Ban on gain-of-function studies ends

The US moratorium on gain-of-function experiments has been rescinded, but scientists are split over the benefits—and risks—of such studies. Talha Burki reports.

For the **framework on funding decisions** see https://www.phe.gov/s3/dualuse/Documents/p3co.pdf

For the **Cambridge Working Group statement** see http://www.cambridgeworkinggroup.org

For the **NSABB's recommendations** see https://osp.od.nih.gov/wp-content/uploads/2016/06/NSABB_Final_Report_Recommendations_Evaluation_Oversight_Proposed_Gain_of_Function_Research.pdf

On Dec 19, 2017, the US National Institutes of Health (NIH) announced that they would resume funding gain-of-function experiments involving influenza, Middle East respiratory syndrome coronavirus, and severe acute respiratory syndrome coronavirus. A moratorium had been in place since October, 2014. At the time, the NIH had stated that the moratorium "will be effective until a robust and broad deliberative process is completed that results in the adoption of a new US Government gain-of-function research policy". This process has now concluded. It was spearheaded by the National Science Advisory Board for Biosecurity (NSABB) and led to the development of a new framework for assessing funding decisions for research involving pathogens with enhanced pandemic potential. The release of the framework by the Department of Health and Human Services (HHS), of which NIH is part, signalled the end of the funding pause.

The situation has its roots in 2011, when the NSABB suppressed two studies involving H5N1 viruses that had been modified to allow airborne transmission from ferret to ferret. They worried that malign actors could replicate the work to deliberately cause an outbreak in human beings. After much debate, the studies were published in full in 2012. HHS subsequently issued guidelines for funding decisions on experiments likely to result in highly pathogenic H5N1 viruses transmissible from mammal to mammal via respiratory droplets. The guidelines were later expanded to include H7N9 viruses.

In 2014, several breaches of protocol at US government laboratories brought matters to a head. The news that dozens of workers at the Centers for Disease Control and Prevention (CDC) might have been exposed to anthrax, that vials of smallpox virus had been left lying around in an NIH storeroom, and that the CDC had unwittingly sent out samples of ordinary influenza virus contaminated with H5N1, shook faith in the country's biosafety procedures. Over 200 scientists signed the Cambridge Working Group declaration arguing for a cessation of experiments creating potential pandemic pathogens "until there has been a quantitative, objective and credible assessment of the risks, potential benefits, and opportunities for risk mitigation, as well as comparison against safer experimental approaches".

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The debate is focused on a subset of gain-of-function studies that manipulate deadly viruses to increase their transmissibility or virulence. "This is what happens to viruses in the wild", explains Carrie Wolinetz, head of the NIH Office of Science Policy. "Gain-of-function experiments allow us to understand how pandemic viruses evolve, so that we can make predictions, develop countermeasures, and do disease surveillance". Although none of the widely publicised mishaps of 2014 involved such work, the NIH decided to suspend funding for gain-of-function studies involving influenza, MERS-CoV, and SARS-CoV.

The new framework stipulates that decisions on whether federal funding should be granted to a particular gain-of-function experiment will be decided on a case-by-case basis by a multidisciplinary review board at HHS. The board will evaluate the scientific merit of the experiment and examine whether there are viable, less risky approaches to tackle the same question. "The funding agency will be responsible for ongoing review as experiments move forward", adds Wolinetz. Aside from the review board, the funding agency and the institutional biosafety committee will supervise the research. "There will be multiple layers of oversight throughout the life cycle of the experiment", said Wolinetz.

In 2016, the NSABB issued a set of recommendations for the evaluation of proposed gain-of-function research. The document, which informs the HHS framework, outlines criteria for assessing the potential risks and benefits. "The first question is: how likely is the research to result in benefits and how great would these benefits be, and how likely is the research to result in harm, and how great would these harms be?", Michael Selgelid (Monash University, Melbourne, VIC, Australia) told *The Lancet Infectious Diseases*. "But risk–benefit assessment is not an exact science, nor is it perfectly objective—a lot of the time, it is going to be very difficult to say what constitutes a situation where the benefits outweigh the risks."

The likelihood of an accident leading to an outbreak, epidemic, or pandemic is extremely difficult to predict, as are the probable scientific advances. Proponents of gain-of-function experiments argue that their work could facilitate vaccine development. "We cannot even predict what the current seasonal influenza strains are going to do from one season to the next", retorts Ian Mackay (University of Queensland, Brisbane, QLD, Australia). "We have vaccines, but they are not much good, and instead of concentrating

on understanding these viruses and improving the vaccines, people prefer to worry about viruses that have not yet become transmissible and may never do so."

Wolinetz points out that the viruses produced by gain-of-function experiments often pale in comparison with potential pandemic viruses that are found in the wild. "These experiments will help us get ahead of viruses that are already out there and pose a real and present danger to human health", she said. "It is the only way we can really understand at a molecular level how these processes occur, and then we can take that information to develop the tools that we need to protect against these diseases".

Arguments over whether a particular non-gain-of-function experiment could deliver the same answer as a proposed gain-of-function experiment could continue indefinitely (Mackay advocates doing more with loss-of-function experiments). And even if this could all be satisfactorily resolved, the question still remains of what to do with the information. "It depends on how risk-averse people are, and this differs between individuals and countries", said Selgelid. Put another way: how should a given improvement in surveillance be weighed against a given chance of an outbreak or epidemic resulting from an accidental or deliberate release?

"Insofar as policymaking should be democratic, you might think that it should reflect the risk-taking strategies of citizens of a democratic country; things become more thorny when an issue crosses borders—is it OK for one nation to impose risks on citizens of another nation?", asks Selgelid. He welcomes USA's willingness to take the lead on one of the most important problems facing bioethics, but stresses the importance of global coordination. Smallpox research, which is overseen by WHO, offers a precedent for this. "There should not be a complete ban on gain-of-function research—there are plenty of cases where it is appropriate and sometimes it may even be less dangerous than non-gain-of-function research", said Selgelid. "But there should be an international review of the most worrisome kind of studies."

Marc Lipsitch (Harvard University, MA, USA) is a founding member of the Cambridge Working Group. "I still do not believe a compelling argument has been made for why these studies are necessary from a public health point-of-view; all we have heard is that there are certain narrow scientific questions that you can ask only with dangerous experiments", he said. "I would hope that when each HHS review is performed someone will make the case that strains are all different, and we can learn a lot about dangerous strains without making them transmissible." He pointed out that every mutation that has been highlighted as important by a gain-of-function experiment has been previously highlighted by completely safe studies. "There is nothing for the purposes of surveillance that we did not already know", said Lipsitch. "Enhancing potential pandemic pathogens in this manner is simply not worth the risk."

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Statistics on the number of breaches in the 1500 or so high containment laboratories in the USA are hard to come by. Serious events are extremely rare, ones that result in an infection in the community are virtually unknown. Nonetheless, the incidents that occurred in 2014 all involved material emerging from high-containment laboratories; dangerous live pathogens were accidentally sent to laboratories that were neither expecting them nor equipped to deal with them. "One cannot legislate for every accident or human error; all manner of things can go wrong, and if an outbreak spreads to the community the consequences could be horrendous", said Mackay.

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Wolinetz notes that there has never been any question of doing gain-of-function experiments in anything other than the highest level of appropriate containment. "That is where you see the fewest incidents", she said. Gain-of-function experiments are typically done in biosafety level (BSL) 3+ facilities; overall, such facilities have excellent records and are long-accustomed to handling dangerous material. "It may well be that the HHS committee requires BSL4 [the highest rating] out of an overabundance of caution", said Wolinetz. "There will certainly be a lot of contingencies when the funding agencies agree to a proposal." Moreover, in time, other nations are likely to start experimenting with gain-of-function research, some of whom might not be used to the kind of strict precautions that prevail in US laboratories. The USA can set an example. "The NIH is really committed to leadership on this; other countries see our system as a potential model", Wolinetz told *The Lancet Infectious Diseases*. "And if we are pursuing this research in an active way, we will be much better positioned to develop protection and countermeasures should something bad happen in another country."

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