To: The NSABB Board (in advance of the September 28, 2015 meeting)

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The following document is a first draft of a literature-research project that started in the summer of 2015. The project is in an early stage, but has gone far enough to make its point: There is an urgent need for international proactive oversight of influenza research that might increase the pathogenicity of influenza viruses. Some of this gain-of-function research may create lab-made potential pandemic influenza viruses.

Even if the probability is small for an escape from a lab in a single year for such a virus, the fact that there are a large number of research projects underway throughout the world, projects that will be conducted for many years, the overall probability of escape from at least one lab is uncomfortably high.

The Potential Pandemic Influenza Research Enterprise

In a recent Letter to the Editor titled *Danger of Potential-Pandemic-Pathogen Research Enterprises* (http://intl-mbio.asm.org/content/6/3/e00815-15.full), I argued that there are likely many labs throughout the world, many not funded by the NIH, that are developing mammal-contagious influenza viruses. Research that makes avian, mammalian, or human influenza viruses more virulent, increases their transmissibility, alters their host range, or evades countermeasures is potentially dangerous and may create potential pandemic pathogens.

Influenza viruses are more likely to fuel an uncontrollable outbreak because of their long history of doing just that. This kind of research got considerable attention in 2011 when Professor Ron Fouchier announced that his laboratory had made the H5N1 highly pathogenic avian influenza virus (HPAI) airborne transmissible by respiratory aerosols from ferret to ferret.

In the context of this analysis of recent publications reported in Pub Med (references (1) through (35)), the larger category of Experiments of Concern (EoC) is used as a guide to look for potentially dangerous research. In 2004, the National Academy of Sciences published a report *Biotechnology Research in an Age of Terrorism* (http://www.nap.edu/catalog/10827.html). The so-called Fink Committee that produced the report was asked to "consider ways to minimize threats from biological warfare and bioterrorism without hindering the progress of biotechnology, which is essential for the health of the nation." The committee recommended that the "Department of Health and Human

Services…create a review system for seven classes of experiments (the Experiments of Concern) involving microbial agents that raise concerns about their potential for misuse." Specifically, the EoC are:

> "1. Would demonstrate how to render a vaccine ineffective. This would apply to both human and animal vaccines…
> 2. Would confer resistance to therapeutically useful antibiotics or antiviral agents. This would apply to therapeutic agents that are used to control disease agents in humans, animals or crops…
> 3. Would enhance the virulence of a pathogen or render a non-pathogen virulent. This would apply to plant, animal, and human pathogens…
> 4. Would increase transmissibility of a pathogen. This would include enhancing transmission within or between species. Altering vector competence to enhance disease transmission would also fall into this class.
> 5. Would alter the host range of a pathogen. This would include making non zoonotics into zoonotic agents. Altering the tropism of viruses would fit into this class.
> 6. Would enable the evasion of diagnostic/detection modalities. This could include microencapsulation to avoid antibody-based detection and/or the alteration of gene sequences to avoid detection by established molecular methods.
> 7. Would enable the weaponization of a biological agent or toxin. This would include the environmental stabilization of pathogens."

These seven classes of experiments "will require review and discussion by informed members of the scientific and medical community before they are undertaken [proactive oversight] or, if carried out, before they are published in full detail." For experiments making deadly avian influenza viruses airborne transmissible, many scientists think they should not be carried out at all.

An excellent system for reviewing potentially dangerous experiments, *Controlling Dangerous Pathogens: A Prototype Protective Oversight System*, was developed in 2007 by The Center for International and Security Studies at Maryland (http://drum.lib.umd.edu/bitstream/1903/7949/1/pathogens_project_monograph.pdf). It recommends a tiered review, from most to least dangerous research. Paraphrased from the Maryland paper:

> International Oversight: *Activities of Extreme Concern* – An international body would be charged with approving and monitoring all research projects of extreme concern. That authority would be narrowly focused only on those ... that could put an appreciable fraction of the human species at risk, such as research with potential pandemic pathogens.
> National Oversight: *Activities of Moderate Concern* – National oversight bodies would be responsible for research activity of moderate concern, such as work with anthrax and other agents already identified as having biological weapons potential.
> Local Oversight: *Activities of Potential Concern* – Concern—This "encompasses those activities that may increase the destructive potential of biological agents that otherwise would not be considered a threat.
> No oversight: *All other research*

In my opinion, there should be two levels of local oversight. The first level is the currently employed Institutional Biosafety Committee (IBC), and the second is an outside committee. There is concern that IBCs will simply rubber-stamp research proposals from labs in their own institution, so I suggest proactive oversight by a committee outside the institution (perhaps at the state level in the US) for experiments of concern on influenza viruses that do not carry an immediate threat of an outbreak from an escape from the laboratory (e.g., vaccine viruses and other attenuated and inactivated viruses).

Because of the potential for some strains of lab-made influenza viruses to cause international outbreaks, research mutagenizing these viruses that could result in increased pathogenicity (gain of function) should be subject to external oversight. At present, there is little national and no international proactive oversight with any authority to guide or ban experiments. See for instance: Gronvall GK, Rozo M. Synopsis of Biological Safety and Security Arrangements. UPMC Center for Health Security.July 2015. Available at http://www.upmchealthsecurity.org/ourwork/publications/synopsis-of-biological-safety-and-security-arrangements.

The literature analysis

To date, only one general Pub Med search term, "avian influenza virus mutagenesis," has been used here to identify potentially dangerous research that might fall under the Experiments of Concern (EoC). To focus on the most recent research, only research over the last two years (September 1, 2013 through August 29, 2015) published Pub Med abstracts were read. Thirty-five potential EoC were identified in 136 abstracts for this single search term. Many of the 136 abstracts (136-35=101) described research that did not constitute EoC; for the most part, they did not employ live viruses.

For each of the 35 abstracts that seemed to describe EoC, parts of the full research papers were read to confirm their EoC status. Since I have only a modest grasp of molecular virology, I may have labeled a few that are not EoC, and I may have missed a few that are EoC.

The actual number of EoC research being carried out today is likely much greater than 35 because of the following:

- Only a single avian influenza search term was used; other influenza search terms would yield additional EoC. In particular, viruses that have already caused pandemics such at the 2009 H1N1 virus.
- Expanding the search back to 2012, and even before that, would yield more EoC.
- There are surely some EoC that are not yet published.
- Search terms involving other pathogens such as SARS, MERS and Ebola would yield more EoC.

A summary of the 35 EoC found from the search is provided in Table 1. Titles and citations for the reference numbers are in the reference list at the end.

Reference Number	Countries of Authors	Viruses	Biosafety Level	EOC Category
1	USA, Korea	H1N1 vaccine strain	?	2
2	**China**	Avian, human H6N1	BSL3	5
3	**China**	H5N1 HPAI	not reported	1, 3
4	USA, Egypt	H5N1 HPAI	?	1, 3
5	**China**	H9N2 avian	BSL3	3, 5
6	**Japan**, USA	H5N1 HPAI	BSL3	3, 5
7	**Netherlands**, UK	H1N1 2009	BSL2	1, 3
8	**China**	H5N1 HPAI	Not reported	3
9	**China**	H7N1 avian	BSL3	3, 5
10	**China**	H9N2, H1N1 2009, H5N1 HPAI	BSL3, BSL3+	3
11	**USA**, Japan	H5N1 HPAI	BSL3	3
12	**China**	H6N1 avian	??	3, 5
13	**Japan**, Thailand	H5N1 HPAI	BSL3	3
14	**China**	H9N2 duck	ABSL3+	3, 5
15	**France**	avian H1N1	BSL3+	3, 5
16	**USA**	A/WSN/1933 H1N1	likely BSL2	5
17	**Netherlands**	airborne trans H5N1 HPAI	animal BSL3+	3, 4
18	**China**	H7N9 HPAI	ABSL3	3
19	**Japan**	H7N9 HPAI	BSL3+	3
20	**China**	H1N1 2009 pandemic	not reported, BSL2?	3
21	**China**	H1N1 2009 pandemic	not reported, BSL2?	2
22	Spain, UK	influenza A vaccine strains	assume BSL2	3
23	**Netherl.**, Germany	HPAI H5N1	BSL3+	1
24	**USA**	H1N1 vaccine strain	assume BSL2	1
25	**USA**	H3N2	BSL2?	2
26	**Germany**	HPAI H5N1	BSL3+	1
27	**China**, USA	HPAI H5N1	BSL3, ABSL3	2
28	**Russia**	nonpath H5N2, HPAI H5N1	not reported, BSL2?	1
29	**Germany**	1968 pandemic H3N2	not reported, BSL2?	3?
30	**USA**	H1N1 vaccine strain	not reported, BSL2?	1
31	**USA**	HPAI H5N1	BSL3	3, 5
32	**UK**	HPAI H5N1	BSL3	3, 5
33	**USA**	H3N2, H1N1	not reported, BSL2?	3?
34	**USA**	HPAI H5N1	ABSL3+	3, 4
35	**USA**	human H3N2, HPAI H5N1	ABSL3+	1

Table 1: The 35 EoC. The boldface in the Countries of Authors column indicates the country where the BSL2, BSL3 research was performed. Much of that research is being carried out in Asia, particularly China.

The 35 published research listed in the Table are described briefly below. The descriptions are a combination of quotes from the Pub Med abstracts and full papers, often paraphrased to make them readily understandable with regard to EoC. The numbers, 1 through 35, at the beginning of each entry below correspond to the numbered reference citations at the end of this document. The **bold-face highlighted** descriptions are the greatest concern in my opinion because the mutated viruses are often more pathogenic than the wild-type strains and are potentially airborne transmissible from human to human.

1. Recombinant influenza viruses were made that have single or double substitutions in neuraminidase N3, N7 and N9 subtypes in a background of an H1N1 vaccine strain. N3, N7 and N9 subtypes have caused human infections. The research discovered resistance to neuraminidase inhibitors in some strains. [Comment: Mutagenesis of vaccine strains are not of the highest concern, unless there is reason to believe that the mutagenesis could make the strain virulent.]

2. Avian H6N1 virus was adapted to human receptor-binding. Receptor-binding was analyzed using isolated H6 proteins. Binding was confirmed using two avian and one human-derived H6N1 recombinant viruses. The research found two HA substitutions important to acquire the human receptor-binding. [Comment: Only one case of human H6N1 infection has been reported to date. Could increasing receptor binding in humans lead to more human cases?]

3. Site-directed mutagenesis was used to generate different patterns of stem glycans on the HA protein of an HPAI H5N1. The results indicated that some glycans were dispensable for the generation of replication-competent influenza viruses. Some combinations of glycans led to a significant decrease of

the growth rates of the mutant viruses in animal cells in comparison to wild type virus. Furthermore, most of the mutant viruses were more sensitive to neutralizing antibodies than the WT virus. [Comment: Could researchers predict results in advance? These are experiments that should be proactively reviewed, as some mutations could have increased virulence or avoided existing vaccines. The outcome is, however, reassuring]

4. Variant H5N1 viruses with five mutations in the HA gene were made. The research indicated that targeted mutation in the HA may be effectively used as a tool to develop broadly reactive influenza vaccines to cope with the continuous antigenic evolution of viruses. [Comment: Could researchers predict results in advance? These are experiments that should be proactively reviewed, as some mutations could have increased virulence or avoid existing vaccines. As viral mutant population sizes are huge, the probability of finding an adaptive mutation is pretty large for RNA viruses.]

5. The research found three mutations in HA, N and PB2 proteins that after four passages conferred high virulence to H9N2 virus in mice. Adaption in mice enhanced the viral polymerase activity and receptor-binding ability, which resulted in a virulent phenotype in mice but not a transmissible phenotype to guinea pigs. [Comment: This additional guinea pig experiment was useful to reduce concern or fear over increased host range.]

6. Mutations made in the PA protein enhanced HPAI H5N1 virus growth capability in human lung cells and increased pathogenicity in mice, suggesting that they contribute to adaptation to mammalian hosts.

7. Mutants made with substitutions in the hemagglutinin of a strain of 2009 H1N1 pandemic influenza virus revealed that single substitutions affecting the loop adjacent to the receptor binding site caused escape from ferret and human antibodies elicited after the 2009 H1N1 pandemic influenza virus infection. The majority of these substitutions resulted in similar or increased replication efficiency *in vitro* compared to that of the virus carrying the wild-type hemagglutinin. However, none of the substitutions was sufficient for escape from the antibodies in sera from individuals that experienced <u>both</u> seasonal and pandemic H1N1 virus infections. [Comment: This is the virus that infected 25% of the world population world-wide in 2009 and killed thousands of people. Any experiment that increases replication efficiency or escapes antibodies should not be carried out in BSL2.]

8. Mutant HPAI H5N1 viruses made with loss of two HA protein glycosylation sites showed increased pathogenicity, systemic spread and pulmonary inflammation in mice compared to the wild-type H5N1 virus.

9. Two mouse-adapted variants of wild-type avian H7N9 made by independent serial passages in mice confer enhanced virulence in mammals. [Comment: This virus has infected and caused fatalities in humans from direct contact with poultry. It would have been informative if the researchers had carried out a single ferret to ferret transmission experiment to see if this mouse-passaged virus has increased host range and virulence in a species (ferrets) that is perhaps a model for humans.]

10. Mouse-adapted PB2 gene reassortants with a phenylalanine-to-leucine mutation contributes to enhanced polymerase activity, enhanced replication, pathogenicity of H9N2 in mice, increased

virulence of H5N1 and 2009 pandemic H1N1. [Comment: Could increasing virulence in the 2009 pandemic flu cause a new outbreak among humans?]

11. The introduction of an arginine residue into PA of HPAI H5N1 significantly increased the viral polymerase activity in mammalian cells and its virulence and pathogenicity in mice.

12. A substitution in the PB2 protein and a substitution in the PA protein enhance virulence and expand the tropism of H6N1 virus in mice. [Comment: Only one case of human H6N1 infection has been reported to date. Could increasing virulence and tropism in humans lead to more human cases?]

13. Introduction of a single substitution into PB1 polymerase of an HPAI H5N1 increased both polymerase activity in chicken cells and the pathogenicity of the recombinant viruses in chickens. [Comment: This translates to humans.]

14. A nonpathogenic duck-origin H9N2 virus was serial-passaged in mouse lungs. Increased virulence was detectable after five passages, and a highly pathogenic mouse-adapted strain was obtained after 18 passages. There were eight amino-acid substitutions in six viral proteins. [Comment: Since serial passage was in lungs, this kind of research could lead to airborne transmission. A single ferret to ferret passage experiment should have been carried out to see if airborne transmission was achieved.]

15. A deletion in the NS segment of a duck-origin avian H1N1 virus showed both increased replication potential and an increased pathogenicity in chicken embryonated eggs and in a chicken lung epithelial cell line.

16. Mutants created in the PB2 subunit identified critical residues required for general polymerase function and specific residues preferentially required in human but not avian cells. [Comment: It is unclear what virus was used in the study. It may have been PB2 mutants reassorted into A/WSN/1933 H1N1 virus. A/WSN/1933 is a derivative of 1918 flu virus and is not around today. This is a mouse brain adapted virus so not a threat.]

17. Five substitutions proved to be sufficient to retain the airborne-transmissible phenotype of HPAI H5N1. [Comment: A large number of substitution experiments on an airborne transmissible, deadly virus were carried out in this study, and a large number of nose and throat swabs and blood samples were taken, all increasing significantly the likelihood of an LAI. This is follow-up research from the Fouchier lab.]

18. An H7N9 virus from a fatal case was used as the recombination background to study the contribution of the E627K mutation in PB2 and of other mutations to the pathogenicity of H7N9 virus infection in mammals. All the mutant viruses generated were likely to be loss-of-function mutants with regard to pathogenicity, compared to the wild-type H7N9. [Comment: The research appears to yield less pathogenic H7N9. Nonetheless, it is not possible to predict pathogenicity at the outset of the experiments. Since the background virus is a fatal case; proactively, the generated viruses could have been more virulent humans. It would have been informative if the researchers had carried out a single

ferret to ferret transmission experiment to see if this virus was more virulent in ferrets, the model for human lung.]

19. Potentially mammalian adapting amino acids were converted individually and in combination to their avian virus-type counterparts in a H7N9 virus. Several mutants were slightly more virulent in mice than the wild-type A(H7N9) virus and exhibited increased polymerase activity in human cells.

20. A single "consensus" PB2 mutation common to swine and the 2009 H1N1 pandemic virus increased pathogenicity. Mutant virus prepared by recombination of a 2009 H1N1 pandemic virus with a segment containing the single PB2 mutation significantly enhanced polymerase activity in mammalian cells. Also, the virus exhibited increased growth properties and induced significant weight loss in a mouse model compared to the wild type. [Comments: This more pathogenic virus could win the battle with the immune system, so cause significant illness.]

21. Reduced sensitivities to oseltamivir were observed in three mutant H1N1 2009 pandemic viruses. A double mutant showed a large increase of IC-50 for the drug Oseltamivir from 0.7 nM for WT to 4,000 nM for the double mutant, a 5,700-fold difference [Comment: Such a large increase in IC-50 would almost certainly make the drug unusable in humans.]

28. A non-pathogenic avian H5N2 was adapted to mice by lung-to-lung passage. Also, the reverse genetics-derived influenza virus containing the HA and NA genes of an HPAI H5N1 in the genetic background of a high-growth H1N1 vaccine strain was obtained. Antibody escape mutants using these two viruses were obtained. Monitoring of effects of HA mutations found in H5 segment escape mutants is essential for accurate prediction of mutants with pandemic potential. [Comment: While H5N2 does not appear to have caused any human infections, adapting it to mice by lung to lung passage could have made it virulent in humans and even airborne transmissible.]

29. Influenza A viruses circulating in humans from ~1950 to ~1987 featured a nonstructural (NS1) protein with a C-terminal amino acid extension present in the H3N2 1968 pandemic flu virus. This research deleted the NS1 extension in the H3N2 in order to compare the wild type H3N2 with the virus with the NS1 deletion. The replication kinetics of the wild-type H3N2 and the deletion mutant were indistinguishable in most experimental systems. However, wild-type virus out-competed the mutant during mixed infections, suggesting that the NS1 extension conferred minor growth advantages. [Comment: The resurrection/rescue of an historical pandemic virus is potentially as dangerous as a lab-made PPP if it escapes from the laboratory, provided that the virus employed is identical to or very close to the 1968 pandemic strain.]

31. A particular point mutation in the PB2 protein of HPAI H5N1 virus, PB2 627K, has been identified as a virulence and host range determinant for infection of mammals, and is present in strains capable of airborne transmission. This mutation in the PB2 gene appeared from day 4 and 5 along the respiratory tracts of mice inoculated intranasally and was complete by day 6 post-inoculation. The mutation correlated with efficient replication of the virus in mice. [Comment: This kind of experiment may be on a path to an airborne transmissible strain.]

32. This research focused on the particular PB2 point mutation in Reference 31, just above. Viruses constructed by reverse genetics were made to contain converse PB2 627K/E mutations in a Eurasian HPAI H5N1 virus and, for comparison, a historical pre-Asian HPAI H5N1 virus that naturally bears PB2 627E. Effects on viral fitness were observed in *in vitro* or *in vivo* experiments. Results suggest that the PB2 627K mutation supports viral fitness in Eurasian-lineage viruses; in contrast, the mutation carries a significant fitness cost in a historical pre-Asian virus.

34. Influenza virus entry is mediated by the acidic-pH-induced activation of HA protein. This research investigated how a decrease in the HA activation pH influences the properties of highly pathogenic H5N1 influenza virus in mammalian hosts. Viruses containing either wild-type HA or an acid-stabilizing point mutation were prepared. Wild-type and viruses with the mutation promoted similar levels of morbidity and mortality in mice and ferrets. The mutation was found to enhance the growth of an H5N1 influenza virus in the mammalian upper respiratory tract, and yet it was insufficient to enable contact transmission in ferrets. Neither virus transmitted efficiently to naive contact cage-mate ferrets. [Comment: It is fortunate that contact transmission was not found.]

35. The research focused on an antigenic cluster associated with a natural single hemagglutinin (HA) substitution that occurred between 1992 and 1995 in the H3N2 virus. Reverse-genetics experiments demonstrated that the HA mutation increases viral receptor binding avidity. The mutation does not prevent antibody binding; rather, viruses possessing this mutation escape antisera simply because the virus attaches to cells more efficiently. [Comment: The H3N2 virus has caused human infections when transmitted from swine. In a 2012 small outbreak, there was no evidence of community transmission. Nonetheless, the virus is an immune escape strain.]

While the search term was not designed to pick up the 2009 human pandemic H1N1 virus, it did pick up a few experiments involving mutagenesis of that strain. While some of this research is carried out at BSL2, it could be classified as research of great concern because that virus is airborne transmissible.

For research involving mutagenesis of vaccine strains, biosafety level was generally not reported. It is assumed that it is BSL2, as vaccine strains are attenuated or inactivated viruses. One concern is that some mutagenesis research could make a vaccine strain virulent. Researchers should be prepared to argue for the safety of their particular proposed vaccine-strain mutagenesis research to defend the lower BSL2 containment.

Several of the EoC (references 7, 10, 14, 17, 20, 21, 28, 29) are lab-made potentially dangerous influenza viruses that could spread from human to human by the airborne route.

Proactive review at the local, national, or international level that considers risk and value (benefits) should be considered before allowing any mutagenesis and related research that might result in Experiments of Concern to go forward, and under what conditions.

Conclusion

Research that employs, makes, or could make airborne transmissible strains is of the greatest concern. All this research should be subject to proactive international review and oversight. There is an urgent need for a binding international process. While the NSABB mandate is likely restricted to NIH-funded research or perhaps any research in the United States, it behooves the NSABB to urge the State Department to seek a binding international agreement for proactive review and oversight of potential pandemic research.

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Comments on the September 28, 2015 NSABB meeting

The comments below are a written version of oral comments presented during the public comment period at the NSABB Sept 28, 2015, meeting on the "robustness" of the process for regulation of GOF research that was in place before the funding pause. By this I mean the general DURC frameworks and the HHS frameworks for H5N1 (1) and H7N9 (2) GOF research. On paper, these processes sound robust. We have some historical record of how the process works – one example of which was published by *Nature* in the case of the University of Wisconsin and the reconstruction of a 1918-like virus (http://www.nature.com/polopoly_fs/7.18249!/file/WISC_Review.pdf). Based on the characteristics of the process so far, there are several areas of concern that in my judgment make that process less than robust.

The fact that the existing DURC process did not even flag PPP research as a separate issue until a confluence of accidents at prominent labs and public activism forced the issue, is a . Ironically, the extension by HHS of the Framework to H7N9 GOF research (2) appeared in the same issue of *Nature* in as a report of GOF studies from the Fouchier lab, funded by the US Government and not captured by this framework (3); see also http://comments.sciencemag.org/content/10.1126/science.1244158 .

More specifically the present Framework for H5N1 and H7N9 GOF that was in place before the funding pause has the following issues:

1. *Expertise*. Much of the responsibility for assessing risks and benefits under the current system lies with the institutional biosafety committee. These committees are mainly composed of laboratory scientists and laboratory safety experts. These committees are essentially expert in occupational health. The difference with pandemic risk is that the risk is a public health, possibly global risk. IBCs do not traditionally include epidemiologists who might be able to identify what is a potential pandemic pathogen experiment or what the likely magnitude of risk would be[1].

   IBCs are not well designed to consider such risks. If you read the IBC minutes from the University of Wisconsin that have been posted by *Nature* magazine, it is clear that the claims of the investigator are often accepted at face value. Most IBCs also have little or no expertise in biosecurity threats. Note that I am not criticizing IBCs' fitness for their traditional task of dealing with occupational health risk of most pathogens in the lab. I am criticizing their fitness for playing the same role in managing global public health risk, an issue that uniquely arises in the potential pandemic pathogen context.

[1] Prof. Yoshi Kawaoka has informed me that the University of Wisconsin IBC includes an infectious disease physician and a representative from the state Division of Communicable Diseases. I do not know whether these areas of expertise were represented at the meeting that approved the 1918-like virus work.

2. *Disinterestedness*. The current process for oversight depends mainly on the funders and the recipients of funding. Neither of these is a disinterested party. Institutional biosafety committees very often see their role as facilitating the research that they regulate and whose indirect costs support the IBC's activities. This may be another reason why IBCs and other reviewers have been prone to accept the claims of investigators, especially on the benefits, at face value even when they are aspirational.
3. *Quantitative considerations*. To my knowledge the existing process makes no effort to quantify risk, either at the IBC level – where we have a written record, or at the HHS level.
4. S*cope*. The policy applies only to institutions applying to the USG for funding for unclassified life sciences research, not to classified research or to non-HHS-funded research.

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August 10, 2015

[Submitted electronically to nsabb@od.nih.gov]

Samuel L. Stanley, MD
Chairman of the NSABB
Office of Science Policy
National Institutes of Health

IDSA Recommendations to the NSABB to consider during the Risk Benefit Assessment Process of Gain-of-function Research

Dear Dr. Stanley,

The Infectious Diseases Society of America (IDSA) is pleased to offer recommendations to the National Science Advisory Board for Biosecurity (NSABB) as it works with Gryphon Scientific to assess the risk and benefits of gain-of-function (GOF) research on pathogens with pandemic potential.

Ongoing technological advances in the life sciences increasingly offer critical new capabilities for understanding and managing human-microbe interactions. The goals of these efforts include health promotion and disease prevention. At the same time, these same capabilities, especially the means of manipulating genomes and, therefore, the properties of bacteria, viruses, and other infectious agents, pose important risks. Efforts to study and/or predict the natural evolution and emergence of pathogenic microbes by deliberately creating pathogens in the laboratory with enhanced disease-causing and transmission-promoting properties pose the greatest concern. Examples of this gain of function research include the recent creation of highly pathogenic avian influenza viruses with altered host range, enhanced transmissibility, and/or the ability to evade certain forms of human immunity.

ID specialists will be among the physicians who will respond to care for affected individuals in any microbial disease outbreak, be it of natural or human origin—either accidental or deliberate. ID specialists are also among those leading research efforts to counter these disease threats. Accordingly, ID specialists are especially well-positioned to understand the risks and benefits posed by potentially dangerous experiments involving pathogenic microbes and can be valuable advisors for those who will need to undertake complicated risk-benefit analyses (RBA).

IDSA applauds the NSABB for its recent efforts to develop a framework to guide the assessment of risk and benefit of GOF research. The framework highlights key considerations on how to structure this assessment, addresses and evaluates possible alternative approaches, includes the issue of human error or malevolent action, and finally considers the effectiveness of medical countermeasures. We are happy to see

that Gryphon Scientific's risk benefit approach significantly improves on the specificity of the framework, addressing several of our concerns with the draft framework. We offer below six additional points for NSABB and Gryphon Scientific to consider as you work together to assess the risk and benefit of GOF research and develop final recommendations to the U.S. Government (USG).

1. Focus on the GOF experiments of special concern

IDSA remains concerned that the NSABB framework's broad definition of GOF may inadvertently capture areas of research that pose a lower risk to the public. For example, while the NSABB recognizes the benefit of research aiding the development or selection of new or more effective vaccines, its framework still targets influenza vaccine production methods that rely on adaptation of viruses for growth in culture as GOF research. The adaptation and manipulation of wild type influenza virus for growth in eggs or mammalian cell lines are critical to vaccine manufacturing. This approach to produce high growth vaccine candidates has been practiced since the 1940s, and is essential to protect the public from both seasonal and pandemic influenza.

IDSA strongly urges the NSABB to narrow its definition of GOF research to be considered for RBA to avoid this inadvertent capture of low risk research, which is not mentioned in the original White House description of the types of research that should be included in the deliberative process. We recommend that the RBA process focus on research that is reasonably anticipated to result in a pathogen that combines high transmissibility with high pathogenicity in humans, as this combination poses the greatest risk to public health. Such research may involve enhancing either of these properties in a pathogen already possessing the other, or the simultaneous enhancement of both. Whereas other types of GOF research are of concern as well, notably that which increases resistance to known medical countermeasures, they are secondary to the above characteristics. IDSA believes that this definition strikes a balance between impeding experiments with lower risk that society has accepted for many years while ensuring that experiments of special concern are assessed appropriately.

2. Address the uncertainty in estimating both risk and benefit

The risk assessment process provided by Gryphon Scientific will have to use estimated data in the models, as it will have to make assumptions on risks and benefits. Although IDSA understands assumptions are necessary to assess risk and benefit, our society is concerned that Gryphon Scientific has not adequately addressed the uncertainty of its models. IDSA urges the NSABB and Gryphon Scientific to hold robust discussions with experts surrounding the uncertainty of its estimates of risk. We also recommend the NSABB and Gryphon Scientific ensure that its analysis of uncertainty not only include uncertainties in the outcome of the research, such as the pathogenicity changes in a GOF organism, but also the uncertainties in the assessments of likelihood of misuse of the science as well as the consequences of accidents, misuse, and regulations on the conduct of the science. Whereas Gryphon Scientific will use a qualitative assessment of the benefit of GOF research, we urge that the uncertainties around the benefits of research be explicitly considered. Finally, IDSA recommends Gryphon Scientific consider communicating specific assumptions used in its modeling as well as error due to uncertainty to assist the NSABB and other policy makers in better understanding the risk/benefit estimates.

3. Seek a wide breadth of expertise to aid in the RBA process

Gryphon Scientific has indicated that it will interview subject matter experts to obtain additional input to aid its RBA efforts. IDSA strongly supports these actions, and also urges the NSABB and Gryphon Scientific to consider seeking additional perspectives to inform the RBA process, including those of a range of experts in vaccine development, microbial risk assessment, public health response, physicians whose work is primarily clinical, as well as through engagement of the public. In addition, the moral and ethical implications surrounding GOF research have not been adequately addressed in the NSABB framework. Several experts in this field are actively engaged in the GOF debate, and their unique viewpoints can be valuable to the RBA process.

Some stakeholders have expressed concern that the experts best positioned to evaluate the risk and benefits of GOF research are in some cases the ones who are actively conducting the research. IDSA agrees this is an issue that should be considered, and strongly believes that while this RBA evaluation needs as many expert perspectives as possible, they must be transparent with all relevant interests disclosed.

4. Risk should account for the impact on the public perception of science.

One important type of risk that is not included in the NSABB framework, or by Gryphon Scientific's mandate, is the ethical, reputational, and credibility risk for science with the public. The recent laboratory mishaps at the nation's most prestigious laboratories have placed strain on the public's trust for scientific research. Should a USG funded GOF study result in an accident or a deliberate act that places the public at risk, the credibility of science as a whole may suffer. This, in turn, could lead the public to question the quality of public stewardship of biomedical funding and the reliability of scientific and medical advice on risk. This loss of public trust could significantly impair science's ability to inform evidence-based policy decisions. IDSA recommends that the NSABB consider recruiting additional perspectives, such as those with sociology and ethics expertise, to asses this risk as it develops its final recommendations.

5. Risk should account for the impact of any new GOF framework on the course of science.

The ability of humanity to protect itself against pathogens of pandemic potential rests on a vigorous and healthy scientific enterprise. Some, including IDSA members, have raised the concern that as controversy swirls around GOF types of experiments that these fields could abandon certain types of scientific approaches that are powerful tools of scientific inquiry. Furthermore, the concern has been raised that the best and brightest will avoid these areas of inquiry simply because of the weight of regulation, the uncertainty in planning careers in areas subject to moratoriums and increased scrutiny and the controversial nature of the work. If this happens, humanity will be more vulnerable to future threats. IDSA recommends that the possible risk of regulation to the scientific enterprise and, in particular, to certain fields of inquiry be factored in the overall risk-benefit analysis.

6. Consider recommendations on how to make GOF research safer

In Gryphon Scientific's assessment approach for GOF research benefit, it states that it will evaluate "other GOF experiment types" in addition to alternative approaches. IDSA believes these efforts will yield valuable information that may be useful in developing constructive recommendations on how GOF research may be conducted more safely. For example, at the

December 2014 National Academies of Science discussion on the GOF pause, one researcher presented data on how to engineer high risk influenza strains to only undergo productive infection in experimental animals, posing minimal risk to public health. This search for pragmatic solutions that lower risk of GOF has not been widely discussed in the debate, and IDSA urges that this be a more prominent component in the NSABB's final recommendations.

IDSA is committed to ensuring that the broader scientific and science policy community participates in efforts to appropriately guide gain of function research. To complement the NSABB's efforts, IDSA calls for a continued series of transparent broad discussions on gain-of-function and dual use research of concern among stakeholders, including scientists, healthcare workers, policy-makers, ethicists, and representatives from the public. These discussions include the consideration of risk-benefit methodologies, governance models, the place, if any, of classified research, social responsibilities of scientists and journal editors, increased vigilance of biosafety and security concerns, societal values, and, finally, the discussion should solicit international input.

IDSA thanks NSABB for this opportunity to comment, and looks forward to continuing to work with the U.S. Government and those who advise it to clarify the decision-making process on how and whether to undertake high-risk life science experiments. Should you have any questions or concerns about these comments, please feel free to contact Greg Frank, PhD, IDSA Program Officer for Science and Research Policy, at gfrank@idsociety.org or 703-299-1216.

Sincerely,

Stephen B. Calderwood, MD, FIDSA
IDSA President

About IDSA

IDSA represents over 10,000 infectious diseases physicians and scientists devoted to patient care, disease prevention, public health, education, and research in the area of infectious diseases. Our members care for patients of all ages with serious infections, including meningitis, pneumonia, tuberculosis, HIV/AIDS, antibiotic-resistant bacterial infections such as those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) vancomycin-resistant enterococci (VRE), and Gram-negative bacterial infections such as *Acinetobacter baumannii, Klebsiella pneumoni*ae, and *Pseudomonas aeruginosa*, and, finally, emerging infectious syndromes such as Ebola virus fever, enterovirus D68 infection, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and infections caused by bacteria containing the New Delhi metallo-beta-lactamase (NDM) enzyme that makes them resistant to a broad range of antibacterial drugs.