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H5N1 infects the biosecurity debate

Governments and life scientists are waking up to the problem of dual-use research

Philip Hunter

For many years, a debate has simmered about the possible control or censorship of dual-use research in biomedicine in an attempt to prevent the nefarious use of biological material or information. The debate was finally brought to the boil this year by two papers on genetically engineered versions of the avian H5N1 flu virus. The initial discussion was about whether the publication of research that could be abused by terrorists or criminals should be restricted, and if so, to what extent, how and by whom. This debate in turn has teased out further issues, such as how to assess and manage dual-use risks in the first place, and whether imposing any form of censorship on publication is counterproductive, in so far as it constrains the development of suitable countermeasures such as vaccines. Although no consensus has been reached, there is at least a general feeling that the two papers have brought matters to a head and have forced governments, funding bodies, scientists and journals to finally confront the problem after many years of discussion.

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The two papers in question both describe a mutated version of the H5N1 virus that has gained transmissibility between mammals through airborne droplets, such as influenza in humans. The crucial aspect of the research that triggered the dual-use concerns is that 'wild-type' avian H5N1 has an even greater mortality than the infamous Spanish flu, which itself killed more people, over the winters of 1918 and 1919, than in the First World War. Although the Spanish flu killed 5–10% of those infected [1], H5N1 has had a higher than 50% fatality rate among the relatively small number of people who have contracted the virus through direct contact with diseased birds. Even if these figures might overstate the virulence of H5N1—as they omit undetected milder cases and because H5N1 might become less virulent once it adapts to spreading among humans—the high mortality rates so far explain why the two papers have caused so much alarm. One of the papers, written by a team comprised of researchers from Japan and the USA, headed by Yoshihiro Kawaoka at the University of Wisconsin–Madison, was published online by *Nature* early in May [2]. The other paper, from a Dutch team led by Ron Fouchier at the Erasmus Medical Center in Rotterdam, was submitted to *Science*, and the journal was on the verge of publishing it at the time of writing.

In both cases, it was the small number of mutations that the teams found to be necessary for the virus to gain airborne transmission between mammals that caused such concern. Fouchier and his team found that just five genetic modifications enabled the virus to pass between ferrets, which is the best known animal model for assessing whether the virus has the potential to spread between humans. Kawaoka's team reported similar findings, but their work raised fewer concerns because they started out with a non-lethal variant of the virus.

Both papers were assessed by the US National Science Advisory Board for Biosecurity (NSABB). The NSABB was set up in response to the US anthrax attacks of 2001, when letters laced with the pathogen killed five people and infected more than a dozen others. The committee's role is to provide advice, guidance and leadership regarding biosecurity oversight of dual-use research. Since its inception, the NSABB has been asked to review only six papers, including two in 2005 that described the reconstruction of the 1918 influenza virus. In that case, the board recommended that the papers simply be amended to spell out the public health benefits of the research.

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As such, the NSABB's recommendation on 20 December 2011 to not publish the two H5N1 papers in full was unprecedented. Moreover, some saw it as an attempt by the NSABB to extend its role to the international stage, given that the journal *Nature* is actually based in the UK. The board stated that although the general conclusions could be published, the papers, then under review at *Nature* and *Science*, should not include "the methodological and other details that could enable replication of the experiments by those who would seek to do harm" (http://www.nih.gov/news/health/dec2011/od-20.htm).

This led to three months of agonized and intense debate involving the NSABB, the US government, the WHO and the journals themselves. At the end of March 2012, the NSABB essentially reversed its position and withdrew its opposition to

publication, having reviewed revised versions of both papers. Three weeks later, on 20 April, Francis Collins, Director of the National Institutes of Health, made a statement to the effect that the US government had formally accepted the NSABB's recommendation to endorse publication. The British journal *Nature*, meanwhile, made its own decision to proceed with publication of the Kawaoka paper [2].

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Yet the publication of the *Science* paper was still pending, as it requires an export license from the Dutch government for the publication of work involving methods with dual-use applications, which has been withheld. At first, Fouchier said he was prepared to defy his government and publish in the US journal without seeking the export permit, but the potential repercussions for his colleagues dissuaded him. "[A]ll authors and the Boards of Directors of our universities would have to agree also, as they may end up in prison as well, and I cannot take that responsibility alone," he explained. Instead, Fouchier decided to apply for the export license after meeting his co-authors, the board of the Erasmus Medical Centre and lawyers. However, their application also disputed the need for a license and asserted that the techniques used were legal, setting a precedent that could be used by the Dutch government in future cases. Fouchier insists he is still opposed to the requirement for a license, which he says would set a terrible precedent for infectious disease research in Europe. "By following this parallel track, we hope to publish the manuscripts without further delays," Fouchier explained in late April. "At the same time, we will continue quibbling with the Dutch Government about whether this legislation applies to manuscripts like ours."

However, the export license is only a small part of the larger debate about responsibility for and control of dual-use research. Although these discussions are new to many molecular biologists, the nuclear physics community has much experience of dual-use and even classified research. Methods of isotope separation, for instance, have various medical applications for both diagnosis and treatment, including radiotherapy for cancer. However, they can also be used for enriching the uranium isotopes needed to construct an atomic bomb. Because of this long history of dealing with dual-use work in other areas, both *Nature* and *Science* already had processes in place for these types of paper and insist that they took great care to assess the risks. "*Nature* did its own

biosecurity checks on this paper," confirmed Philip Campbell, the journal's Editor-in-Chief, referring to the Kawaoka work. "These were firmly in favour of publication," he added, "so the NSABB's initial stance was not in accordance with all the advice we received."

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Although the NSABB has attracted criticism for its initial position, especially in the light of its subsequent change of mind, it has received support from the publishing world, including from Lynn Enquist, Editor-in-Chief of the *Journal of Virology*. "I have always believed that science is best done in the open with full disclosure, but these H5N1 manuscripts were the first that gave me pause," she said. "My concerns from the beginning on these H5N1 manuscripts centered on the fact that these experiments were of concern, by definition, since they changed the transmission mode of a zoonotic virus from faecal/oral to aerosol/respiratory."

Enquist went on to argue that such experiments of concern should always be evaluated for risks and benefits from the outset of the research, and not just during a journal's editorial and peer review process. "They should not have proceeded to the point of being completed, submitted to high-end journals and then reviewed for biosafety and biosecurity issues by editors or the NSABB. The process was flawed." This view is shared by forensic biologist Randall Murch, who worked as a special agent on counterterrorism for the FBI, and who is now Associate Director of Research Program Development, National Capital Region, at Virginia Tech in the USA, as well as a member of the NSABB. "There are many valuable lessons to be learned from the events and conditions surrounding the controversy over publication of the Kawaoka and Fouchier papers," he said. "Perhaps the most important one is that to anticipate and minimize the impacts and risks associated with research that involves or could involve dual-use research, thoughtful, balanced and well-crafted policies and processes should be in place before the fact, not after the fact."

One important lesson that is now being enshrined in US policy is that restricted publication is impossible. A paper must either be published in full and made available to everyone—providing they subscribe to the relevant journal—or it must be withheld completely. One idea, initially proposed as a compromise by some journals, was to have a restricted list of scientists and centres allowed to see the publication, in order to minimize the risk of abuse. This is already done in the world of computer security, in which new threats are first reported to a few groups with the expertise to develop a fix, before being released to the wider IT community. The idea originally won some support from *Science*. "I can imagine ways of restricting circulation providing the numbers are small," commented Bruce Alberts, the journal's Editor-in-Chief. "Might one lab in Indonesia, for example, be enough to give the nation the mutant monitoring capacity it needs?"

However, Peter Jerram, CEO of the publisher PLoS (Public Library of Science) dismissed this idea, arguing that journals themselves should be the arbiters of publication and distribution of dual-use research. "Journal editors are keenly aware of responsible publication standards and are best suited to address security issues regarding sensitive research," he said. "We do not think that a restricted list is likely to achieve any level of security that cannot be provided by the type of responsible publication practices we have outlined."

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Philip Campbell commented that *Nature* had given some thought to the idea of controlling the circulation of dual-use papers, and establishing a committee to advise on its distribution. "But the more we thought about the criteria this committee would have to act upon, in terms of who should be eligible, the more we realized it was fundamentally impossible," he said. "You simply cannot predict who will make use of biological information." Indeed, according to Murch, the NSABB had failed to consider the legal implications of its initial stance over the two papers: "It thought it had three options: full publication, partial publication and no publication. But, closer analysis of certain existing US laws took the partial publication option off the table."

Given that restricted publication seems to be impossible, there is still the question of who decides whether to block something completely from being published. Howard Bauchner, Editor-in-Chief of the *Journal of the American Medical Association*, thinks that the situation, in which a single US committee attempts to impose its views on journals around the world, is unsustainable. "As publishing is no longer landlocked by country, the process of reviewing these papers, and whether or not [the decisions] are binding, should be sorted out before the next case," Bauchner said. "Perhaps WHO would be more acceptable."

But these particular cases of the engineered H5N1 virus also highlight how decisions can change as a situation unfolds and more information becomes available. A key point in the NSABB's reversal was that none of the ferrets infected by the airborne virus died. "In the first version of the manuscript that was reviewed by the NSABB, this information was included but overlooked, perhaps because we did not dedicate a specific display item to it because the manuscript is about transmission, not about virulence," Fouchier explained. "We also provided information on the fact that when the virus was applied at a high dose directly into the lower respiratory tract of ferrets, the animals died as they would upon inoculation via the same route. However, this is not a natural route of infection, but that point apparently was not considered by the NSABB." The fact that no deaths occurred when the virus was transmitted through the air, as it would be during the course of a pandemic, suggested that the engineered strain was not as virulent as had been thought. The situation was similar for Kawaoka's work given that the researchers used a non-lethal strain. As Campbell noted, the risk posed by the viruses was not as great as had been feared. "Our author gave an exemplary presentation [to the NSABB] and made it clear that the virus was not fatal in any of his experiments," Campbell explained.

Bauchner insists that in the case of potential dual-use research, it is essential to establish the underlying science clearly before making decisions. Fouchier

believes that had this been done, it would have been clear that publishing his paper was in the public interest because it sheds light on influenza transmission. Publication could help stop a future pandemic, whether natural or an act of terrorism. "The fundamental science behind aerosol transmission of influenza virus is the main significance of our work," Fouchier said. "We will now understand better how bird viruses adapt to mammals to become airborne. The second point is that by showing that A/H5N1 (influenza virus subtype H5N1) viruses can be transmitted via aerosol or respiratory droplets in mammals, scientists will now agree that it is not impossible for A/H5N1 virus to cause a pandemic in the future."

Of course, both papers identify individual mutations and biological traits that could help with surveillance in areas where a pandemic might arise. "If we identify viruses in outbreak areas that have accumulated several biological traits that may yield airborne viruses in the future, hopefully those countries will do everything in their power to stop the outbreaks," Fouchier commented. "And finally, we now have viruses with the biological traits of a potential pandemic virus, which will help us to better evaluate available vaccines and antivirals."

Notwithstanding the publication of the Kawaoka and Fouchier papers, these cases will inevitably lead to more caution over dual-use research among the life science community and those who regulate it. It seems probable that biosecurity concerns and implications will not be left to journal editors in the future, but will be considered from the point at which a proposal is received and reviewed. Murch commented that the US government has so far failed to recognize the importance of biosecurity and dual-use for the work it has funded, but that it is taking steps to rectify this. "The US Government has finally issued a policy which seeks to prepare for and address [dual-use research] that it sponsors or performs. Perhaps other countries will follow suit and closely examine their policies and practices and act appropriately," he said. Indeed, recommendations from the NSABB, and new guidelines from the US government try to address this issue to identify dual-use research much earlier in the process. Other countries are not as far in their thinking or policies as yet, but the commotion over the H5N1 papers might lead to similar regulations elsewhere. This is a new reality the life science community has to accept, even if it is not yet clear how it might have an impact on the funding and approval of certain types of research. There is always the danger that it could merely roll back the curtain of censorship from publication to the point of funding research proposals in the first place.

CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

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