By **Jocelyn Kaiser**

The catalyst

This past July, Harvard University epidemiologist Marc Lipsitch sat down with a group of other experts worried about controversial flu experiments. The studies create potentially dangerous new viruses that critics fear could escape from laboratories and cause a pandemic or be used as bioweapons; Lipsitch and his colleagues hoped to find ways to persuade governments to rein them in. But the agenda took an unexpected turn. Phones began ringing: Journalists wanted reaction to several recent lab accidents involving dangerous pathogens—and to news that four of the 18 scientists participating in the meeting had just been abruptly dismissed from a high-profile panel that advises the U.S. government on biosecurity. "It quickly became clear to us that this was an opportunity," Lipsitch says.

His group seized it. They came up with a name—the Cambridge Working Group (CWG)—and crafted a statement that they distributed widely. "Experiments involving the creation of potential pandemic pathogens should be curtailed" until risks and benefits could be thoroughly weighed publicly, it argued. The 14 July statement drew extensive media attention, and nearly 300 researchers eventually signed on. Then came an online response a few days later from Scientists for Science—an opposing alliance of researchers who support the controversial flu experiments, arguing that they are adequately regulated and potentially valuable. Still, to Lipsitch's surprise, they gave a little ground: They agreed that researchers needed to publicly air the issues. Soon, plans were being firmed up for a symposium later this year at the National Academy of Sciences in Washington, D.C., and perhaps a broader discussion organized by the U.S. government.

The turn of events highlights Lipsitch's rapid rise as a prominent voice in the debate over risky research, which has roared back to life after a lull lasting nearly 2 years. The one-time philosophy major turned biologist has recently shown a knack for being in the right place at the right time, with a message and data that have helped shape the conversation.

Earlier this year, for instance, Lipsitch published a critical analysis that argued for safer alternatives to the controversial flu studies—just as other scientists reported new experiments that rekindled concern. He and colleagues highlighted the accident risks facing the growing number of labs working with dangerous pathogens—just before a spate of biosafety and biosecurity incidents at government labs. And despite Lipsitch's relatively extreme views—he'd like to essentially end most of the contested research—even some opponents say his persistence has helped force the opposing camps to try to reach consensus.

"I appreciate the concern" that Lipsitch and others have helped articulate, says virologist Ron Fouchier of Erasmus MC in Rotterdam, the Netherlands, who published one of the most controversial of the flu studies. "Hopefully, the meetings … will address the facts properly, and as a consequence be more constructive."

Lipsitch is "an incredibly thoughtful guy who's able to step back a bit and take an unbiased, dispassionate position," says David Relman, a CWG member and a microbiologist at Stanford University in Palo Alto, California. "He bends over backward to hear both sides and find common ground."

Lipsitch, 44, is a relative latecomer to the debate over how to balance science and safety in studies of dangerous pathogens. In the United States, the September 2001 anthrax attacks (see timeline, p. 1113) led to a vast expansion of federal funding and labs for biodefense research—and a slew of new safety and security rules for U.S.-funded scientists working with "select agents." Journal editors pledged to think twice before publishing "dual use" results that could be used for good or evil.

The most recent chapter in the debate began 3 years ago this month, after Fouchier presented a startling study at a meeting in Malta. His lab had altered the H5N1 avian flu virus, which can kill humans who catch it from birds, so that it could spread more easily among mammals (*Science*, 2 December 2011, p. 1192). A short time later, it became known that another researcher—Yoshihiro Kawaoka of the University of Wisconsin, Madison—had conducted similar experiments. The researchers—who had submitted their papers to *Science* and *Nature*, respectively—argued the work would help

PHOTO: KENT DAYTON/HARVARD SCHOOL OF PUBLIC HEALTH

Marc Lipsitch is worried about accidents at high-containment laboratories, such as the U.S. Army Medical Research Institute in Maryland.

PHOTO: AP PHOTO/PATRICK SEMANSKY

Marc Lipsitch wants to turn the bitter debate over risky virus research into a search for solutions

the world better prepare for a flu pandemic.

Critics were appalled: Some said the work amounted to a recipe for bioterrorists; others raised the specter of a catastrophic lab escape. A U.S. government advisory panel—the National Science Advisory Board for Biosecurity (NSABB)—recommended that journals publish the studies only if editors cut key details. That idea proved unworkable, however, and 2 years ago the studies were published in full. But the uproar led flu researchers to voluntarily declare a yearlong moratorium on "gain-of-function" studies that enhance dangerous pathogens. It also prompted the U.S. government to develop new rules aimed at strengthening funding reviews for so-called DURC, or dual use research of concern (see sidebar, p. 1115).

The controversy fascinated Lipsitch, who is not an influenza virologist. He's a mathematical modeler and experimental bacteriologist who studies the spread of pathogens including influenza, and he has always been interested in the world beyond science. He studied philosophy at Yale University, and before going abroad to earn his doctorate in zoology at the University of Oxford, he spent a summer working at a newspaper, *The Jewish Daily Forward*, where he says he learned to write fast. In his hometown of Atlanta for a postdoc at Emory University in the late 1990s, he persuaded about 50 scientists to sign a letter protesting a state plan to put a disclaimer in biology textbooks that cast doubt on the evidence for evolution. "I do think scientists have a responsibility to use what we know to be socially useful," says Lipsitch, who comes across as resolute yet soft-spoken.

That outlook drew him into the H5N1 controversy soon after Fouchier gave his Malta talk. Lipsitch was intrigued by the challenge of weighing the potential risks and benefits of the studies. On the benefit side, the H5N1 researchers had argued that their genetic tinkering, which enabled the virus to gain the ability to move more easily between ferrets, would help identify mutations useful to vaccine developers and public health officials on the lookout for dangerous new flu strains. The risk was that if strains like those created by Kawaoka or Fouchier ever

A risky research timeline

Debate over biosafety and biosecurity has deep roots

September 2001
Anthrax mail attacks kill 5, infect 17 in U.S.

February 2003
U.S. tightens regulation of labs studying dangerous "select agents"

October 2003
U.S. National Academies identifies 7 types of risky research, recommends government advisory board on biosecurity

June 2005
First meeting of U.S. National Science Advisory Board for Biosecurity (NSABB)

October 2005
Science publishes sequence of 1918 flu virus (after NSABB consultation)

December 2011
NSABB recommends against publishing H5N1 papers

January 2012
Flu researchers impose voluntary moratorium on gain-of-function studies

March 2012
NSABB, in split vote, recommends publishing H5N1 papers

New U.S. policy for oversight of biomedical dual use research of concern (DURC)

January 2013
Flu research moratorium ends

February 2013
New U.S. rules for reviewing H5N1 studies

August 2013
U.S. drafts rules for university oversight of DURC; new rules for H7N9 flu studies

June 2014
Anthrax accident at Centers for Disease Control and Prevention (CDC)

July 2014
Live smallpox found in storage at National Institutes of Health

CDC reveals H5N1 accident; suspends some lab work and shipments

August 2014
White House announces new biosafety reviews, asks labs to inventory pathogens

escaped—by design or accident—they might sicken or kill large numbers of people.

Lipsitch and others were skeptical of the alleged benefits of lab studies. Such studies in the early 2000s had suggested that a mutation making the H1N1 flu strain resistant to the antiviral drug Tamiflu would never emerge in nature because it lowered the virus's fitness. But in fact, the resistance mutation did appear and spread widely in 2007 and 2008. Such results, Lipsitch says, suggested that the arguments for the H5N1 studies "make sense only if you think that there's a high chance that what you see in the limited number of strains you can study in a lab is strongly predictive of what will happen in nature."

When Lipsitch examined the safety of laboratories working with H5N1 and other dangerous viruses, he began to think the risks of such work had been downplayed. It is typically restricted to the most secure laboratories—so-called biosafety level 3 (BSL-3) and BSL-4 laboratories, which have contained workspaces and can require employees to wear respirators or head-to-toe "moon suits." But he found that government data show U.S. biosafety labs have plenty of accidents: between 100 and 275 potential releases of pathogens each year in labs that handle select agents, or two to four per week, between 2008 and 2012. (Lipsitch's critics point out that the reports include mundane things like spills and record-keeping errors; rarely has a lab worker become infected.) And many researchers suspect that a 1977 H1N1 flu outbreak resulted from a lab escape.

"I had always found biosafety a pretty dry topic, to be honest," says Lipsitch, who runs his own small BSL-2 lab. "But when you start to think of it in terms of a contagious disease and the risk of a new pandemic, it suddenly becomes something that's more connected to what I am interested in."

The accident data helped persuade Lipsitch that gain-of-function experiments that create potential pandemic pathogens—what he and others call PPPs—simply aren't warranted. An inadvertent humanmade pandemic would be inflicted by scientists on people who had no say in whether the risks were justified, he argues. And in June 2012, he and three co-authors summed up their views in an opinion piece for *Science* (22 June 2012, p. 1529), arguing that proposed PPP studies posed an "exceptional level of risk" and calling for a new U.S. government body to conduct risk-benefit analyses.

Not long after the *Science* paper appeared, the controversy faded and the H5N1 studies ultimately resumed. But beneath the surface, the debate continued to simmer. And earlier this year, it boiled over once more after Fouchier, Kawaoka, and other researchers published a new series of virus studies (see box, p. 1114). Although some had been reviewed by U.S. officials under the new rules, they again raised questions about risky research—and who should decide whether a study gets funded or published.

Just as those papers were drawing attention, Lipsitch and Yale epidemiologist Alison Galvani argued that such studies are not only risky, but also unnecessary. Their 20 May *PLOS Medicine* paper laid out detailed alternatives to gain-of-function studies, including using computers and lab work with benign strains to identify important mutations. The paper also marshaled recent data on lab accidents, finding that if just 10 BSL-3 laboratories operated for 10 years, the chances of lab-acquired infection would be nearly 20%. About 1100 U.S. BSL-3 labs are now registered to work with select agents (some are clustered in one facility); that's nearly triple the number that existed in 2001.

The paper drew media attention and, in the scientific world, stirred strident reactions. Fouchier said it overstated the risks, pointing out that there had been only 11 nonfatal infections in U.S. labs over 7 years, and none involved viruses. Kawaoka argued that studying only benign flu strains could produce misleading results. Columbia University's Vincent Racaniello, who has dismissed Lipsitch's efforts as a "crusade," bashed the paper's ethical, scientific, and safety arguments on his popular podcast, *This Week in Virology*, along with several guests. "I'm disturbed. … [A]ll of its points are really unfounded," Racaniello said. In reaction, one Lipsitch defender, bioethicist Nicholas Evans of the University of Pennsylvania, wrote a blog post calling the podcast "a platter of incorrect statements, bad reasoning, and some all-out personal attacks."

Tensions rose in mid-June, after the U.S. Centers for Disease Control and Prevention (CDC) disclosed that a high-security biodefense lab had mishandled live anthrax cultures, potentially exposing dozens of workers. Within days, Lipsitch had submitted a commentary to *The New York Times,* which it published with the headline: "Anthrax? That's Not the Real Worry." Experiments creating PPPs were a "[m]uch more troubling" threat, he wrote.

Lipsitch's uncanny timing continued in the following weeks. First came news that scientists had discovered forgotten vials of smallpox dated to 1954 in a refrigerator on the National Institutes of Health (NIH) campus, ramping up worries about lab safety. Then came the Cambridge meeting. Its organizers, Lipsitch and Peter Hale of the Foundation for Vaccine Research in Washington, D.C., had told invitees that the plan was to discuss "strategies and tactics" for influencing the debate on PPP experiments.

But 3 days before the Monday gathering, CDC chief Thomas Frieden held an unusual press conference to discuss the anthrax and smallpox incidents—and unveil a new revelation that made Lipsitch and Galvani look remarkably prescient. A CDC lab, Frieden announced, had shipped out a relatively benign poultry flu sample that workers had accidentally contaminated with the more dangerous H5N1 virus. Frieden halted some research and shipments and launched a broad biosafety review. The message was unmistakable: Even the best, most regulated labs in the world make errors.

Lipsitch's skeptical message got yet another coincidental boost that weekend. News surfaced that the Department of Health and Human Services was completely remaking the membership of its NSABB biosafety advisory group, excusing all the remaining members who had helped found the panel in 2005 and served through the H5N1 controversy. Though NIH officials said it was a routine turnover, some observers saw it as another sign that government biosafety efforts were in worrying disarray.

By that Monday in July, it was an obvious step for the CWG to piggyback on such news with its statement, Lipsitch says. But reaching consensus wasn't easy: Some group members resisted calling for a complete moratorium on PPP studies. For instance, microbiologist Arturo Casadevall of Albert Einstein College of Medicine in New York City and Michael Imperiale of the University of Michigan disagree with Lipsitch and Galvani's argument

Controversial papers

Three papers this year have helped renew debate over efforts to create or enhance dangerous pathogens:

2 April, *Journal of Virology*
H7N1 is not on the U.S. government's list of flu strains requiring special review, but Daniel Perez's lab at the University of Maryland, College Park, makes it transmissible in ferrets while remaining highly pathogenic.

10 April, *Cell*
Ron Fouchier's lab at Erasmus MC in the Netherlands identifies specific set of mutations that make H5N1—a bird flu that does not spread readily in mammals—transmissible in ferrets.

11 June, *Cell Host & Microbe*
Yoshihiro Kawaoka's group at the University of Wisconsin, Madison, creates a virus similar to 1918 flu using genes from current bird strains.

that the flu experiments aren't justified because they are of limited scientific value. Such work may not be able to pinpoint mutations that could emerge in nature, but it can be "of huge value" in answering broader questions, such as whether a particular bird strain could ever become transmissible in mammals, Casadevall says. He says he finally agreed to the word "curtail" because under U.S. rules the gain-of-function flu experiments "are already curtailed."

Still, Lipsitch's impact on the public conversation was clear when Scientists for Science weighed in a few days later with its response, which was partly organized by Racaniello and has attracted more than 170 signers. "[O]nly by engaging in open constructive debate can we learn from one another's experience," the Scientists for Science statement says. And, in a sign of how eager some are to reach detente, a few researchers, including Imperiale and Columbia University virologist Ian Lipkin, signed both statements. "There has to be a coming together of what should be done," Lipkin says. "It doesn't help for people to be pissing on one another."

Lipsitch is clearly pleased by the more polite turn. "The good thing is that I think the temperature of the rhetoric is much cooler now." And he's willing to accept some credit for helping establish a middle ground "that has been suddenly occupied from both sides," he says. "Whatever the outcome, I think there's reason to expect that it will lead to less risk of accidents than allowing the status quo to continue. And luckily everybody seems to think [the issue is] worth discussing."

It's not easy to see how the two sides might strike a truce. Kawaoka and Fouchier both hope that if their critics better understand the safety and security measures in their labs, they will agree that the flu studies should continue. Some researchers, such as Casadevall, have suggested technological solutions, such as engineering a gene sequence into experimental viruses that could prevent them from replicating in humans. Others believe more inclusive and powerful government review bodies are needed to oversee proposed experiments.

Whatever the outcome this time, the current drama has helped place the spotlight on a new player. Lipsitch "is one of the bravest scientists I know," says epidemiologist Lone Simonsen, a CWG member and longtime friend and collaborator now at George Washington University in Washington, D.C. "If he feels strongly about an issue he will pursue and talk about it, even though it is a point of view most of his sympathetic colleagues share but would not discuss aloud." ■

A policy morass

By **David Malakoff**

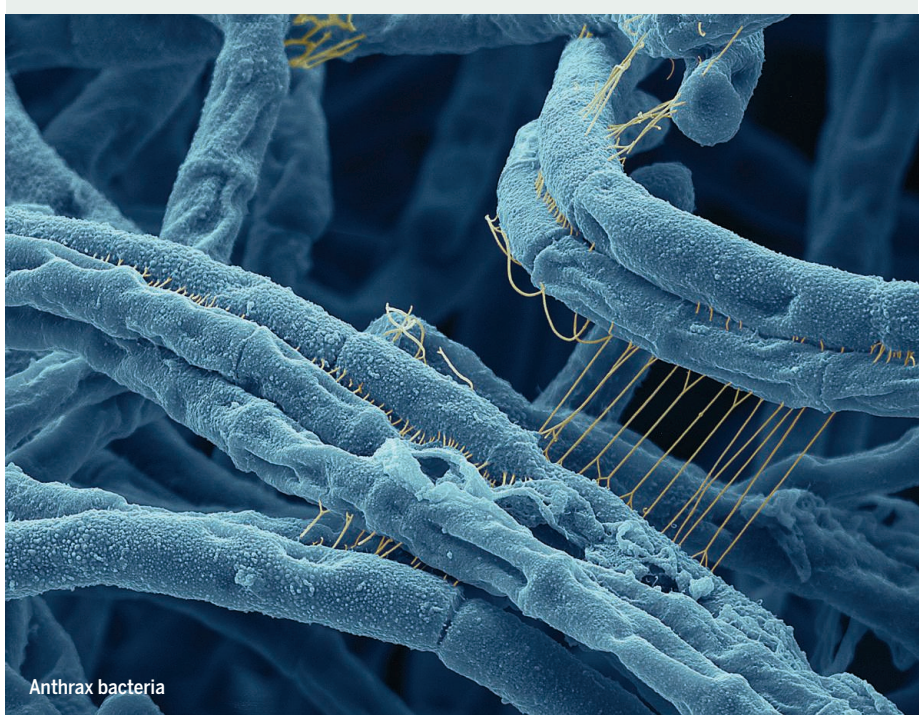
Even as scientists and government officials struggle anew with the question of how to regulate risky biological research, the United States and other nations are still working to fully implement the rules and policies that emerged from the last big debate, over the 2011 studies that made H5N1 more transmissible.

Some of the biggest changes have occurred in the United States, by far the single largest funder of potentially risky research. Under rules adopted in 2012, the National Institutes of Health (NIH) and other funding agencies now screen proposals for "dual use research of concern" (DURC)—work that could be used for good or bad ends. At NIH, proposals deemed DURC get a special review and, if funded, special requirements, including that researchers submit manuscripts for prior review before sending them to a journal. As of this past June, NIH tells *Science*, it had reviewed about 30 DURC papers from extramural researchers and six from intramural researchers. In addition, it was monitoring eight DURC projects and had requested changes to some experiments.

A second U.S. government policy, which calls on universities and other institutions to play a bigger role in identifying DURC and mitigating risks, has been in limbo since a draft was released in April 2013. It has drawn criticism from both academic officials, who fear it could be too onerous, and biosafety advocates, who fear it is too lax. The issue got new attention this past June, when Yoshihiro Kawaoka of the University of Wisconsin, Madison, published a study on a flu virus similar to the deadly 1918 strain. University reviewers had judged the study was not DURC, *Nature* reported, but federal officials disagreed. (They nonetheless agreed to fund it.)

Other new rules require NIH to give special reviews to projects aimed at giving new capabilites to two dangerous flu viruses—H5N1 and H7N9. As of June, one grant and one contract had received those reviews, NIH says.

Critics argue that the new reviews are still not preventing NIH from funding questionable studies—but there is wide disagreement on whether or how the process should be altered. In the meantime, some researchers are also calling for clearer rules for journal editors, who often must decide whether to publish findings that could be misused. Others see the need for new government oversight bodies to decide which results should see the light of day. ■



Anthrax bacteria

PHOTO: EYE OF SCIENCE/SCIENCE SOURCE