“Outbreak” redux: Is lab research on influenza worth the risk of a pandemic?

What happens when you mix human error, deadly disease, and lab animals? Why, you get the 1995 thriller Outbreak starring Dustin Hoffman and the world’s most menacing Capuchin, of course.

The fear that any tinkering with infectious disease is bound to result in catastrophe runs deep, and it’s not without cause. Hollywood horror and “superflu recipe” headlines aside, the sort of research that could result in a pandemic is being done.

A new paper in PLOS Medicine by epidemiologists Marc Lipsitch (Harvard) and Alison Galvani (Yale) is the culmination of several years of controversy within the influenza research community. In it, Lipsitch and Galvani analyze in concrete terms the risk of a lab-developed strain of influenza getting loose and causing exactly the sort of pandemic it was meant to help prevent. They point out that the H1N1 “swine flu” strain, which was first indentified in 1977 and has caused hundreds of deaths since 2009, “is thought to have originated from a laboratory accident.”

A brewing storm: History of the “gain of function” controversy

Science journalist Maryn McKenna, writing at her Wired blog Superbug, offers a recap of the storm brewing over the risk and benefits of certain influenza research:

> The controversy over gain-of-function research dates back to 2011, when Ron Fouchier at Erasmus Medical Centre in the Netherlands and Yoshihiro Kawaoka at the University of Wisconsin both disclosed that their labs were tinkering with the H5N1 strain of avian flu. At that point, public health had been watching H5N1 for about 6 years as it spread slowly from southeast Asia. The strain caused severe illness, killing up to two-thirds of people made sick by it, but except in rare instances only occurred in people who had some direct contact with poultry, and did not transmit easily person-to-person. The discovery that transmissibility was being added to the virus’s toolkit, even if just between ferrets in the confines of moderately high-security labs, caused an uproar.

Publication of Fouchier and Kawaoka’s work was held up by the controversy but their findings were eventually published in full in 2012. Since then, every time anyone has attempted “gain of function” research using ferrets and the flu to create “potential pandemic pathogens” (PPPs), a new outcry has been raised. The GLP’s Tabitha Powledge wrote in mid-2013 on the controversy surrounding new research with the H7N9 strain of bird flu:

> The well-known virologist Vincent Racaniello […] has summarized the research plans at his Virology Blog. The researchers are proposing gain-of-function experiments, which will provide the virus with new tricks–for example, the ability to travel from mammal to mammal through the air. Says Racaniello: “. . . the point of these experiments, in my view, is not to simply identify specific changes that lead to aerosol transmission. Such work provides information on the mechanisms by which viruses can become adapted to aerosol transmission,

still an elusive goal."

Modifying a pathogen

The methodology behind most of these controversial studies is roughly the same. Ferrets are used as a model of human-to-human virus transmission. A strain of the flu is taken and modified through a process of forced transmission. Researchers dab some nasal fluid from one infected ferret into the nose of an uninfected one, and over and over, through multiple generations of the disease. It simulates, in theory, a compressed version of the natural process by which the vagaries of infection, mutation, and breeding could eventually result in a sub-strain of flu able to be transmitted through the air between mammals.

Sometimes, the mutations that allow the strain to be transmissible result in a less virulent disease. Sometimes they don't. The worry is that scientist using these methods to apply artificial pressure to a virus in the lab might create a very transmissible, very virulent strain and — despite safety measures like Biosafety Level 3 (BSL-3) labs — let it loose into the wider world. There is also the secondary fear that publishing the findings of this research could provide a "recipe" for superflus to terrorists who want to cause harm or even just to careless epidemiology enthusiasts who do *not* have BSL-3 labs to work in.

Promises or pitfalls?

These are the typical promises of gain of function research that aims to create potentially dangerous pathogens: By creating the diseases in a lab, in a controlled setting, we'll be able to understand how these dangerous forms arise in nature. We'll be better at watching for the signs of an impending pandemic, and we'll be able to speed up vaccine development thanks to a lab-generated "sneak peek" at the pandemic strain.

Lipsitch and Galvani take issue with these promises. First of all, the path from mutation to pandemic is not nearly as clear as we'd like to believe. They offer several examples where the same mutation, influenced by the genetic background of the particular strain in question, can have wildly different effects. A mutation that results in increased avian pathogenicity in one particular sub-strain may have the exact opposite effect in another. Furthermore, even when we do have effective foreknowledge of a potentially pandemic strain we fail to act effectively on it.

And as far as vaccines go? "Many, if not all, vaccines have been developed without a detailed molecular understanding of transmission," the contend. The authors go on to lay out a table of alternate approaches that yield more direct benefits for public health research without the risk of creating a lab-borne pandemic.

Lipsitch and Galvani, despite their take-down of PPP research so far, are not hard-line opposed to any such research, but they lobby for a more thorough analysis of risks and benefits. To achieve this a new framework is going to need to be established for thorough review.

The problem of oversight

Earlier this year, the controversy spiked again with the publication of research in the Journal of Virology (JIV) making the H7N1 strain more contagious among ferrets used as a model for humans. Again the

promise was that the benefits would outweigh the risks, yet no-one seemed to provide a clear, quantitative assessment of either.

Robert Roos, news editor for the University of Michigan's Center for Infectious Disease Research and Policy (CIDRAP), encapsulates the response of several concerned scientists in a commentary accompanying the JIV research:

> As things stand now, journal editors are the sole arbiters of whether manuscripts describing [processes that could be used for good or ill] should be published, the authors say. They note that the NSABB [National Science Advisory Board for Biosecurity], which established the criteria for DURC [dual use research of concern], is not set up to routinely advise editors on such decisions.
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> Although the definition of DURC is clear, editors have to make a judgment call about whether research findings can be "*directly* misapplied to pose a threat to society," and they may not feel qualified to do that, the authors say. And if they reject a paper, it may well be submitted to another journal, "with no guarantee that the information would be handled responsibly."

Ultimately, the critics call for a national board that can assess DURC research. A group outside of the small sphere of funding groups, researchers, and publishers that can look at the public health risks, potential benefits, and provide oversight. Lipsitch and Galvani likewise call for an overhaul of the evaluation process, emphasizing that it would need to take into account international interests and incorporate a broad range of stakeholders.

Ultimately, the controversy and the struggle to establish a new framework of evaluation can be boiled down to a single question asked by Lipsitch and Galvani: "What *unique* public health benefits do PPP experiments offer?"

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Additional Resources:

- "Flu researchers propose controversial 'gain-of-function' studies for H7N9 virus," Helen Branswell | Globe and Mail
- "Pandemic bird flu risk stoked by gene changes, study says," Jason Gale | Bloomberg
- "Genetics versus new bird flu: The race is on," Kenrick Vezina | Genetic Literacy Project