, which some people say has the potential to help bioterrorists.

Science talked to Ron Fouchier of Erasmus MC in Rotterdam, the Netherlands, who carried out one of the two studies that triggered the international debate. (His paper is under review at *Science*.) Fouchier's answers have been translated from Dutch and edited for clarity and brevity. An extended transcript of the interview is posted online at http://scim.ag/RFouchier.

–MARTIN ENSERINK

Q: Who took the initiative for this announcement?
R.F.: The initiative came from Adolfo Sastre-García [an influenza researcher at Mount Sinai Medical Center in New York City who has a grant from the National Institute of Allergy and Infectious Diseases that funded Fouchier's study], Yoshihiro Kawaoka [whose H5N1 study, in press at *Nature*, has also been reviewed by the U.S. National Science Advisory Board for Biosecurity (NSABB)], and myself. We discussed it with a group of about 10 scientists who are doing similar studies themselves; then we asked another 30 or so influenza researchers who are not working on these studies but who could do them, if they wanted to sign. They all agreed wholeheartedly. So it's not a Fouchier show. It's an initiative that is supported very broadly.

Q: Why did you take this step now?
R.F.: We were advised by various organizations, and of course we've followed the press coverage and the political debates. We had the impression, based partly on advice from third parties, that it would be sensible to announce a moratorium.

Q: Which third parties?
R.F.: The organizations that fund our research, but also governments that we are talking to. So much is happening at the moment that it makes sense to take a break, to give the infectious diseases field time to think this over and talk about how to handle this kind of research in the future.

Q: Are you doing this because if you don't, governments might move to halt the research?
R.F.: The debate is so controversial that we can't rule that out. We'd rather have everybody take a breather to reflect carefully on how to handle this.

Q: How do you feel about the moratorium yourself?
R.F.: It's a pity that it has to come to this. I would have preferred if this hadn't caused so much controversy, but it has happened and we can't change that. So I think it's the right step to make. It's comparable to what happened in 1975 at the Asilomar conference. But I think that was driven more by the scientists themselves; this time it's mostly the public controversies that drive it.

Q: Has the scale of the controversy surprised you? Had you expected this when you first discussed the study at a meeting in Malta in September?
R.F.: When we presented this, of course we expected that there would be some commotion, and that we would have to explain to the public and the press why we're doing this and how you can do it safely.

out," says Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Maryland, who discussed the idea at length with Fouchier. "I have concerns that people [who are] understandably concerned about security may put restrictions on important research that might go a little bit too far. We have to be extremely sensitive to safety and security, … but what I would not want to see is an overreaction."

The announcement has drawn mostly positive reviews. "Anything that moves us toward a thoughtful and comprehensive discussion is really helpful," says flu expert Michael Osterholm, a member of the NSABB and director of the Center for Infectious Disease Research and Policy at the University of Minnesota, Twin Cities.

That view is also shared by an outspoken critic of NSABB's redaction request, virologist Vincent Racaniello of Columbia University. "A dialogue to identify the crucial issues and develop plans to address them, while continuing this important line of research, is certainly welcome," he says. Indeed, 2 days before the moratorium announcement, Racaniello was one of 18 researchers who signed a letter to Osterholm and other NSABB members, asking them to reconsider its recommendation that the papers be redacted. Such a request "warrants pause and a rational discussion of the scientific facts." The signers also included Eckard Wimmer of Stony Brook University in New York, the author of a controversial 2002 study that demonstrated how to assemble a synthetic poliovirus (*Science*, 9 August 2002, p. 1016), and NSABB critics Peter Palese and Adolfo García-Sastre of the Mount Sinai School of Medicine in New York City. (Both also signed the moratorium letter, and García-Sastre leads an NIAID-funded center that subcontracted for Fouchier's work.)

Fact checker. WHO's Fukuda says a flu summit will help clarify issues.

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On the other side of the debate, smallpox expert Donald Henderson of the Center for Biosecurity at the University of Pittsburgh in Pennsylvania, who has backed NSABB's decision and criticized the studies, calls the moratorium "wise. … This has to be a societal decision," and the pause will "provide an interval for [people] other than the laboratory scientists to weigh in," including political and religious leaders.

Another vocal critic of the flu studies, however, is not impressed, calling the moratorium "pure PR." It's telling, says Richard Ebright, a biologist at Rutgers University in Piscataway, New Jersey, and the Howard Hughes Medical Institute, that the researchers' statement emphasizes the safety and benefits of H5N1 research but "rejects, out of hand, the need for enhanced biosafety, biosecurity, and dual-use oversight." If the researchers had proposed a moratorium that lasted until those issues were addressed, "it could be taken seriously," he says. Without that, the letter "is strictly symbolic. An empty gesture."

Ebright would like to see all research on H5N1 strains engineered to be transmissible among mammals halted until the WHO dis-

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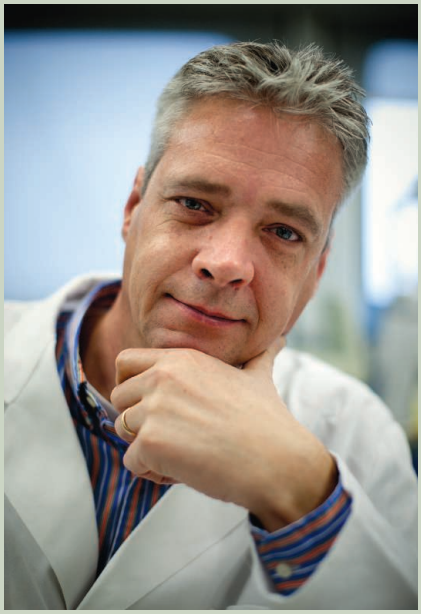
I think we have done that very well in the Netherlands. We were very proactive; before we submitted the paper for publication, we informed all the relevant authorities so they knew what was happening and had the time to prepare, and when the story started making the rounds in the U.S. media, we spent 3 days talking to [Dutch] newspapers, TV, and radio. And that nipped the debate [in the Netherlands] in the bud. In the U.S., this hasn't happened. And the people who are the most vocal in the press are the biosecurity experts. It's a pity that so few people from the flu field have jumped in front of the cameras, especially in the U.S.

Q: Did the NSABB recommendations take you by surprise?

R.F.: Absolutely. This was something that was unprecedented, and something I wasn't counting on at all.

NSABB has said that the risks outweigh the benefits, and now many people are saying, "In that case, you shouldn't do this research at all." That's a very logical response. But the infectious-disease community doesn't agree with NSABB on this. What NSABB should explain better is what the risks are exactly. How much bioterrorism have we seen in the past? What are the chances that bioterrorists will recreate these viruses? And is it really true that publication of this research would give bioterrorists or rogue nations an advantage? That's what I would like to hear from the NSABB.



"It's a pity that it has come to this."

—RON FOUCHIER, ERASMUS MC

Q: You think it doesn't give them an advantage?

R.F.: No. Because bioterrorists can't make this virus; it's too complex, you need a lot of expertise. And rogue nations that do have the capacity to do this don't need our information. … Meanwhile, NSABB gives very little credit to the public health benefits, while the entire influenza community is crying just how important that is. For them the balance between risk and benefit is very different than for NSABB.

Q: In a policy forum you co-authored and which was published last week on *Science*'s Web site, you suggest that you cannot promise to always keep the key details from your paper secret. Under what circumstances would you decide to reveal them?

R.F.: Well, *Science* and we have said that we're going to try to adhere to NSABB's recommendations. The U.S. government is now searching for a mechanism to share the key details with people who have a legitimate need to see them, but this is far from easy; there are all kinds of legal issues. So what that mechanism will look like and whom that information can be shared with is very unclear. Meanwhile, the World Health Organization has said: This research is super-important, but it's just as important that the data are shared, or it could mean the end of the *Pandemic Influenza Preparedness Framework*. … Also, as researchers, we work very closely with people in Indonesia. It would be very unwise for us not to share our results with our close collaborators.

cussions produce stringent global controls, including limiting the total number of labs working with the strains to just two. He also supports the creation of a global oversight panel—similar to the WHO panel that oversees smallpox research—to review studies and ensure that experiments occur only under the most stringent safety conditions.

WHO's Fukuda, however, notes that "we are not a regulatory agency. We know we are not going to put out any regulatory framework." Instead, he says a first step will be simply getting the facts. NSABB members haven't briefed WHO on their reasoning, he notes, and "my overall sense is that most people are pretty confused about what are all the issues. Most people are standing back to see if they should feel one way or another. … One country or research group doesn't reflect the concerns of others."

Then, he says, he hopes the group will first tackle the most urgent issues, such as deciding how best to deal with potentially sensitive information in the papers. The journals have said that they will not publish the papers until that is resolved, and the U.S. government has reportedly asked to have until at least late February to figure it out. "The first thing I would tell everyone," Fukuda says, is "convince me that [redacting the papers is] the only option out there. Let's talk about what's the nature of the sensitivity. … What are the concerns, what do we hope for in getting the information out, and then what are the options? We want to go in not prejudging any of the issues."

One big concern will be how any information-sharing system might affect WHO's new Pandemic Influenza Preparedness (PIP) Framework, agreed to earlier this year after 4 years of often-acrimonious debate. The PIP, which stipulates that countries that provide virus samples should also receive at least some benefits of influenza research, such as vaccines, "is in a vulnerable period," Fukuda says. "As we work through this quite complicated set of questions, we want to make sure … that the whole global system of providing viruses and sharing benefits doesn't take a pause." The issue is especially sensitive, other researchers note, because WHO's global lab network provided the H5N1 isolates used by Fouchier and Kawaoka.

Fukuda says other questions may have to wait a bit longer for answers, such as: "How do we make sure we continue research but do it in a way that doesn't cause people and countries undue anxiety?" In the end, however, he is optimistic the group can reach consensus, noting that "at WHO we often deal with tough issues. … We can start the discussions and see how far we get. Starting with 60 days doesn't mean you can't do something afterwards that keeps the pressure down."

Whether the moratorium and summit will reduce growing pressure for tighter research oversight in the United States, however, remains unclear. A multiagency group has restarted work on formalizing 2007 recommendations from NSABB on procedures for reviewing dual-use research, with a draft statement due sometime this spring. NIH has briefed staff members for several key lawmakers—including senators Joe Lieberman (I–CT) and Susan Collins (R–ME), the top members of the U.S. Senate Committee on Homeland Security and Governmental Affairs. So far, however, Congress has been notably silent on the controversy.

–DAVID MALAKOFF

With reporting by Martin Enserink, Gretchen Vogel, and Jon Cohen.

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