Four

Avian Flu Controversies: Lessons for Scientists to Learn from the Public Debate over Mutant H5N1

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Abstract

The way in which scientists communicate their work to the general public can have a profound impact on how it is perceived and regulated. As such, there are three specific lessons that both scientists and policymakers should learn from the recent controversy over two lab-engineered strains of H5N1:

1. Scientists must actively engage with governments in the debate over how to regulate dual use research
2. A diverse group of scientists, policymakers, and other experts should consider the impact of the research in question
3. Scientists must responsibly and clearly convey information to the public

This report further analyzes the danger posed by these new flu strains and recommends that at least one strain be consigned to Bio Safety Level-4 facilities until future data proves otherwise. The most important message, however, is that scientists should address questions generated by controversial research in a manner that is proactive, broad, and comprehensive.

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INTRODUCTION

The last several decades have witnessed a drastic acceleration in the rate of biotechnology innovation. From new processes, techniques, and discoveries to market-ready products, this trend has been fundamentally positive. However, some of these advances are accompanied by challenges that are not strictly scientific. Certain research (e.g. nuclear power) can give rise to issues that transcend a specific discipline and have profoundly positive and negative implications for society. As with past controversial research projects it is critically important that scientists themselves recognize the potential effects of their work on society and actively involve themselves in the public discussion. Scientists who design and implement sociotechnical systems need to be aware of, and participate in conversations about, the consequences of such systems. In the case of the recently-disclosed strains of mutant H5N1 virus (Enserink 2011; Grady and McNeil Jr 2011; Butler 2011), the manner in which the scientific community addresses these questions will have massive impacts on funding, public opinion, and governmental regulation regarding new research. Moreover, the controversy and response to these new strains has highlighted severe shortcomings within the science and science policy communities that are nevertheless fixable through both informal and policy-based channels.

Science and technology have been subject to civil law since ancient times. Often cited as one of the first artifacts of human government, Hammurabi's code prescribed death for a builder whose faulty craftsmanship caused the collapse of a building and resulted in death of the owner (King 2008). Compared to civil engineering, the various disciplines of biotechnology are quite new and therefore the rules and regulations surrounding them are still developing. During this period of nascent policy-making, active and clear participation of scientists is essential to ensure an informed discussion.

This is not meant to imply that there has been no effort to address controversial biotechnology research previously. The early 1960's and 70's saw the emergence of powerful molecular biology technologies and techniques. As technological capabilities grew, so did concerns about what new and terrible experiments could be performed. It was in this climate that molecular biologists themselves took the initiative to organize a meeting in February of 1975 at Asilomar in California to self-regulate their field and lay a framework for what would be allowed and what would not, including absolute and conditional moratoriums on a variety of research (Berg et al. 1975; Berg and Singer 1995). Furthermore, participants actively sought to educate the public about their research and its implications, inviting people outside of the molecular biology community and even those foreign to science altogether. By reviewing their own work and demonstrating a willingness to rigorously and responsibly regulate it, scientists quelled public fears and largely maintained their ability to govern their field under only general federal regulations (such as the BSL system that will be discussed later).

As new issues in these fields arise, it will become increasingly important for civil leaders and scientists to collaborate to formulate policies that are responsible, workable, and balanced between research and public safety interests. Using the recent controversy surrounding two strains of lab-generated H5N1 virus, I will show that it is critical for stakeholders – especially scientists – to address these questions in a manner that is proactive, broad, and comprehensive.

BACKGROUND

The H5N1 strain of influenza typically infects fowl (thus the vernacular "bird flu" or "avian flu"), but can occasionally make the jump to mammals and infect humans. When it does, the virus is particularly deadly, boasting an official mortality rate of 59 percent. Although that number is likely high and there is some debate surrounding it, most scientists agree that an H5N1 pandemic would far exceed official numbers assumed in preparedness plans and even top the 2.5 percent mortality rate of the 1918 flu epidemic (Butler 2012d; Cohen 2012a). Humans contract the disease through contact with poultry. Therefore, outbreaks were previously dealt with by culling entire populations of birds. Hong Kong, for instance, killed every domestic fowl within the province in 1997 and in December 2011 sacrificed twenty thousand more amid another H5N1 scare ("Hong Kong Avian Flu Outbreak in 1997" 2012; Liu and Khan 2011). Outbreaks accompanied by human deaths have been reported across Asia – from Egypt to Vietnam – and the virus is endemic (stably present) in many wild bird populations ("H5N1 Avian Flu (H5N1 Bird Flu)" 2012; Butler 2012b). Until recently, the fact that the disease cannot make the jump to humans very effectively appeared to be our best defense.

That assumption was disproven in September of 2011. At a conference in Malta, Dutch researcher Ron Fouchier announced that his lab had produced a strain of H5N1 that spread readily among mammals (Harmon 2011). In a study funded by the United States National Institutes of Health (NIH), Fouchier's group from Erasmus Medical Center in Rotterdam found five mutations that would allow the virus to become "airborne," spreading between ferrets[i] just as regular seasonal flu strains do among humans. Moreover, Fouchier's group originally claimed[ii] that those mutations did not compromise any of the strain's virility. Independently, Yoshihiro Kawaoka's lab at the University of Wisconsin-Madison (UW) found another set of four mutations that would enable ferret-to-ferret spreading. The UW researchers, however, found that their new strain was not as potent as wild-type H5N1 and was susceptible to antiviral treatments (Young 2012).

In December as both groups were poised to publish their papers in *Nature* and *Science*, respectively, the U.S. National Science Advisory Board for Biosecurity

(NSABB)[iii] recommended that certain parts of those reports be withheld, an action unprecedented in the board's 8-year history. The NSABB was concerned with dual use issues – that is, both positive and potentially negative applications of research – and worried that full disclosure of the types and locations of the mutations could give terrorists, rogue nations, or malevolent individuals the means for unleashing a doomsday scenario straight out of Stephen King's *The Stand*.

While some in the scientific community welcomed the NSABB's recommendations, the prevalent (or at least louder) sentiment from scientists was that the papers should be published without any restriction (Butler 2012b; Editorial Board 2012; Fouchier et al. 2012; Butler 2012c; Kawaoka 2012). Others expressed outrage over the fact that scientists would create something so dangerous. As a result, many called for stricter oversight of research with dual use issues. *The New York Times* ran a scathing editorial, dubbing the work "an engineered doomsday (Editorial Board 2012)." At a World Health Organization (WHO) meeting in February 2012, 22 flu and public health experts threw the WHO's global weight behind the publish-in-full cause (Grady 2012a; Cohen 2012b), but also reacted to the growing firestorm of criticism in the popular media by pledging to observe a 60-day moratorium on H5N1 gain of function research (Butler 2012a). At the very least, the move signaled that the scientific community was not deaf to the concerns of the general public.

After reviewing the manuscripts at the recommendation of the NIH, the NSABB reversed itself and voted to allow full publication of both papers (Butler and Ledford 2012). Both papers have now been published and virologists around the globe are emerging from their self-imposed moratorium on H5N1 research (Malakoff 2012b). Nevertheless the issue remains contentious within the scientific and policy communities (Malakoff 2012a). Even as events unfold, it is important to pause to try and glean what lessons we can learn about how scientists can better share their work with regulatory agencies, policymakers, and the general public.

DISCUSSION

Civic Engagement

Although a rare measure, the moratorium sent the message to the public and policymakers that scientists were cognizant of the risks associated with their research and willing to take necessary measures to responsibly mitigate them. Moreover, it called to mind the actions of scientists at Asilomar who, sensitive to civil and popular concerns over their research, took similar steps nearly four decades ago. If H5N1 researchers (and any other pathologists interested in conducting gain of function studies) wish to avoid regulatory interference by governments across the globe, they must follow Asilomar's

example and act now to show the public their resolve to conduct their research in a manner that is both responsible and secure.

Currently, the NIH is formulating a new set of guidelines to evaluate H5N1 gain of function studies before they are funded. Two critical questions will be whether 1) the experiments have "high significance to public health" and 2) whether "feasible alternative methods" exist instead. If the proposed research fails either of these tests, it will trigger a more stringent review. While there is still more than a little controversy regarding benchmarks and thresholds for approval, the evaluation criteria are an excellent first step for moving from a reactionary stance to a proactive one (Malakoff 2012a). In fact, the NIH may do well to consider instituting a similar rubric for other pathogens with dual use potential.

Breadth of Expertise

Although no other government took such an active role in the Kawaoka and Fouchier papers, the NSABB's recommendation to partially censor the methods and conclusions of the controversial papers was still within its jurisdiction. Nevertheless, it is not in the U.S.' interest to be the sole actor on this issue (even though both projects were funded by the NIH). The research in question was conducted on two different continents and has the potential to help or harm public health across the globe. Governments across the world, especially those in Southeast Asia and the Middle East (the regions most at risk for outbreaks) should join the discussion about what to do with Fouchier and Kawaoka's research. Recently, Malaysia and Indonesia (two such "at-risk" countries) have weighed in, expressing support for gain-of-function studies (studies where researchers make a virus, pathogen, etc. more potent in order to better understand and prepare for what may happen in nature). They have called for greater effort toward studies more focused on strains that already exist within their borders or on work that would directly aid vaccine and drug development (Malakoff 2012b). This is valuable feedback, and other nations with equally large stakes need to assert themselves similarly.

The response must also be broad, not only in number of actors, but in the backgrounds of those involved as well. Asilomar brought together over 140 stakeholders to discuss the issue, including doctors, lawyers, policymakers, and media members. In contrast, the February 2012 WHO summit convened a panel comprised entirely of 22 flu researchers. In light of its makeup, the panel's recommendation to publish in full was unsurprising. The question of what to do with these new strains of H5N1 is incredibly complex. Weighing the risks and benefits of any decision requires input from a diverse set of backgrounds: the engineers who design the biosafety containment systems, the public health officials who track the disease's spread in populations, and many others. Needless to say, this is not an issue that can fully be solved by flu researchers alone.

Public Engagement

When speaking to "lay" people or the general public, scientists must be mindful of how their work will be perceived and offer complete, substantive arguments to support their positions. In the wake of the NSABB decision recommending redaction, many researchers denounced the move on the basis of "freedom of speech" and "don't censor science."(Palese 2012) These arguments are specious at best. Science for the sake of science may be a noble idea in a vacuum, but when measured against the risks of a project that involves creating a deadly pathogen, it is far from compelling. Those in favor of redaction are not anti-science or anti-free speech and to brand them as such is reckless and counterproductive. Embracing adversarial tactics will only invite more of the same from opponents and risk politicizing the questions at hand – something scientists have generally been loath to do (Keller 2009). By replacing hollow clichés with a substantive analysis of the costs and benefits of H5N1 mutation research, scientists can help steer the conversation towards an objective, reasoned examination of the issue at hand.

While it should go without saying, scientists should hold truth and accuracy above all else. It seems that a great deal of confusion (and possibly even the original NSABB ruling recommending redaction[iv]) has stemmed from Ron Fouchier's public statements concerning the potency of his lab's mutant H5N1 strain. Preliminary reports indicated that the Erasmus virus maintained the potency of wild type H5N1 (Enserink 2011; Butler 2011). Recently, however, the researchers and oversight boards have switched tracks, asserting that it's not so deadly, after all (Young 2012; McNeil Jr 2012). Fouchier's actions – intentional or not – directly fueled what one scientist called a "gross and pervasive misunderstanding" about the nature of the new viruses (Grady 2012b).

Containment

While the NSABB's self-reversal and recommendation that the papers be published in full marks the end of the debate over disclosure ("Findings and Recommendations" 2012), it does not mean the conversation about what to do with these new flu strains in completely over. Currently, work in the Erasmus and Wisconsin labs is done in what are called Bio-Safety Level 3 Enhanced facilities with containment measures that include decontamination of lab wear and dedicated air and power systems to ensure that the virus does not escape the laboratory. The work is assumed to pose "high individual, low community risk" and the pathogen can be treated with available drugs or vaccines (Centers for Disease Control 2009). The Wisconsin strain falls under this category. The Erasmus strain, at least according to preliminary reports, merits further examination.

A good comparison for handling and containment of the Rotterdam virus is smallpox – a *variola* type virus (similar to chickenpox) that was officially eradicated in 1980 after an extensive worldwide vaccination campaign. Neither virus is believed to exist in nature, but both are quite contagious and quite deadly. Table 1 compares the risks

and regulations associated with smallpox and Fouchier's virus, as well as "natural" H5N1 and the UW strain.

Table 1: Comparison between Smallpox, H5N1, and H5N1 variants.

Virus	Smallpox	H5N1	H5N1-Kawaoka	H5N1-Fouchier[v]
Human Mortality	~20%	Officially 59%[vi]	Unknown, suggested lower	Unknown, suggested similar to H5N1
Contagious?	Yes, airborne	No	Yes, airborne	Yes, airborne
Treatment available?	Vaccine	Only marginally effective	Suggested effective	Suggested resistant
Present in Nature?	No	Yes	No	No, but isolated single mutations observed
BSL classification	BSL-4	BSL-3 Enhanced	BSL-3 Enhanced	BSL-3 Enhanced

As can be seen from Table 1, Fouchier's H5N1 shares many of the same characteristics as smallpox, and in some instances is even more dangerous. Since smallpox is considered a BSL-4 agent based on its transmissibility and mortality,[vii] it would behoove authorities to classify the Erasmus strain in the same way, at least until the data shows otherwise. Pathogens with close antigenic relationships to known BSL-4 agents are typically treated as BSL-4 agents until proven safe (Centers for Disease Control 2009); it makes sense to exercise similar caution for pathogens that are functionally, rather than structurally, similar. Although a higher BSL level will undoubtedly reduce the number of lab and researchers that are able to study the virus, it is initially necessary to ensure public safety and by no means permanent. Just as the Asilomar conference set strict limits on molecular biology research with the understanding that the limits would be relaxed when it was shown to be safe to do so, flu researchers should voluntarily adopt a similar policy.

CONCLUSION

We can expect that the pace of innovation – in both biotechnology and other fields – will only quicken and that controversies similar to the ones involving Ron Fouchier and Yoshihiro Kawaoka's lab-produced flu viruses will become more frequent. It is therefore critical that scientists understand the need to work with the general public and experts from other disciplines to allay fears over perceived threats and mitigate risks from real ones. An effective strategy is one that:

1. Proactively engages the public and takes a leadership role in determining rules and regulations governing potentially dual-use research.
2. Broadly involves a diverse group of scientists, policymakers, and other experts to consider the impact of the research in question across many disciplines.
3. Is measured, responsible, and clear in the information that it conveys to the public.

The discourse surrounding the recently disclosed mutant strains of H5N1 met some of these criteria and fell well short regarding others. Furthermore, researchers should employ precautionary principals and treat all new gain-of-function viruses as BSL-4 pathogens until it can be proven otherwise. Nevertheless, scientists can learn from this debate and move forward to work positively with civil leaders to create policy that is conducive to innovative research, sensitive to public concerns, and protective of the public good.

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[i] Ferrets are a popular animal for flu studies. They are susceptible for the human virus via the same cellular receptors and are widely accepted as a useful non-rodent model. Of course, ferrets, like any model, have their limits. In one instance a ferret study set off what turned out to be false concern about a seasonal H1N1 strain in 2009.

[ii] I say claimed because early reports out of Erasmus were that the virus was still fully potent. In later accounts however, the researchers have claimed this is not the case.

[iii] The NSABB is an advisory body within the department of Health and Human Services formed to consult with the government on matters involving biotechnology and biosecurity. The 23-member voting body is made up mostly of experts from academia (there are also several *ex-oficio* members from various government agencies). Although the board has the power to recommend things, they lack any real ability to enforce those recommendations.

[iv] The NSABB said they reconsidered and eventually voted in favor of publication for both papers after they saw new information showing the virus to be less potent.

[v] It must be noted that this table uses Fouchier's initial statements regarding the potency of the new virus strain as a "worst case scenario" for the Erasmus strain.

[vi] Most experts also admit that this number is likely high due to underreporting of cases where the patient falls ill but recovers. How high, however, remains an important point of contention.

[vii] From the CDC regulations describing a BSL-4 pathogen: "Biosafety Level 4 is required for work with dangerous and exotic agents that pose a high individual risk of aerosol-transmitted laboratory infections and life-threatening disease that is frequently fatal, for which there are no vaccines or treatments, or a related agent with unknown risk of transmission."