Commentary and Revised Proposal: Decision Mechanism for Creating and/or Researching Potential Pandemic Pathogens

Lynn C. Klotz, PhD,
Senior Science Fellow, Center for Arms Control and Non-proliferation.
Dr. Klotz may be reached at lynnklotz@live.com

June 7, 2016

The NSABB defines Gain of Function Research of Concern (GOFROC) as "research that has the potential to generate pathogens with pandemic potential in humans…"[1] While GOFROC accurately defines the research we are concerned with here, saying and reading the word "GOFROC" is unappealing. In this commentary and revision, I will use the NSABB's old term "studies of concern," to mean the same as GOFROC.

Presumably, NSABB's role will end with suggesting a detailed procedure for making decisions:

> "[T]he White House Office of Science and Technology Policy and Department of Health and Human Services today announced that the U.S. Government is launching a deliberative process to assess the potential risks and benefits associated with a subset of life sciences research known as "gain-of-function" studies…The NSABB will serve as the official Federal advisory body for providing advice on oversight of this area of dual-use research, in keeping with Federal rules and regulations…[and] will inform the development and adoption of a new U.S. Government policy regarding gain-of-function research."

A chain of steps should be followed to make a decision whether a study of concern should or should not be conducted. The steps are:

1. Identifying studies of concern
2. Expert review of studies of concern
3. Making decisions on particular studies of concern.
4. Continuing oversight of conducted studies of concern

In order to protect us from an escape of a laboratory-generated potential pandemic pathogen (PPP) each link in the chain must be strong. The main goal of this commentary is to make suggestions to strengthen each link in the chain.

1. Identifying studies of concern

The review and oversight process cannot begin unless Institutional Biosafety Committees (IBCs) report to NIH potential studies of concern at their institution. There should be severe penalties for failure to report. Penalties should be at least as severe as those for violations of the Select Agent Program, which are up to $500,000 fines, and for some violations up to five years imprisonment. Severe penalties should

force IBCs to err on the cautious side. We must take a cautious approach as potential pandemic pathogens could seed an uncontrollable outbreak.

The IBCs must understand clearly the definition of studies of concern. As of May 24, 2016, the NSABB defines GOFROC (studies of concern) as

> "GOF research of concern is research that can be reasonably anticipated to generate a pathogen with both of the following attributes:
> 1. The pathogen generated is likely highly transmissible and likely capable of wide and uncontrollable spread in human populations.
> AND
> 2. The pathogen generated is likely highly virulent and likely to cause significant morbidity and/or mortality in humans." [2]

These two rules define PPPs. But the definition is a bit complicated, and taking literally the connecting conjunction "AND" could result in not reporting some research that should be reported as studies of concern.

The phrase "can be reasonably anticipated to generate a pathogen" with certain attributes appears to convey the same message as the word "likely" in the two rules; however, the word "likely" modifies the words "highly transmissible…in human populations" and "highly virulent…in humans" What exactly is meant by "highly virulent" or "highly transmissible" in rules 1 and 2? Higher or lower virulence and airborne transmissibility of pathogens in ferrets or mice cannot be extrapolated reliably to humans. We don't know how virulent or transmissible lab-generated PPPs will be in humans, as they are not present in human populations.

With a slight change in wording from my previous commentary to re-state and slightly expand upon the latest NSABB language, I rewrite the two NSABB rules as:

> A study of concern is research that can be reasonably anticipated to generate a pathogen or employs a live laboratory-created pathogen, not presently in nature, with one or both of the following attributes:
> 1. could cause significant morbidity and/or mortality in humans.
> OR
> 2. could be transmissible in humans by aerosol-droplets or other means of transmission not requiring direct physical contact.

The rules have been expanded to include research that employs a previously-created live PPP, as escape from a laboratory would be just as dangerous. The rules have also been expanded to include pathogens such as Ebola virus, which is an example of efficient (non-airborne) transmission without direct person to person physical contact. "Not present in nature" excludes pathogens already in the community prepared from plasmids, as is common today for influenza viruses. It also excludes natural strains of pathogens (not laboratory-created) already in the community, such as MERS.

The word "could" takes into account that we don't know if lab-generated pathogens will be less or more virulent or transmissible in humans than animals, as they are not present in human populations.

The word "AND" in the NSABB definition has been changed to "OR". The conjunction, or, has the logical meaning of and/or. Changing to "or" would give expert reviewers more latitude in deciding whether a study should not be conducted. In some instances, it might make sense to decide that only one of the two both attributes would be necessary to decide that a study should not be conducted. In others, both might be necessary.

To make the discussion more real, take two examples of already conducted research.

2009 pandemic H1N1 and H3N2 influenza viruses were made potentially capable of causing more widespread infection by selecting mutants that could escape immune responses generated against the parent viruses. These antigenic escape mutants could infect and be transmissible in those previously immune. This research might not be captured as a study of concern with the NSABB definition, since the virus strains might not be judged to be highly virulent in humans because the 2009 H1N1 flu virus was not particularly deadly. Regardless of anyone's definition of "highly" that pandemic did cause significant morbidity and mortality world-wide, and so should be considered a study of concern to be reviewed.

Mammalian-airborne-transmissible, highly-pathogenic avian influenza viruses (matHPAI): Some of these potentially dangerous matHPAI viruses have been created in the laboratories of Ron Fouchier and Yoshihiro Kawaoka. If one of these viruses escaped a laboratory, it could seed a pandemic with thousands to millions of human fatalities. By almost everyone's definition, these strains would qualify as studies of concern because they "could" be highly virulent and highly transmissible in humans.

Both the NSABB rules and my rules are focused narrowly to humans. Similar rules and decision-making chains for plant and agricultural animal pathogens should be considered.

2. Expert review of studies of concern

A proactive and on-going review process for studies of concern should involve three committees. After an Institutional Biosafety Committee (IBC) refers a potential study of concern to NIH for review and recommendations[3], the actual decision process should then be in the hands of a third committee (here called the White-House Committee or WHC). This committee would include members from the National Security Council (NSC), the Office of Science and Technology Policy (OSTP), the Department of State, and the Department of Health and Human Services (DHHS).

WHC membership should include non-government experts as well--in particular, members of the National Academy of Sciences (NAS) and other non-government experts. This group would include experts in molecular virology, epidemiology, public health, ethics, and international law. The non-government experts would have an advisory non-voting role on decisions for each study of concern. Because many of the nation's most respected scientists are NAS members, the NAS should have the major role for nominating non-government experts to the WHC.

This WHC Committee composition would help ensure that dual-use security concerns, biosafety risk to the community, and international ramifications are addressed.

3. Final decisions about proposed studies of concern

Final decisions about proposed studies of concern--whether the study could be conducted, protocols and restrictions that must be followed, and biosafety requirements—will be made by the WHC. The kinds of decisions that might be made range from:

- Outright banning a particular study in the U.S.
- Allowing a study to proceed and be funded at an appropriate biocontainment level BSL3, BSL4 or BSL4+[4]

with many possible decisions in between.

Decisions must take into account risk-benefit, biosafety, biosecurity, ethical, and international consequences such as demands for reparations for morbidity and mortality from a laboratory escape or theft. Allowing the most dangerous research to proceed sends a message to other nations that such research is acceptable; and it may send the wrong message that the U.S. is embarking on the most-dangerous-imaginable biological weapons development.

There is a framework in place to guide funding decisions for studies of concern. The 2013 framework outlines the criteria for funding. The NSABB has suggested a somewhat different framework for studies of concern:[5]

> **"Principles that should guide the review of and funding decisions about research proposals anticipated to involve GOF studies of concern:**
> i. The research proposal has been evaluated by a peer-review process and determined to be scientifically meritorious, with high impact on the research field(s) involved.
> ii. The pathogen that is anticipated to be generated must be judged, based on scientific evidence, to be able to arise by natural processes.
> iii. An assessment of the overall potential risks and benefits associated with the project determines that the potential risks as compared to the potential benefits to society are justified.
> iv. There are no feasible, equally efficacious alternative methods to address the same scientific question in a manner that poses less risk than does the proposed approach.
> v. The investigator and institution proposing the research have the demonstrated capacity and commitment to conduct it safely and securely, and have the ability to respond rapidly and adequately to laboratory accidents and security breaches.
> vi. The results of the research are anticipated to be broadly shared in compliance with applicable laws and regulations in order to realize its potential benefits to global health.
> vii. The research will be supported through funding mechanisms that allow for appropriate management of risks and ongoing Federal and institutional oversight of all aspects of the research throughout the course of the project.
> viii. The proposed research is ethically justifiable."

I have some concerns over the wording in this new framework. In general, they should be labelled Guidelines, not Principles. My main specific concern is over Principle iv. The mutations responsible for airborne transmission of matHPAI strains found by Fouchier can be found by alternative methods that do not employ live viruses, so the risk of a lab escape seeding a pandemic is effectively zero. There is always a risk that a strain will escape a laboratory by accident or theft. Alternative methods are likely faster at finding these mutations. However, they don't prove a role in transmissibility, only suggest it, but that disadvantage is more than offset by the fact that risk is essentially eliminated. There are a number of publications that compare gain-of-function methods with alternative methods (for instance, here, here, here, and here[6]).

I would judge the alternative methods "equally efficacious;" however, in general, this judgement should be a consideration of the reviewing committee on a case-by-case basis, not stated as an absolute Principle. The words "equally efficacious" should be deleted. Principle iv would then read: "There are no feasible, alternative methods to address the same scientific question in a manner that poses less risk than does the proposed approach.

Some final thoughts

To be kept informed of decisions, an appropriate Congressional Committee or Caucus will be notified of the final decisions and explanations. The Congressional Biomedical Research Caucus[7] is perhaps the appropriate congressional group to keep informed.

Completion of the NSABB deliberative process should not mean the funding pause should be lifted. All studies subject to the funding pause should remain unfunded by the NIH until a new review process, such as that proposed here, is put in place and new reviews are carried out for all existing studies of concern.

The U.S. government should also consider pausing all studies of concern regardless of funding source until they are reviewed again. The many scientists who signed the Cambridge Working Group statement feel that studies such as these should be "curtailed" until further reviewed:

> "For any experiment, the expected net benefits should outweigh the risks. Experiments involving the creation of potential pandemic pathogens should be curtailed 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."

In order to maintain continuity in the review and decision-making process, civil service employees should manage that process, as most political appointments will change with changing elected officials.

This proposal does not address the dual-use concern that someone will repeat the research for hostile purposes.

---

[1] Joseph Kanabrocki May 24 presentation titled: *NSABB Working Group Draft Report: Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research*

[2] ibid

[3] Called Federal review by the National Science Advisory Biosecurity Board. Federal review is likely review by the NIH Recombinant DNA Advisory Committee (RAC) or the NIH Office of Biotechnology Activities (OBA). It may also include review by the Department of Health and Human Services (HHS).

[4] An additional level of biosafety -- call it BSL-4-plus -- that adds special protections for laboratory work with dangerous PPP research. BSL4+ differences from BSL4 include (1) Train full-time technical staff who are dedicated to working with highly dangerous pathogens. These staffers would carry out experiments directed by scientists who would never need to be present in the BSL-4+ laboratory. With modern audio-video technology, research scientists can remotely monitor lab work as if they were present. (2) Require lab staffers to follow up extended work shifts with periods of quarantine before they leave the biocontainment area. Such procedures would assure that no potential pandemic pathogen escapes from a BSL-4+ lab through a laboratory-acquired infection; anyone accidentally infected would show symptoms while still in quarantine.

[5] Joseph Kanabrocki May 24 presentation *op. cit.* titled: *NSABB Working Group Draft Report: Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research*

[6] M Lipsitch, *Comment on "Gain-of-Function Research and the Relevance to Clinical Practice"*, J Infect Dis., in press.

[7] The Congressional Biomedical Research Caucus (CBRC)…is a bipartisan, bicameral Caucus…Seventy five Members of the House of Representatives and nine Members of the Senate comprise the Caucus Membership...
The Caucus seeks to support the excellent efforts of the congressional committees and Members of Congress with jurisdiction over the National Institutes of Health (NIH), the National Science Foundation (NSF), science research, and health issues.