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H5N1: A Case Study for Dual-Use Research

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Acronyms

BSL-3	biosafety level 3
BSL-3+	biosafety level 3+
BSL-4	biosafety level 4
BWC	Convention on the Prohibition of the Development, Production, and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction
CDC	Centers for Disease Control and Prevention
CEN	European Committee for Standardization (*Comité Européen de Normalisation*)
DIY Bio	do-it-yourself biology
DURC	dual-use research of concern
FDA	Food and Drug Administration
GISN	Global Influenza Surveillance Network
GMO	genetically modified organism
HHS	Department of Health and Human Services
HPAI	highly pathogenic avian influenza
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NSABB	National Science Advisory Board for Biosecurity
PIP	Pandemic Influenza Preparedness
SARS	severe acute respiratory syndrome
WHA	World Health Assembly
WHO	World Health Organization

Introduction

Biological research is inherently dual-use, in that a great deal of the scientific knowledge, materials, and techniques required for legitimate research could also be used for harm. The potential for a bioterrorist to misuse legitimate research is particularly acute for scientific studies of contagious pathogens. In order to find out how pathogens function—how they are able to get around the human body's immunological defenses, replicate in great numbers, and go on to infect other people in a continuous chain of infection—scientists necessarily learn what conditions make pathogens more deadly or difficult to treat. This research is widely shared. But the fear that this openness could be exploited has sparked concerns about specific scientific publications, prompting media storms and even congressional disapproval, as in the 2002 case when poliovirus was synthesized from scratch in a laboratory.[1]

Nonetheless, the benefits of publishing research have always been perceived to outweigh the risks. Redaction of legitimate research was never seriously considered until a pair of H5N1 avian influenza manuscripts were submitted for publication in 2011, describing specific mutations that allowed the deadly bird virus to become transmissible in mammals. The U.S. government, which had funded the work, recommended redaction of methodological details, which led to six months of public discussion, a series of high-profile international meetings, a reversal of the U.S. government stance, and ultimately, the publication of the articles in leading scientific journals. Disagreement remains, however, about whether the so-called gain-of-function research, which deliberately introduced transmissibility between mammals as a new characteristic for H5N1, should be pursued or funded. U.S. policy for research governance has changed, in an attempt to prevent a dual-use situation from occurring again with so little warning. Washington will likely take further actions to govern dual-use research of concern (DURC), which the U.S. government describes as "life sciences research that . . . could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel or national security."[2]

But just as it is a certainty that the world will face another pandemic—whether H5N1 or H7N9, which is currently causing concern as the case numbers climb, or another emerging disease—it is certain that another dual-use research event will cause concern worldwide.[3] The H5N1 debate is therefore instructive because many of that work's contentious factors will persist: scientific and medical experts will assign different weights to the risks and benefits of the research; security communities will likely reach different conclusions than the majority of scientists; safety concerns will increase, especially as more consequential research is performed in laboratories—or even garages—all over the world; and a gulf will remain between the quick pace of laboratory research and the real-world application of that knowledge, whether for disease surveillance or the development of drugs and vaccines.

The next dual-use research event that causes worldwide concern may focus on influenza, but, given the diversity and global nature of the life sciences, it could result from any kind of biological re-

search—from agriculture research, to gene therapy, to synthetic biology, which involves the reengineering of biological systems. To reduce concerns and aid in assessing the value of the work, policymakers and scientists should undertake several steps. First, there should be more effort to promote awareness of the dual-use dilemmas in scientific practice. Second, every effort should be made to use the scientific information that is generated productively, so as to improve public-health surveillance for emerging pandemics. Finally, there is a tremendous need to promote global norms for biological safety, education, and monitoring. While the H5N1 work was judged by many experts to exhibit the highest safety standards, there is no guarantee that the influenza studies will be replicated with the same attention to detail, or that the next dual-use event will be performed as safely.

Waiting for H5N1

For years, the world has been waiting for—and experts have predicted—an H5N1 influenza pandemic. H5N1 influenza was thought only to affect birds until it crossed over to humans in Hong Kong in 1997, killing six people and sickening twelve more.[4] There was no evidence of human-to-human transmission in those cases, suggesting that the virus was not contagious. In the following years, there were additional human cases reported in China, Thailand, Vietnam, Indonesia, Cambodia, Egypt, Azerbaijan, Djibouti, Pakistan, Myanmar, and Bangladesh. In addition, avian cases were reported in all of those countries, as well as in Korea, Japan, Malaysia, Russia, Kazakhstan, Mongolia, Romania, Turkey, Croatia, Bulgaria, Greece, Italy, Germany, France, Switzerland, and Poland. In other words, highly pathogenic H5N1 could be found in wild birds, poultry, and, occasionally, in people, throughout a wide swath of the world.[5] Though there remains no evidence of sustained human-to-human transmission to this day, the disease's exceptionally high fatality rate makes the prospect of an H5N1 influenza pandemic especially frightening. Since 2003, the World Health Organization (WHO) reports that there have been 622 laboratory-confirmed cases of H5N1, of which 371 resulted in death.[6] A mortality rate of 60 percent sounds even worse when compared to the 2.5 percent fatality rate of the 1918 influenza pandemic, the most devastating influenza pandemic of the twentieth century, which killed at least fifty million people.[7]

In watching H5N1 cause crossover human infections and deaths, it is uncertain whether the world is witnessing the first steps in an emerging pandemic or the statistical noise of a virus that will forever remain an avian disease. There are few precedents to look to for clues. In the years preceding the 1918 pandemic, public-health surveillance and molecular tools were just not available to monitor emerging viruses. But the possibility that H5N1 could jump to humans and become contagious—with even a *fraction* of its high mortality rate—has prompted grave fears among experts and preparations by some nations.

A great deal of the global progress in influenza preparedness in the last decade stems from the fear of an H5N1 pandemic. The WHO issued warnings, as did influenza experts. Prototype pre-pandemic vaccines were developed and stockpiled, and influenza preparedness plans were crafted. The United States had additional incentives to get ready: in 2005, contamination problems in the United Kingdom's Chiron influenza vaccine–manufacturing plant resulted in the loss of roughly half the U.S. supply of influenza vaccine that year.[8] With at-risk elderly patients waiting in long lines for a short supply of vaccine, it became clear that the United States had no domestic capacity for influenza-vaccine production, and that only two companies had Food and Drug Administration (FDA) approval to market influenza vaccines in the United States. These events contributed to major investment in planning for a pandemic in 2006, including $3.3 billion toward domestic vaccine capacity, state preparedness, influenza research, and development of an H5N1 vaccine.[9] Should H5N1 become a human-transmitted disease in the near future, the strain that would be passed from person to person would be different than what vaccine manufacturers have been using. Nonetheless, it was hoped that

these pre-pandemic vaccines would be protective, giving nations a head start in protecting their populations.

However, the people most vulnerable to an emerging H5N1 influenza outbreak are not necessarily the same populations that would receive protection from a presumably expensive new vaccine. This prompted a contentious debate. In 2007, Indonesian officials learned that an Australian pharmaceutical company had developed a prototype H5N1 pandemic–influenza vaccine using a sample isolated from an H5N1-infected bird in Indonesia. The Indonesian officials believed that the company would profit from the sample, but that the vaccine would be unaffordable for most Indonesians. In protest, Indonesia pulled out of the WHO Global Influenza Surveillance Network (GISN), which monitors the influenza burden in the world and helps select the predominant flu strains incorporated into the seasonal influenza vaccine each year.[10] Indonesia also invoked the 1992 United Nations Convention on Biological Diversity, claiming that it was an act of "biopiracy" for pharmaceutical companies to profit from the Indonesian avian samples.[11] Given that Indonesia recorded more human cases and deaths from H5N1 than any other country, this was terrible news for influenza surveillance, as well as for the development and refinement of diagnostic tests and prototype H5N1 vaccines.[12]

The Indonesian sample-sharing crisis ended after four years of complex and contentious negotiations through an agreement with the WHO—the Pandemic Influenza Preparedness (PIP) Framework—which was adopted by the World Health Assembly (WHA) in May 2011.[13] In this agreement, the WHO promised to address inequities in vaccine availability, created a transparent mechanism for material transfer agreements that discourages treating virus samples as intellectual property, and increases access of middle- and low-income countries to pandemic vaccines and diagnostics. Vaccine producers, pharmaceutical manufacturers, and diagnosticians who participate in the WHO global influenza surveillance-and-response system are obligated to contribute up to 50 percent of the program's operating costs.[14]

Though the sample-sharing crisis ended with the PIP agreement, problems remain in getting the necessary biological samples to do adequate surveillance for H5N1 and other flu viruses.[15] Even after the International Health Regulations of 2005 went into effect in 2007—requiring that countries report public-health events of international concern to the WHO, including novel influenza viruses—real-time monitoring of influenza outbreaks is still not a reality.[16] The lack of thorough disease surveillance leaves the world vulnerable to unwelcome disease surprises.

A prime example of an influenza surprise was the 2009 H1N1 pandemic. While most influenza experts' energy was concentrated on identifying emerging influenza epidemics in Southeast Asia, a new avian/swine hybrid virus started spreading in Mexico. For months, the virus caused illness and deaths until it was identified as H1N1 by a laboratory in San Diego.[17] While the H1N1 outbreak of 2009 was not nearly as deadly as experts feared H5N1 would become, it nonetheless caused unusually high rates of illness and death among young people and pregnant women.[18] As manufacturing for the regular seasonal-influenza vaccine had already begun when the pandemic started, the process needed to begin anew for the H1N1 vaccine. The process to make influenza vaccine normally takes six months, which is almost as long as it took for the H1N1 vaccine to be widely available.[19] By the time the vaccine was ready, many people had already decided it was not necessary, as the virus had already passed through their communities, and others refrained from taking a vaccine that they perceived as "rushed" through production.[20] For most of the world, access to the vaccine was not even an option. Through this experience, it became clear that if a new pandemic emerged, whether H5N1 or

something else, many people would not be able to benefit from the vaccine. It would arrive too late for most in wealthy countries, while remaining inaccessible to those in poorer countries.

As in many past pandemics, H1N1 not only caused loss of life, but, to some observers, a loss of reputation and political effectiveness. The WHO found itself in a defensive position, amid charges that it held a conflict of interest due to overly close ties with influenza-vaccine manufacturers, which damaged its reputation as a neutral party.[21] At the time of the pandemic, the outbreak was seen as relatively mild. However, the true impact of the disease was not understood until after the pandemic had passed.

For all of the world's experience with seasonal influenza outbreaks and even modern-day pandemics, there is a great deal of mystery surrounding why a particular virus would become a pandemic, and what happens at the genetic level when a virus adapts from being a bird-only strain to one that is infectious to humans.[22] Certain animals, such as pigs, are thought to be prime mixing vessels for multiple strains, allowing new strains to emerge that could be more transmissible to humans. There are known characteristics that would allow a virus particle to attach preferentially to a mammalian cell rather than an avian cell, and vice versa. The viruses that have caused the last several pandemics—in 2009, 1968, 1957, and even 1918—have all been genetically sequenced and analyzed in depth. Still, despite the vast body of knowledge about influenza in general, and H5N1 in particular, it is unclear why H5N1 has not yet emerged as a pandemic strain, leading some scientists to theorize that H5N1 was never going to become a pandemic. Experiments were undertaken to try to make H5N1 into an infectious strain, but they were unsuccessful, adding weight to that conclusion.[23]

At long last, fourteen years after the first outbreak in 1997, an H5N1 virus was found that was transmissible not just between birds, but from one mammal to another. It was not found in Southeast Asia, but in the Netherlands and in Wisconsin—deliberately created in two independent influenza-research laboratories.

What Makes a Pandemic Go?

At the European Scientific Working Group on Influenza's conference in Malta, held in mid-September 2011, Ron Fouchier of the Erasmus Medical Center in the Netherlands shared research that suggested it was too soon to write off H5N1 as a threat. In dramatic fashion, Fouchier described how he and his colleagues had pushed the virus to evolve under controlled circumstances so that it was contagious between ferrets, the preferred animal model for studying influenza. Their inelegant methods—Fouchier described it as a "really, really stupid" experiment—nonetheless demonstrated that what happened in a laboratory could happen in nature.[24] When the transmissible strain was isolated from the ferrets and genetically sequenced, it was found to differ from the starting strain in only five areas. All of the mutations that had been laboratory-evolved were already seen in samples isolated from sick birds in nature, though not all together in one strain.[25] This suggested that if H5N1's progression to pandemic were incremental, the virus would be well on its way to becoming a mammalian contagion. At the time of the Malta conference, Fouchier was preparing to submit his paper to *Science*, a leading U.S. scientific journal.

Fouchier was not the only one to create a H5N1 strain with increased transmissibility. Yoshihiro Kawaoka, a scientist who runs virology laboratories at both the University of Wisconsin–Madison and University of Tokyo, performed a different type of experiment that produced the same general conclusion: H5N1 could be transmissible among humans. His experimental design was perhaps more elegant, and, some thought, safer, than that pursued by Fouchier. Kawaoka's strain was created using just a portion of the H5N1 virus (the H5 hemagglutinin head), along with components of the 2009 H1N1 strain. The virus was susceptible to antivirals, the current H1N1 vaccine was protective, and it was not lethal to the ferrets.[26] Kawaoka submitted this work to *Nature*, another leading scientific journal. The funding for the work of both these scientists came in large part from the U.S. government.

The Perfect Test Case for Dual-Use Research of Concern

The potential for legitimate biological research, published in the open literature, to be used for nefarious purposes has been considered by groups of scientists, ethicists, and policymakers in the past, often precipitated by a scientific paper that drew concern and shaped the argument over what should be done. In 2001, one such paper came from an odd source: an Australian government program working on a viral birth control for mice, to reduce the yearly mouse plagues that destroy crop lands and rural infrastructure.[27] Published in the *Journal of Virology*, their work demonstrated that by adding a single gene to mousepox virus, the virus became more lethal even to vaccinated mice.[28] As mousepox is a distant cousin to the human smallpox virus, which had a mortality rate in excess of 30 percent before it was eradicated, this research raised fears that the vaccine for human smallpox could be defeated by the same genetic modification.

Even before the attacks of September 11, 2001, and the anthrax letters, a National Research Council committee had been formed to study how the scientific community should deal with dual-use research like the mousepox example, and the anthrax letters added weight to their deliberations. Chaired by Dr. Gerald R. Fink, a renowned yeast geneticist at the Massachusetts Institute of Technology, the committee produced a report, *Biotechnology in an Age of Terrorism*, which made the case that biologists have an "affirmative moral duty to avoid contributing to the advancement of biowarfare or bioterrorism."[29] The Fink Report recommended that scientists give extra consideration and review before undertaking projects that do the following:

- demonstrate how to make a vaccine ineffective
- confer resistance to therapeutically useful antibiotics or antiviral agents
- enhance the virulence of a pathogen or render a nonpathogen virulent
- increase a pathogen's transmissibility
- alter the host range of a pathogen
- enable the evasion of a diagnostic and or detection modalities
- enable the weaponization of a biological agent or toxin

While these seven warnings were not incorporated into the normal review of scientific work, they did form the starting point for the newly created National Science Advisory Board for Biosecurity (NSABB) to consider the issue. The NSABB federal advisory committee on dual-use research was created in 2004 at the recommendation of the Fink Report. It has twenty-five voting members with a variety of scientific expertise—as well as expertise in law enforcement, national security, and scientific publishing—and fifteen *ex-officio* government members who attend all meetings.

Scientific-journal editors also committed to addressing dual-use concerns. In 2003, the editors of *Science*, *Nature*, the *Journal of Virology*, and more than a dozen other scientific publications released a

"Statement on Scientific Publication and Security," which recommended the development of dual-use review for scientific work, and stated that "there is information that, although we cannot now capture it with lists or definitions, presents enough risk of use by terrorists that it should not be published."[30] There is no formal system in place for journal editors to consult the NSABB on particularly problematic papers, but it has performed this service upon request. In 2005, the NSABB was asked to review a paper about the reconstruction and study of the 1918 influenza virus—the virus responsible for more than fifty million deaths in the worst influenza pandemic of the twentieth century—and it recommended publication.[31]

NSABB Recommends Redaction

The NSABB reviewed the H5N1 manuscripts in October 2011, and its decision became public on December 21: the committee recommended that the authors and editors of the journals modify the articles to remove methodological information that "could enable replication of the experiments by those who would seek to do harm."[32] In the deliberations process, the NSABB had received briefings from members the U.S. intelligence community, including the FBI, and it was concerned that the research could be misused by international and domestic terrorist groups. However, given the significance of the findings for public health and influenza research, the NSABB recommended that "the general conclusions highlighting the novel outcome be published."[33] The committee also recommended that the scientific community self-impose a moratorium on the communication of experiments that show enhanced virulence or transmissibility of microbes like H5N1.[34] The U.S. Department of Health and Human Services (HHS) agreed with the NSABB committee's recommendations and provided the assessment to the authors and editors.

At this point, the debate was no longer academic. On January 7, 2012, a *New York Times* editorial, "An Engineered Doomsday," took the position that the research should never have been undertaken and should not be published, even in redacted form.[35] While the editor of *Science*, Bruce Alberts, was open to withholding details in the manuscript, he said that it was up to the U.S. government to develop a system whereby scientists worldwide who needed the information could access it.[36] The Erasmus Medical Center team estimated that more than one thousand scientists had a need to know this information, representing more than a hundred laboratories worldwide.[37] The *New York Times* editorial argued that this was far too many people, that the transmissible strains should be destroyed, and that future research should be regulated as smallpox research is currently regulated, now that the virus is eradicated, with each experiment receiving international approval.[38] In response to claims that the research would provide valuable information needed to counter influenza, the editors responded that "we cannot say there would be no benefits at all from studying the virus. We respect the researchers' desire to protect public health. But the consequences, should the virus escape, are too devastating to risk."[39]

Under pressure, Ron Fouchier, Yoshihiro Kawaoka, and thirty-seven other influenza experts announced a voluntary sixty-day hold on research with the laboratory-created strains, and any research involving the generation of additional transmissible strains.[40] The moratorium was enacted, they wrote, to promote discussions in an international forum.[41] Anthony S. Fauci, the director of the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH), the agency that funded the work, had apparently urged the scientists to consider a moratorium due to the incredible polarization in the scientific world and a looming concern that biosecurity experts might impose excessive restrictions on the research.[42] The last time there was a self-imposed moratorium on biomedical research in the United States was from 1974 to 1976, to evaluate the safety of recombinant DNA research.

Why the Concern?

Without the actual scientific data in the public domain, a great deal of focus was placed on the personalities involved; Fouchier made himself available to the press, while Kawaoka did not.[43] There was also confusion and disagreement about how dangerous the studies actually were. Was Fouchier's strain as lethal as H5N1 when it crossed over to humans? Was Kawaoka's strain much less lethal, as was commonly supposed, and would that make a significant difference to its dual-use potential? Both Fouchier and Kawaoka wrote that fears of these laboratory-created viruses were exaggerated.[44] Debate continues over the acceptable parameters for lethality and the relevance of ferret data to humans. It will likely remain unknown if this ferret-adapted virus would be equally transmissible in humans, as animal models are often imperfect.

The biggest challenge in this dual-use crisis was that for many observers, scientific experts, and biosecurity experts, the risk-benefit equation for this research yielded different, but equally valid, answers for how to resolve the debate. There were a variety of different objections raised to the research or its publication, each of which requires different courses of action to address.

BIOSECURITY THREATS

The NSABB committee objected to the publication of the papers due to the threat to biosecurity. It acknowledged that there would be public-health and research benefits, which is why the committee agreed that the general conclusions of the articles should be published, but not the methodological details, as they were too likely to be misused. Rather than reacting to a specific threat, the NSABB argued that "publishing these experiments in detail would provide information to some person, organization or government that would help them to develop similar mammal-adapted influenza A/H5N1 viruses for harmful purposes."[45]

It is increasingly challenging to keep redacted information secret, particularly regarding a paper that was widely discussed in the press. In addition, many people had already heard about Fouchier's research through his presentation at the influenza conference in Malta. It was also pointed out that researchers and publishers would be prime targets for hackers.[46] As scientific research is incremental, many of the mutations associated with enhanced pathogenicity or communicability in mammals were already known in the literature (one observer termed them "obvious").[47] As Kawaoka wrote in an article objecting to the NSABB position, "there is already enough information publicly available to allow someone to make a transmissible H5 HA-possessing virus."[48] The techniques Fouchier described in the Malta conference were, as he put it, "stupid"; they were well known and, while not easy, it was straightforward to let the virus naturally evolve toward ferret-to-ferret transmission.[49] An editorial in *Nature Biotechnology* compared redaction to a "cat-less bag" or a "horse-less stable."[50]

While the ability to create a new influenza strain that has the ability to transmit from mammal to mammal may be straightforward—and well within the expected capability of any nation's clandestine biological-weapons program—the publication of the sequence of a transmissible influenza nonetheless lowers the bar for a government or nonstate actor to achieve the same result. Over the last decade, the ability to synthesize long tracts of genetic material has progressed, allowing entire genes to

be synthesized from scratch. There are even companies that perform this service, though many screen for potentially problematic orders, particularly as H5N1 is a "select agent" and therefore requires special clearance. Other possibilities include performing the work undetectably with readily available equipment, or making targeted mutations of the genetic material of another influenza strain.

None of this is easy even for well-trained scientists, and there would be many technological hurdles along the way. But it will only become easier over time as the ability for individuals to manipulate biological materials grows more powerful. Some experts worried that publication of the genetic sequence would allow many more scientists around the world to participate in this work, including amateur scientists.[51] In the last decade, there has been a huge growth of citizen science, known as do-it-yourself biology (DIY bio), with amateur laboratories set up for instruction in basic biological and molecular techniques.[52] There have also been synthetic biology competitions, called iGEM, that have involved undergraduates—and, more recently, high school students and entrepreneurs—who develop new functionalities using standardized genetic parts.[53] There is no evidence that these new biologists, whether amateurs or students, are anything other than a positive development for the future of biotechnology and scientific literacy, but it is undeniable that the advanced skills required to manipulate genes are much more available. As such, if a bioterrorist wished to cause harm by producing transmissible H5N1, the barriers would be reduced by publishing the sequence.

BIOSAFETY CONCERNS

Many national-security experts and scientists objected to the work simply because they believed it was not safe, or because they thought that it might be possible to derive the same research benefit by alternative means.[54] Accidents in laboratories are usually only a problem for the laboratory worker and, potentially, close contacts, but an accident involving a highly transmissible strain of influenza could theoretically spread to become a global concern. Those with concerns about the safety of this work pointed to several laboratory accidents involving severe acute respiratory syndrome (SARS) coronavirus in China, Taiwan, and Singapore.[55] The most devastating biological laboratory accident is not generally known to the public: 1977's "seasonal influenza" is widely thought by experts to have originated in a Russian laboratory.[56] That virus was identical to a strain that had not been seen since 1957, with no hint that it had undergone any mutations over time, which suggests its origins were not in the field, but in the freezer.[57]

The work done at the University of Wisconsin and the Erasmus Medical Center was performed in biosafety level 3 (BSL-3) laboratories with some enhancements, which was determined to be appropriate by the biosafety committees at both institutions and the NSABB. Termed biosafety level 3+ (BSL-3+), these laboratories required scientists to work in a room with negative pressure, wear respirators, and shower out. Some scientists and outside experts felt that the work should have been done in biosafety level 4 (BSL-4) laboratories, which practice the highest level of biological containment.[58] BSL-4 laboratories typically have more engineered safeguards, including requiring scientists to wear full-body suits, and often require more training and inspections. However, BSL-4 laboratories are a great deal more challenging to work in and would make the work slower and more expensive.

Still, accidents happen. Not every laboratory has personnel who have been trained for years on how to work with influenza viruses and a demonstrated record of safety, as the Erasmus and Wisconsin laboratories do. Given safety concerns, should this type of research be available for anyone to

pursue? In recent years, there has been a building boom in high-containment laboratories across the globe. Countries with newly built biocontainment laboratories might insist on pursuing this type of potentially risky research.[59] While there is considerable information available on biosafety techniques and practices, there are no established international biosafety norms to build confidence that work is being undertaken in a manner that will protect public health.[60] Some felt that in the absence of such global standards, all scientific work with those influenza strains should be handled in the same way that smallpox work is handled: the virus is only allowed in two laboratories, in the United States and in Russia.[61] All experiments with the virus need to have the approval of the WHO committee on variola research.

THE BENEFITS OF KNOWLEDGE

Besides safety and security concerns, there were also objections to the work due to questions about its usefulness. Kawaoka and Fouchier both cited the importance of these mutations being available to assess new influenza strains collected in the field, but influenza surveillance is not that high-tech or timely. For some areas of the world where H5N1 strains are already endemic, it can take up to six months to receive new influenza strains, so real-time information about new mutations is a distant goal. If there is political turbulence, then the delays can be compounded or worse: an Egyptian surveillance laboratory was actually looted during the Arab Spring. Some argued that even with effective and responsive surveillance, the mutations that could give rise to a transmissible flu might be different than what emerged in the laboratory. In addition, knowledge of those mutations might not change surveillance procedures, making the research moot.[62] Others cast doubt on whether H5N1 would indeed develop those mutations, or similar ones, in the natural environment.[63] Estimates on the risk and impact of a fully transmissible H5N1 virus are based on a diverse array of expert opinions.[64]

Certainly, surveillance appears to be lacking. In March 2012, *Nature* published an analysis of animal-flu-virus monitoring, which found that there were tremendous gaps in sample collection, that surveillance was typically an ad hoc response to disease outbreaks or the result of temporary research projects, and that there is a substantial delay—typically more than three months, and, occasionally, years—before samples are placed in the public domain for other scientists to see.[65] The study also found that while avian influenza surveillance is incomplete, the monitoring of pig influenza viruses is even worse—and pigs can be co-infected with both human and avian strains, serving as influenza "mixing vessels" for new viruses that could infect humans.[66]

These debates over H5N1 influenza research—whether termed gain-of-function research or dual-use research of concern—are not new, not even to the field of influenza research. In 2000, the Centers for Disease Control and Prevention (CDC) started experiments with H5N1 strains isolated from the 1997 Hong Kong outbreak, performing "reassortment" studies to determine whether one of those influenza mixing vessels was likely to produce a human pandemic strain.[67] Virologist Albert Osterhaus of Erasmus University—one of the coauthors of the controversial Fouchier study and Fouchier's mentor—started doing similar work with H5N1 as well as H7N7, another potential pandemic strain. The importance of safety considerations became clear after the SARS laboratory accidents, which prompted the CDC to expand its review to include discussion of the appropriate safeguards with the FDA, WHO, HHS, and Nobel-laureate Joshua Lederberg before going ahead.[68] Just a month before the NSABB announced its decision on the Kawaoka and Fouchier manuscripts, a simi-

lar study led by CDC researchers was published in the journal *Virology*.[69] In contrast to the Fouchier and Kawaoka studies, however, the mutations in H5N1 did not lead to ferret infections after exposure to respiratory droplets.

How the H5N1 Research Was Published

The editors of *Science* and *Nature* agreed, in principle, with the decision to redact problematic information as the NSABB suggested, and scheduled the journal articles for publication in March 2012. However, a meeting at the WHO changed that decision. During February 16–17, the WHO convened a small group meeting, dominated by influenza scientists, that was closed to journalists and the public.[70] The group concluded that the papers should be published in their entirety, with no fundamental details redacted. This decision was made by consensus, with the exceptions of Paul Keim, the chair of the NSABB, and Anthony S. Fauci, the director of NIAID.[71] Keiji Fukuda, the top influenza official at the WHO and the meeting's chair, told journalists afterward that the biggest consideration in favor of publishing was to advance public-health efforts and scientific research. But there was another reason why it was important to publish in full: publishing a redacted form for public consumption would be difficult, and it remained essential that the details be relayed to those scientists who needed them. As Fukuda said, "Who would do it? Under what conditions would they be done? What would be the principles? Who would make those decisions? And who would make the decisions about who should get the articles?"[72]

Though there were complaints about the closed nature of the WHO meeting in Geneva, more details about the research itself were discussed at the meeting, leading some observers, including NIAID director Anthony S. Fauci, to remark that the Fouchier virus was not as dangerous as first thought and that there was "substantial clarification" about the research.[73] Fauci said there were plans to reconvene the NSABB, because "we wanted to give them the benefit of the same discussion that took place in Geneva."[74] At an American Society for Microbiology conference streamed online, Fouchier provided more details about the research, telling the audience that the viruses that were created in his laboratory were not as lethal as wild-type H5N1 and that ferrets who got sick did not die, unless the virus was deposited at high doses directly in their lower respiratory tracts. The lower levels of virus shedding, lower mortality, and difficulty in transmission seemed in line with Kawaoka's description of the viruses made in his laboratory.[75]

The NSABB met a second time from March 29–30 to read revised copies of the manuscripts and discuss the findings with the authors. The revised Fouchier manuscript included a greatly expanded description of how the virus was not lethal to ferrets when transmitted by sneezing and coughing, but only by deliberate insertion deep into their tracheas, which mirrored Kawaoka's findings.[76] The NSABB was under the impression that the virus maintained its lethality when transmissible by respiratory droplets, a misunderstanding ascribed to the brevity and tone of the original presentation of the data.[77]

In the end, the NSABB reversed its earlier stance on publication with redactions, and recommended complete publication.[78] There was unanimity recommending the publication of the Kawaoka manuscript, but the revised Fouchier manuscript was only recommended by a vote of twelve to six. Although both research projects were still considered to be dual-use research of concern, the NSABB determined that the risks of publication did not outweigh the benefits, as the data were not

"immediately enabling," given that the mutations did not confer high fatality along with mammalian transmission. Information in the controversial papers was judged to be valuable for public-health and surveillance efforts, and withholding that information was found to be problematic, as there was "concern that the United States would be perceived as redacting information with potential public health benefits and that this could undermine valuable international collaborations."[79] The NSABB emphasized that both studies were conducted under "rigorous biosafety conditions, including appropriate biosafety containment, practices, training, and occupational health programs," noting that H5N1 is a select agent and therefore subject to those controls and reviews as well.[80] The board had two additional recommendations: the U.S. government should continue to develop policies to oversee and communicate dual-use research of concern, including gain-of-function studies, and develop a mechanism to provide controlled access to sensitive scientific information that is important "to support public health, safety, and security efforts."[81]

The question of who had a need to know turned out to be more legally complicated than the NSABB first thought. The board had hoped that scientific information could be transmitted to those who had a legitimate scientific or public-health reason to need the information, regardless of their citizenship. But this was not a legal possibility. Given freedom-of-information laws that prohibit government-funded research from remaining secret, the only options would have been to either publish in full, or classify the research. The latter option would make it inaccessible to many scientists and officials with a legitimate, if not legal, need to know, and was viewed as a threat to the WHO's PIP agreement. The Netherlands pursued another option regarding the Fouchier paper, invoking export controls barring the research from being transmitted outside of the country. Export controls are generally not assigned to basic research intended for publication, which describes both the Kawaoka and Fouchier papers. However, the Dutch government argued that the Fouchier study was actually applied research, in that it was intended to inform disease surveillance and medical countermeasure development. If the United States pursued the same course of action, it could potentially isolate a great swath of biological research under the same protection, which was not seen as a productive option for biological research as a whole. For the NSABB, the fact that selective sharing with scientific experts was not a viable option tipped some of the members' opinions regarding what should be done.

By June 21, 2012, both articles were published.[82] The Kawaoka paper was published in *Science* and the Fouchier work was published in *Nature*, after waiting several weeks for the Dutch government to lift export control restrictions.[83] In March, the Dutch newspaper *Volkskrant* reported that government officials were going to deny an export license for the research in an attempt to "prevent the recipe for the new flu virus" from being shared with the world.[84] While the Netherlands, the European Union, and the United States do not place export controls on basic scientific research, the Dutch argued that given the practical benefits of the work—such as testing antiviral drugs and vaccines, benefits that Fouchier himself touted—it was applied research and thus subject to export-control restrictions.[85] Charging that the government's actions amounted to censorship, Fouchier originally planned to flout the Dutch requirement, even when threatened with six years in jail, but eventually obtained an export license.[86]

The voluntary moratorium on avian influenza transmissibility work, intended only to last for two months, formally ended after a year. When the moratorium was lifted, it became public knowledge that work similar to the Fouchier and Kawaoka studies was performed in a laboratory in China over a year before.[87] When the moratorium was lifted, it became known that Chen Hualan and colleagues at Harbin Veterinary Research Institute submitted an article to Science that apparently found similar results to the studies by Kawaoka and Fouchier.[88] Her work demonstrates that H5N1 could reassort with H1N1 to become contagious between guinea pigs, with no lethality, suggesting that H5N1 reas-

sortment could occur naturally.[89] Some scientists have reacted negatively to the publication; Lord May of Oxford, past president of the Royal Society, called it "appallingly irresponsible," citing safety concerns.[90] Given the H5N1 controversy, however, the fact that this work just became known demonstrates the limitations of knowledge about what biological research is being performed in the world, and by whom.

The U.S. Response

During the NSABB meeting on March 28, 2012, the Obama administration issued a new policy for federal agencies to oversee dual-use research of concern. The policy formalized a process for regular federal review of U.S. government–funded or –conducted research with high-consequence pathogens, identifying DURC and implementing mitigation measures.[91] While the controversial studies received federal funding, the leadership of NIH was unaware of the research and its potential implications until the manuscripts were submitted for publication; the new policy was intended to address this problem. This policy put in place regular review of U.S. government–funded or –conducted research involving a specific set of pathogens and toxins for its potential to be DURC, to "mitigate risks where appropriate," and to inform policy. Risk mitigation could involve modifying the design or conduct of the research, conducting periodic progress reviews by the agency, and determining how results will be published or otherwise communicated.

The NIH conducted its review of funded research that could be classified as DURC and found 381 extramural and 404 intramural projects using pathogens designated for special attention, of which ten extramural and no intramural projects were eventually designated as DURC projects.[92] According to the testimony of Anthony S. Fauci before the Senate Committee on Homeland Security and Governmental Affairs on April 26, 2012, the NIH determined risk mitigation steps with the researchers for these DURC cases.[93]

On February 21, 2013, the White House Office of Science and Technology Policy formally put forward the U.S. government policy for institutional oversight of life-sciences DURC for public comment, changing a few details from the earlier version released in 2012.[94]

The policy is limited to fifteen biological pathogens, including highly pathogenic avian influenza and botulinum toxin, all of which are already regulated as select agents. Scientists are asked to determine if the work on one of those agents falls into the category of DURC and could be "directly misapplied to pose a significant threat."[95] The research institution would need to form or designate a committee to review research involving DURC and appoint an institutional contact that will oversee applicable projects. The policy does not include what would happen if there is a disagreement over the mitigation plan or even the classification of DURC.[96] Also, the rules call for institutions to make their review procedures accessible to the public, but not to publish the details of cases or the minutes of the relevant committee's proceedings. This could be problematic in states with expansive freedom-of-information laws.[97]

Another set of rules released on the same day concerns how HHS will fund research projects which are "anticipated to generate HPAI (highly pathogenic avian influenza) H5N1 viruses that are transmissible among mammals by respiratory droplets."[98] HHS set out criteria for experiments to be eligible for departmental funding: the virus in question could emerge through a natural evolutionary process; the research addresses a scientific question with high significance to public health; there are no feasible alternatives to the proposed approach; biosafety and biosecurity risks can be mitigated and managed; the research will be broadly shared to realize its potential benefits to global health; and

the facilities where the research will take place will have appropriate oversight of both the conduct and communication of the research.[99] U.S. government officials stated that the two controversial studies that prompted this policy would likely have been approved, though they would have undergone this additional review.[100] The policy is limited to gain-of-function H5N1 research and does not include routine characterization of naturally derived viruses, or of gain-of-function research with other microbes.[101]

The scientists involved in the H5N1 controversies are continuing to pursue their work on the virus. Fouchier is also interested in exploring whether the same mutations produce the same results for other H5N1 viruses, and for other subtypes, including H7N7. He will also conduct similar research on SARS, as well as a newly discovered SARS-like virus.[102]

History Will Repeat Itself

The controversial papers have been published, new policies are in place in the United States to screen for dual-use science involving select agents, and H5N1 transmissibility research has resumed. With the increasing numbers of H7N9 infections occurring in China, it is likely that research on that strain is also underway. With the exception of the Dutch export-control restrictions and the WHO biosafety guidance, there has been no change in the way that research is funded or practiced in other nations. In the future, influenza transmissibility research will no doubt be conducted and communicated differently from the manner that precipitated the H5N1 dual-use research controversy. However, even though this particular dual-use crisis is over, there will be more examples of dual-use research in the coming years that draw international concern. Concern may be focused on H5N1; on the new influenza virus, H7N9; or another pathogen altogether. Given the pace of research at the intersection of engineering and biotechnology, it is possible that the next alarming development in biotechnology may stem from something that is not a pathogen at all.

Whenever that next DURC event occurs, it is likely that the debate over what should be done will begin anew. In other words, the resolution of the H5N1 controversy did not settle the underlying issues that H5N1-research opponents had with the work. Most proponents and opponents of the research were basing their opinions on the same information. However, the weights ascribed to those variables—such as the value of particular experiments to public health and disease control, the safety of the experiments and their replication, and the importance of the open exchange of research results to public health and innovation—lead to vastly different conclusions. It is hard to know, without extraordinary insight into the minds, plans, and skill levels of would-be terrorists, just how useful a particular scientific insight or series of papers is likely to be.[103] Even though the methods sections of scientific papers exist to enable replication of the work, these sections are not nearly as descriptive as a recipe in a cookbook; a great deal of knowledge is assumed, not explained. A plethora of high-level meetings of experts, more than a year of discussion, dozens of articles, and a government-review policy did not change some observers' minds about the value of the research, and these factors are not likely to do so in the future. Next time, the balance of these equations will likely be tipped one way or another by the specifics of the research in question, the researchers involved, the urgency of the threat that the research is trying to address, and assessment of the danger that the information could be applied toward a biological weapon. These qualities are difficult to predict, particularly in global, diversified fields like biological research and biotechnology.

This is not to say that the H5N1 controversy had no effect on how dual-use research will be dealt with next time, or that there are no lessons to be learned from the experience. Despite the uncertainty over the nature of the next dual-use research event, there are steps that scientists, journal editors, funders, research institutions, and policymakers should take from H5N1 in order to both reduce concerns and aid the public discussion of dual-use science. First, if research is "worth the risk," as the H5N1 research was decided to be by NSABB, then the results need to be used productively to justify the risk. Second, it would be helpful to increase awareness of the dual-use issue among scientists and

their funders, publishers, and research-institution colleagues. Finally, safety should be a top priority for all scientists and standards should be enacted for exceptionally consequential research. No matter what is created in the laboratory, and no matter where public and expert opinion falls on the value of the work, the result will be less dangerous if it is properly contained.

IF THE RESEARCH IS WORTH DOING, APPLY THE RESULTS

In the H5N1 dual-use research controversy, one result in particular was a point of contention. Was the information on the mutations that led to mammalian transmissibility important for public-health surveillance, or did knowledge of those mutations not matter? In reality, the mutations found in the laboratory have little impact on public-health surveillance due to inadequate collection and analysis of samples, and the time delay in acquiring samples to be analyzed. However, if the information could be applied, then it might be useful. As Ruth Faden, a bioethicist at Johns Hopkins University and one of the contributors to the Fink Report put it, if the research goes forward in a dual-use case, there is the moral obligation to ensure that the results of the research are used for global health. Although "current surveillance systems may not be sophisticated enough to make optimal use of these findings, that is an argument for investing in enhanced surveillance and molecular diagnostics, rather than withholding potentially valuable information."[104] Earlier detection of an influenza pandemic strain could result in vaccine being available weeks, or months, earlier during a pandemic.

BE AWARE OF DUAL-USE AND BIOSAFETY RISKS

Scientists need to know their work may lead to dual-use dilemmas and could spark a debate over whether their work is beneficial to society. Gerald L. Epstein, who has written extensively about the governance of dual-use research, argues that "when scientists are asked whether they have addressed the potential that their research might be misused to inflict deliberate harm, the answer must never be, 'we can't afford to constrain science' or 'you know, we never thought about that.'"[105] If scientists are prepared for the issue to arise, they may be able to mitigate the risk of misuse and prevent misunderstandings over why the research was undertaken in the first place.

Reaching every scientist may seem like an impossible task, but the life sciences are not, generally, performed in isolation; there are almost always colleagues, institutions, funders, journal editors, and others who share some knowledge of the work and its aims. Even amateur scientists discuss their work and learn from others, whether in community laboratories or in online forums. To date, the efforts that have been made to increase awareness of dual-use issues need to be expanded, so that even if the next dual-use event does not center on a scientific field that has gone "on alert" like the influenza community, the relevant scientific field has some awareness of the issues. It could be that the next dual-use dilemma arises in synthetic biology, or HIV, or some subset of the biosciences that has not experienced this issue as part of its work.

Journal editors can help raise awareness of dual-use research and biosafety by requiring published papers to include detailed explanations of why the work was undertaken despite the potential risks, as well as detailed safety information. One of the NSABB recommendations given to Fouchier and Kawaoka was to include a great deal more information than usual about why the work was performed, why it was important for public health, and what safety precautions were taken. Given the ability to publish more information online than might be available in print, there is no longer any excuse to

withhold a full listing of all the scientific and safety steps that were taken, thereby encouraging those methods to be adopted. It is currently standard practice that research involving animals and human subjects includes a statement that the study was reviewed by the appropriate institutional committee; it would help if research was described as being evaluated by the research institution's biosafety committee and to describe the safety precautions taken, such as use of vaccines, respirators, or personal protective equipment.[106]

INCREASE BIOSAFETY STANDARDS WORLDWIDE

Most experts, including the NSABB, agreed that the work performed in Kawaoka's and Fouchier's laboratories was done with extraordinary attention to biological safety. While some argued that the work should not have been done at BSL-3+ but in a BSL-4 laboratory, these are relatively small distinctions and a matter of slight degree, particularly when applied to experienced scientists who are thoroughly trained in working with influenza. Yet, once the work is published and could be replicated by others without the same training, what guarantee is there that the same attention to biosafety will be present?[107] While most laboratory accidents are limited to the laboratory worker and perhaps a few close contacts, a contagious pathogen like influenza escaping laboratory containment has the potential to spark a pandemic.

The WHO recognized the potential for H5N1 research to proliferate unsafely, and released guidance for researchers interested in studying H5N1 transmission.[108] The WHO recommended that national authorities identify, approve, and oversee the laboratories which may study these strains and that "facilities that are NOT able to identify and appropriately control the risks associated with these agents REFRAIN from working with them."[109] The WHO also stated that laboratories that work with these strains should be able to adhere to recommended biosafety levels of containment and to a biorisk-management standard like CWA 15793, which is an expert best-practices document—termed a workshop agreement—developed through the European Committee for Standardization (*Comité Européen de Normalisation* or CEN). While institutions around the world may choose to adopt this "Good Housekeeping" standard for biosafety, it is a voluntary, nonbinding standard, and it is set to expire in 2014.

In the coming years, the risks will change, but even the most dangerous pathogen cannot cause significant harm to populations if it does not escape containment. The WHO guidance for H5N1 is appropriate, but technical guidance from the WHO, professional associations, or national biosafety systems will not provide confidence that potentially pandemic-causing work is being performed safely on a global scale.

Internationally, biosafety is the WHO's responsibility more than that of any other international organization or instrument. The WHO publishes technical guidance for research institutions and laboratory workers on how to perform a risk assessment in the laboratory and how to safely perform research on a variety of pathogens. In 2005, the World Health Assembly, which governs WHO member states, issued WHA Resolution 58.29, "Enhancement of Laboratory Biosafety," which acknowledges that the release of certain pathogens could have global ramifications and aims to prevent outbreaks through authorization of the WHO to help member states achieve high levels of biosafety.

For other international instruments, biosafety is inferred or is tangential; it is not the principal aim of the agreement. For example, the Convention on the Prohibition of the Development, Production,

and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction (more commonly known as the BWC) has often discussed biosafety as an important treaty component, including issuing shared statements about preventing unauthorized access to pathogens, safe handling of pathogens to protect people and the environment, and the importance of biosafety training, but the primary aim of the BWC is to prevent the development and use of biological weapons. The International Health Regulations requires all WHO member nations to increase their laboratory capacity to be able to detect public-health events of international concern; however, while biosafety is an inferred component of laboratory capacity, it is not an explicit part of the regulations.

Though the available technical guidance is excellent, there is a lack of guidance for developing and maintaining a *national* biosafety system that oversees biosafety practices, provides training, and records laboratory-acquired infections. Without national-level standards for biosafety and some interest in making sure that research institutions that perform potentially high-consequence research adhere to those standards, there will remain insufficient financial or regulatory incentive to commit the resources required to achieve high levels of biosafety in individual laboratories and institutions. Without support from the top, it is difficult to sustain investment at the bottom.

ENGAGE THE PUBLIC

When the moratorium on gain-of-function H5N1 was announced, it deliberately mirrored the last time science deliberately paused an area of research: the 1970's, when the field of recombinant DNA biology was new and the potential safety concerns of autonomously replicating bacterial plasmids were not yet clear. In a letter published in *Science* in 1974, leading scientists and Nobel laureates recommended that certain types of recombinant DNA experiments—those with toxins, oncogenic viruses, and antibiotic resistance—be off limits until their safety could be evaluated and assessed in a conference held a year later.[110] That conference was held at Asilomar, California in February, 1975, and was attended by scientists, government officials, and members of the press, and led to a lifting of the moratorium in 1976, as well as the creation of a new regulatory system for recombinant DNA work funded by the U.S. government. The regulatory system is still in place, but now many experiments are exempt, given increased knowledge of the safety of the field. Efforts of the scientists to self-govern may well have forestalled restrictive national legislation.[111] Asilomar now symbolizes scientists' attention to the public's concerns, as well as the scientific community's capacity to self-govern.

The backdrop of the H5N1 controversy is quite different than the 1970s DNA debate in myriad ways: the global pervasiveness of biotechnologies and expansion of biological sciences fields; the clear pandemic threat of emerging influenza strains; the perception that dual-use concerns are a rich-country phenomenon and a tool to keep profitable biotechnologies out of reach for poor countries; the proliferation of more jaundiced views about regulation, engaging the public, and science; and increased worries about bioterrorism. Scientists today may fear the introduction of regulation that is not commensurate with the risks—such as the genetically modified organism (GMO) bans in Europe—which requires a strict regulatory structure for scientists in the name of biosafety, irrespective of actual biological safety risks. Yet, while Asilomar is an imperfect analogy to dual-use concerns today, the attention that was paid to *why* and *how* the scientific work was being done is still instructive. The next time there is a dual-use controversy, information about why the work is important and the safety precautions taken should be easily available for the public to consider. It may be that despite

the information—or because of it—the decision is made that the risks outweigh the benefits and some scientific information or technologies should not be pursued. However, in an information vacuum, or in the face of a laboratory-created disaster, that decision would be guaranteed.

Conclusion

Yoshihiro Kawaoka's and Ron Fouchier's H5N1 gain-of-function research sparked controversy for multiple reasons, chief among them the possibility that the research could be misapplied for nefarious purposes, and that a biosafety breach could result in a pandemic. The potential benefits to science and public health were ultimately determined to be worth the risks of publication, though there is still disagreement about whether that was the right decision and whether this line of research should continue.

The debate over H5N1 will certainly be repeated in future dual-use controversies; the dual-use and safety concerns of this and other types of biological research are likely to increase as more consequential research is performed in laboratories all over the world and by relative newcomers to research. The H5N1 case therefore points to steps that should now be taken by scientists, research directors, publishers, and policymakers that would promote a reasonable consideration of the risks and benefits of dual-use research: first, scientists should be more aware of the potential for dual-use concerns in their work, and be prepared to explain the value of the work and how risks were mitigated. Second, if the decision is made to publish the work, the results should be beneficial—in the H5N1 case, those results should inform disease surveillance. Finally, biosafety should be a top priority, and there should be global standards for biosafety to provide reassurance that no matter where consequential work is being performed, there is a monitoring and training system in place, and that infectious creations, no matter how potentially dangerous, are properly contained.

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