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A Proposed Oversight and Decision Mechanism for Creating and/or Researching Potential Pandemic Pathogens

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May 12, 2016

Introduction

About two years ago, the White House ordered (here and here) a "deliberative process and research funding pause" for gain-of-function studies on viruses that "would have enhanced pathogenicity [virulence] and/or transmissibility in mammals via the respiratory route." This White-House-ordered activity is now near completion; the National Advisory Board on Biosecurity has just issued its Draft Final Report

The viruses that are the subject of the White House order include highly pathogenic Asian influenza viruses that can transmit disease from mammal to mammal by the respiratory route (airborne transmission). Such viruses have already been created in the laboratory, in particular but not limited to 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. These are called GOF studies of concern by the National Science Advisory Board for Biosecurity (NSABB), or simply studies of concern.

Any review mechanism for studies of concern must take into account risk-benefit, biosafety, biosecurity and other international consequences such as demands for reparations for morbidity and mortality from a laboratory escape. 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.

A proactive and on-going review process for studies of concern that involves several committees is proposed here:

- A means of identifying which studies could seed a pandemic in humans if a laboratory-created pathogen escaped.
- A Committee of Outside Experts (COE) to review such research to supplement the current Institutional Biosafety Committee (IBC) review and Federal review, presumably NIH internal review.[1]
- A White-House Committee (WHC) charged with making decisions when there is disagreement among the three committees whether the studies should or should not be conducted (banned) in the U.S.

The WHC could include members from the National Security Council, the Office of Science and Technology Policy, the Department of State, the Department of Health and Human Services (HHS) and perhaps others. This committee composition would help ensure that dual-use security concerns, biosafety risk to the community, and international ramifications are addressed. The WHC would recommend to the President to ban a particular study of concern.

The just released NSABB Draft Final Report in its Findings and Recommendations has come to some of the same conclusions as the proposal here; for instance, the possibility of banning some studies of concern:

> **"Finding 5.** There are life sciences research studies, including possibly some GOF research of concern, that should not be conducted because the potential risks associated with the study are not justified by the potential benefits."

Summaries of the current state of affairs, criticisms of the NSABB rules, and discussion of this Proposal follows:

Problems with the NSABB rules for identifying "studies of concern"

In the Gain-of-Function Research Symposium held at the National Academy of Sciences (March 10-11, 2016), the NSABB gave a presentation (Slides 12 and 13) summarizing its conclusions on funding and oversight for GOF studies of concern. The NSABB concluded:

> "Research proposals involving GOF studies of concern…should be reviewed carefully for biosafety and biosecurity implications, as well as potential benefits, prior to determining whether they are acceptable for funding. If funded, such projects should be subject to ongoing oversight at the NIH and institutional levels."

GOF studies of concern needed to be defined. The NSABB offered the following three rules:

> "A GOF study of concern is one that could generate a pathogen with all of the following attributes:
> 1. The pathogen generated is highly transmissible in a relevant mammalian model.
> 2. The pathogen generated is highly virulent in a relevant mammalian model.
> 3. The pathogen generated is more likely capable of being spread among human populations than currently circulating strains of the pathogen."

In its presentation, the NSABB emphasizes that all three rules must apply by underlining the word "all". The White House called for a "deliberative process and research funding pause" for GOF studies on viruses that "would have enhanced pathogenicity [virulence] and/or transmissibility in mammals via the respiratory route." The "and/or" was usually interpreted as "or". The NSABB changing now to the word "all" fundamentally changes the discussion, and could allow dangerous virus strains to escape their studies-of-concern designation.

In the Draft Final Report, the NSABB has dropped Rule 3, but still insists that both Rules 1 and 2 must be met to be a GOF study of concern. In slightly different language:

> "To be considered [Gain of function research of concern] GOFROC, the research must, in a single step or over the course of manipulations, be reasonably anticipated to generate a pathogen with both of the following attributes:

i. The pathogen generated is likely highly transmissible and likely capable of wide and uncontrollable spread in human populations.
ii. The pathogen generated is likely highly virulent and likely to cause significant morbidity and/or mortality in humans."

To make the discussion more real, let's concentrate on one type of pathogen: mammalian-airborne-transmissible, highly-pathogenic avian influenza viruses (matHPAI). Some of these dangerous matHPAI strains created in Fouchier's and Kawaoka's laboratories might not qualify as studies of concern under the NSABB rules. For instance, a strain that is highly transmissible and only modestly virulent in ferrets might not be captured as a study of concern. We would certainly not like to see such a strain escape from a laboratory. The problem here is that both rules must apply to qualify according to the NSABB.

What exactly is meant by "highly virulent" or "highly transmissible" in Rules i and ii? Higher or lower virulence and airborne transmissibility of pathogens in ferrets cannot reliably be extrapolated to humans. We must take a careful approach by assuming many of these pathogen strains might seed an uncontrollable outbreak (pandemic), unless they are deemed not dangerous after careful analysis.

Proposed new rule for Identifying studies (research) of concern

Many of us active in the deliberative process use the expression "potential pandemic pathogens" to better identify pathogens of concern, which would focus disagreements on pandemic potential, not on the vague word "highly."

Pathogens that exhibit, or reasonably could be expected to exhibit, pandemic potential are abbreviated PPPs, obviously standing for potential pandemic pathogens.

"Reasonably could be expected to exhibit" is an important phrase here, as pathogens of concern are laboratory-created and are novel, so their pandemic potential has not been observed in nature. With this definition of a PPP, the two NSABB rules might be rewritten simply as a single rule:

A study of concern is one that creates in the laboratory or studies a live laboratory-created PPP not present in nature that reasonably could be expected to be virulent in humans or transmissible in humans by aerosol-droplets or other means of efficient transmission not requiring direct physical contact.

The focus for this proposal is narrowly defined to humans. The NSABB's "relevant mammalian model" is not necessary as part of the definition, although demonstration of mammalian airborne transmission of HPAI in ferrets was the original trigger for widespread concern and will remain a trigger for concern.

Ebola is an example of efficient (non-airborne) transmission with and without direct 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.

This rule is an attempt to find a rule(s) that is not too narrow so as to exclude some studies of concern, and not too broad so as to include safe studies. From the many discussions leading to this rule, it is clear that drafting a perfect rule is likely not possible. The Committees described here will sometimes have to make decisions to include or exclude particular studies based on their assessment of virulence, transmissibility, and other factors. With experience, the rule may well be modified.

A Committee of Outside Experts to supplement IBC and NIH review

An NSABB quote in this article refers to "NIH and institutional" review. History tells us that institutional review followed by NIH review has been ineffective.

Review by institutional biosafety committees (IBCs) has been incompetent to non-existent. See, for example, the discussion in Chapter 7, "Who's Minding the Store," in Breeding Bio Insecurity where it is suggested why IBC's do not effectively carry out their duties:

> "The root of these failures probably lies in the free-spirit culture of scientists unaccustomed to regulations and suspicious of them, and the inability of the already-dysfunctional Institutional Biosafety Committees to deal with the new era of security regulations."

The review and oversight process cannot begin unless IBCs contact NIH about questionable research project proposals. There should be stiff and enforced penalties for failure to report to the NIH.

The history of NIH review is concerning as well. Again, from Breeding Bio Insecurity:

> "[M]ost of the law's oversight provisions are guidelines and not legally enforceable…the NIH can withhold funding from those violating the guidelines. But the agency doesn't and won't: too much vital research might be impeded. Even prestigious universities pay only lip service to the guidelines, many not even that."

Recent NIH grant awards for the studies that created and researched live matHPAI viruses do not inspire confidence in that particular NIH review. It appears that these studies were funded with little questioning of their risk, certainly without public discussion.

IBC and NIH review should be supplemented by a Committee of Outside Experts (COE) review. From the scientists, ethicists, lawyers, and international policy experts who have participated in the deliberative process, it should be possible to put together a committee that represents all facets and views.

The NSABB Draft Final Report agrees that a third committee is needed:

> "**Finding 3.** Oversight policies vary in scope and applicability, and do not cover all potential GOFROC, therefore, current oversight is not sufficient for all GOF research of concern."

and

> "**Recommendation 1.** Research proposals involving GOF research of concern entail significant potential risks and should receive an additional, multidisciplinary review, prior to determining whether they are acceptable for funding."

Final decisions about proposed studies of concern

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+[2]

When the three committees (the IBC, NIH, and the COE) all agree on a decision that does not call for banning the study, the NIH can notify the researchers' Institution of the decision. If one or more of the three committees recommends banning the proposed research, the Final Decision will be made by the President from the advice of the WHC.

The obvious reason for high-level WHC review is that a lab escape of a live pathogen could cause an uncontrolled outbreak, with thousands to millions of fatalities. Even the relatively mild 2009 H1N1 pandemic flu killed over 200,000 people around the world.

But there are other reasons as well for Executive-branch review. Casualties outside the U.S. could make the U.S. liable for reparations, and certainly international condemnation. Also failure to ban the most dangerous research sends a message to the rest of the world saying 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 already a framework in place to guide funding decisions for matHPAI research. The 2013 framework outlines the criteria for funding.

> 'Such proposals will undergo additional funding agency review as well as [HHS] Department-level review in order to determine its acceptability for funding by HHS…the funding agency will determine whether the proposed research is in accord with the following criteria:
> 1) The virus anticipated to be generated could be produced through a natural evolutionary process;
> 2) The research addresses a scientific question with high significance to public health;
> 3) There are no feasible alternative methods to address the same scientific question in a manner that poses less risk than does the proposed approach;
> 4) Biosafety risks to laboratory workers and the public can be sufficiently mitigated and managed;
> 5) Biosecurity risks can be sufficiently mitigated and managed;
> 6) The research information is anticipated to be broadly shared in order to realize its potential benefits to global health; and
> 7) The research will be supported through funding mechanisms that facilitate appropriate oversight of the conduct and communication of the research."

Presumably, this framework allowed funding of the Kawaoka and Fouchier matHPAI studies before the 2014 funding pause and deliberative process. A Committee of Experts could well decide that these studies should not be conducted. And the many scientists who signed the Cambridge Working Group statement feel that studies such as these should be "curtailed" until they are reviewed again.

> "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."

To be kept informed of decisions, an appropriate Congressional Committee or Caucus will be notified of the Final Decision, along with the three committee's decisions and explanations. The Congressional Biomedical Research Caucus[3] is perhaps the best congressional group to keep informed.

Conclusions

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 stopping all studies of concern regardless of funding source until they are reviewed again.

This proposal does not address the dual-use concern that someone will use the research for hostile purposes. How to decide what is dual-use research of concern and decisions about its publication might follow a procedure similar to that outlined here.

I thank Richard Ebright and an anonymous reviewer with considerable expertise in controversial science/technology issues for many rounds of comments on this Opinion article, particularly on definitions, the rules, and whether the rules are too narrow or too broad.

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[1] 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).

[2] 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.

[3] 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.