Compiled Written Public Comments to the National Science Advisory Board on Biosecurity (NSABB)

December 14, 2022 – January 27, 2023

Public Comments:

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16. John Purdy, Pacific University Oregon

Submission Date: 12/14/2022

Name: Nir Eyal, Nancy Fiedler, Anjali Gopal, Daniel Hausman, Monica Magalhaes, Bridget Williams and Signatories

Name of Organization: *Assorted (refer to attachment)*

Comment:

Dear Dr Parker and Ms. Young,

The NSABB has invited kindly public comments on the review of federal enhanced potential pandemic pathogen (ePPP) research and of other dual-use research of concern. Please find attached a comment on the bioethics aspects of this review, whose signatories include some of the world's leading bioethicists.

Please let us know if you would like for authors to come and speak before the NSABB or otherwise clarify our comment.

Thank you in advance for your attention,

Nir Eyal (corresponding author), Nancy Fiedler, Anjali Gopal, Dan Hausman, Monica Magalhaes, and Bridget Williams

Nir Eyal
Henry Rutgers Professor of Bioethics
Rutgers University

Additional Comment (attachment):

Dear Members of the National Science Advisory Board for Biosecurity (NSABB),

We are writing to you about the review of federal enhanced potential pandemic pathogen (ePPP) research and of other dual-use research of concern (DURC). Our comments and insights are reflective of our professional experience and our scholarly research. These are our personal comments as subject matter experts and do not represent any official position of the institutions with which we are affiliated.

In a word, we recommend:

> ***1. Stronger regulation:*** **Regulate ePPP research and other DURC, whenever funded by- or located in the U.S., through legally binding, exceptionless regulation.**
>
> ***2. Better regulation:*** **Increase the independence, competency, and transparency of ePPP and other DURC review and oversight.**

*

Imagine that you learned that researchers are conducting a study on U.S. soil that puts millions of Americans' lives at significant risk, without securing their consent or undergoing institutional review. That may sound like science fiction, or a story that could only unfold before the Common Rule and modern research ethics oversight systems. In fact, it is a legal possibility in the U.S. today, and many ePPP and DURC studies have done so.

First, the Common Rule and other U.S. research ethics regulation is almost exclusively focused on the protection of human study participants [3,4]. Yet ePPP research and DURC rarely have any human study participants. Still, ePPP research and DURC can critically affect a great many people who are not study participants. The potentially mortal effects of accidental or intentional release of engineered pandemic strains might affect millions or billions who, unlike normal study participants, will have never provided their consent to being placed at risk. Governments should not treat these potential effects more lightly than they do the effects of clinical studies, social science research, and non-ePPP animal research.

Additionally, the Common Rule covers only research conducted or funded by a US federal agency (§46.101). It does not cover privately funded, or foreign-government funded, studies in the U.S. But private or foreign-funded ePPP research and other DURC on U.S. soil could pose grave danger to the population of the U.S. In some cases of ePPP research on U.S. soil, one reason cited for the absence of institutional review was absence of federal funding [1,2].

This regulatory lacuna is not only a technical imperfection. It represents one of the foremost dangers to U.S. and global public health. COVID-19 has reminded us of the steep social, economic and health costs of infectious disease outbreaks. Biosafety incidents risk sparking outbreaks that could be on this scale or greater. Even well-meaning research on ePPP and DURC more generally could give malevolent actors clues for the design of pathogens with worse features than SARS-CoV-2, for example, more communicable or more lethal viremia [6]. Such pathogens could then be released, intentionally or unintentionally, as possibility demonstrated by the significant historical rate of biosafety breaches [5].

It is true that ePPP research and other DURC may occasionally have high social value, for example, in improving our understanding of microbial genetics of high PPP risk pathogens to improve vaccine responses [7]. But for much ePPP research, the expected value of the knowledge gained is questionable [8]. The potential of some ePPP and other DURC for high social value means that careful independent screening of studies for ones with sufficient social value to warrant their high social risks is needed.

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We make two suggestions:

1. Stronger regulation: **Regulate ePPP research and other DURC, whenever funded by- or located in the U.S., through legally binding, exceptionless regulation.**

The Potential Pandemic Pathogen Care and Oversight (P3CO) and DURC policies should be codified into law, and NSABB would ideally recommend that it is. Regulating research funded by the USG or located in the U.S. was a NSABB recommendation in 2016 and should remain one until implemented [9]. Legal teeth are key to assuring that all qualifying research goes through a review process. Even if 90% of qualifying research went through review, the societal impacts from even one unregulated study protocol causing a biosafety or biosecurity incident would remain too high. Every bit of review, in the US and elsewhere, reduces this important source of risk, and matters a lot.

While a permanent moratorium on ePPP research is a blunt policy tool, a temporary moratorium until stronger and better regulation is put in place (perhaps with an exception for *low-risk* research on enhanced SARS-CoV-2) would stave off the largest sources of risk.

2. Better regulation: **Increase the independence, competency, and transparency of ePPP and other DURC review and oversight.**

First, just as a clinical researcher should not serve on their own institutional review board (IRB), decisions about the review of ePPP studies and other DURC should not be left to these studies' principal investigators. The current partial reliance on scientific self-governance lets potential foxes guard the henhouse, risking accidents and dangerous abuse. Instead, review and oversight should always be fully external to the study team.

Second, review and oversight of ePPP studies and other DURC should not be tasked to IRBs, either. They lack the capacity and subject-matter expertise, and do not represent all relevant disciplines [10]. For example, the complex and partly normative assessment of a study with a low chance of causing enormous harm to the health and welfare of large populations requires expertise in decision science and in population-level bioethics. The P3CO process should be staffed by experts in all relevant disciplines.

Third, given that we are all at risk from ePPP research and from all DURC, members of the general public should also be included in the review process, as they are in human-subjects review in many countries.

Fourth, the criteria and processes for the review and oversight must be clear and transparent. Currently, ePPP- and other DURC scientists who seek to comply with regulations and to conduct safe research are sometimes puzzled and uncertain about what is expected of them, and which regulations apply [2].

Fifth, we suggest examining the feasibility of creating a tiered system of review for ePPP and DURC research, partially analogous to the federally-designated categories of IRB review for human subjects research, so as to reserve the typically most onerous review to the riskiest studies. The existence of such guidance would also encourage researchers to select lower-risk approaches whenever possible.

Sixth, individual researchers and anyone else with a conflict of interest must not serve on the committee. To that purpose, the content of the deliberations and the identities and conflict-of-interest statements of the review panel should be made public.

Lastly, in order to help motivate the difficult transition to a safer review system, we call for a federal examination of why only three out of what appears to be at least 11 qualifying ePPP studies have been sent to the P3CO committee since 2017 [11]. In an area where failsafe policies are needed, this low figure indicates that current ePPP and DURC structures remain too weak.

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NSABB Members, you have a one-time, historical opportunity to address one of the foremost risks to U.S. and international public health. Please do not maintain the *status quo*. Take thoughtful, bold action. You have the power to begin an institutional transformation that could save a legion of lives.

Sincerely,

Writers:

- Nir Eyal, *Rutgers Center for Population-Level Bioethics; Rutgers School of Public Health [corresponding author]*
- Nancy Fiedler, *Rutgers School of Public Health*
- Anjali Gopal, *MIT*
- Daniel Hausman, *Rutgers Center for Population-Level Bioethics*
- Monica Magalhaes, *Rutgers Center for Population-Level Bioethics*
- Bridget Williams, *Oxford University Philosophy Department*

Signatories:

- Arthur Caplan, *Drs. William F. and Virginia Connolly Mitty Professor of Bioethics and Founding Director of the Division of Medical Ethics at New York University Grossman School of Medicine*.
- Roger Crisp, *Professor of Moral Philosophy and Director of the Oxford Uehiro Centre for Practical Ethics, University of Oxford, UK*.
- Nancy S. Jecker, *Professor of Bioethics and Humanities, University of Washington School of Medicine; President, International Association of Bioethics*.
- Maria W. Merritt, *Associate Professor, Berman Institute of Bioethics and Bloomberg School of Public Health, Johns Hopkins University.*
- Julian Savulescu, *Chen Su Lan Centennial Professor of Medical Ethics; Director, Centre for Biomedical Ethics, National University of Singapore*.
- Udo Schuklenk, *Professor of Philosophy and Ontario Research Chair in Bioethics; Joint Editor-in-Chief, Bioethics & Developing World Bioethics*.
- Peter Singer, *Ira W. DeCamp Professor of Bioethics, University Center for Human Values, Princeton University*.
- Bastian Steuwer, *Assistant Professor of Political Science, Ashoka University, India*.
- Marcel Verweij, *Professor of Philosophy, Wageningen University, The Netherlands; co-editor, Public Health Ethics*.
- Rhenzong Qiu, *Professor & Director, Program in Bioethics, Institute pf Philosophy, Chinese Academy of Social Sciences; Professor & Director, Institute of Bioethics, Center for Ethics and Moral Studies, Renmin University of China*.

The work of NE, DH, and MM is funded by Longview Philanthropy, a nonprofit dedicated to protecting the long-term future of humanity.

Citations

[1] Boston University. NEIDL Researchers Refute UK Article about COVID Strain. BU. https://www.bu.edu/articles/2022/neidl-researchers-refute-uk-article-about-covid-strain/.

[2] Branswell, H. Boston University researchers' testing of lab-made version of Covid virus draws government scrutiny. Stat News. https://www.statnews.com/2022/10/17/boston-university-researchers-testing-of-lab-made-version-of-covid-virus-draws-government-scrutiny/

[3] Kimmelman J. Medical research, risk, and bystanders. IRB. 2005;27(4):1-6;

[4] Eyal N, Holtzman L. Symposium on risks to bystanders in clinical research: An introduction. Bioethics. 2020;34(9):879-82. Epub 2020/11/23. doi: 10.1111/bioe.12830. PubMed PMID: 33222256.

[5] Henkel RD, Miller T, Weyant RS. Monitoring select agent theft, loss and release reports in the United States—2004-2010. Applied Biosafety 2012;17(4):171-80.

[6] United Nations Secretary-General, 2020. Remarks to Security Council Open Video-Teleconference on the Maintenance of International Peace and Security: Implications of COVID-19, 2 July, New York, available at https://www.un.org/sg/en/content/sg/speeches/2020-07-02/remarks-security-council-maintenance-of-international-peace-and-security-implications-of-covid-19

[7] Lipsitch M [@mlipsitch]. BU Experiments]. Twitter. https://twitter.com/mlipsitch/status/1582573645821796354.

[8] Lipsitch M, Inglesby TV. Moratorium on research intended to create novel potential pandemic pathogens. mBio. 2014;5(6). Epub 20141212. doi: 10.1128/mBio.02366-14. PubMed PMID: 25505122; PMCID: PMC4271556.

[9] NSABB. Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research. 2016. https://osp.od.nih.gov/wp-content/uploads/2016/06/NSABB_Final_Report_Recommendations_Evaluation_Oversight_Proposed_Gain_of_Function_Research.pdf

[10] Wikler D. Bystanders and ethical review of research: Proceed with caution. Bioethics. 2020;34(9):937-40. Epub 20201022. doi: 10.1111/bioe.12823. PubMed PMID: 33090500.

[11] Kaiser, J. Making Trouble: U.S. Weighs Crackdown. Science. doi:10.1126/science.adf3762. https://www.science.org/content/article/u-s-weighs-crackdown-experiments-could-make-viruses-more-dangerous

Submission Date: 1/24/2023

Name: Nariyoshi Shinomi, Jusaku Minari, Go Yoshizawa, Simon Whitby, Lijun Shang, Malcolm Dando

Name of Organization: *Assorted (refer to attachment)*

Comment:

Dear Ryan,

On behalf of the UK and Japan research groups, here I send our proposal for the coming NSABB meeting. Because of the time difference, I don't think I can listen to the meeting in real time.

Thank you for your help in advance.

Best regards,

Nariyoshi

Nariyoshi Shinomiya, M.D., Ph.D.
President
National Defense Medical College

Additional Comment (attachment):

Public comments for the coming NSABB meeting

January 25, 2023

Proposals for future governance of GOF research of the kind that creates ePPPs

by Nariyoshi Shinomiya[1], Jusaku Minari[2], Go Yoshizawa[3], Simon Whitby[4], Lijun Shang[5] and Malcolm Dando[6]

[1]President, National Defense Medical College, Saitama, Japan.
[2]Uehiro Research Division for iPS Cell Ethics, Center for iPS Cell Research and Application (CiRA), Kyoto University, Kyoto, Japan.
[3]Innovation System Research Center, Kwansei Gakuin University, Hyogo, Japan.
[4] Bradford Disarmament Research Centre, University of Bradford, Bradford, United Kingdom.
[5]Professor of Biomedical Sciences, School of Human Sciences, London Metropolitan University, London, United Kingdom.
[6]Section of Peace Studies and International Development, University of Bradford, Bradford, United Kingdom.

GOF studies of the kind that create ePPPs have focused on avian influenza viruses, SARS viruses and MERS viruses. A common feature of these pathogens is that they tend to cause aerosol-mediated respiratory tract infections and have the potential to be readily transmitted to non-immune populations. Thus, intentional mutation of pathogens derived from animal hosts to induce properties that make them infectious to humans makes them capable of causing pandemics.

Many emerging infectious diseases are caused by mutations in pathogens that originally infect animals and jump the species barrier to become infectious and contagious to humans. So far, the main objectives of GOF research to create ePPPs have been (1) to elucidate the mechanisms that lead to the transmission from animals to humans, (2) to contribute to the anticipation and surveillance of predictions of outbreaks such as endemics and pandemics, and (3) to select suitable vaccine strains. On the other hand, since ePPPs are artificially created through research, there is a risk of inadvertent leakage or intentional misuse that could lead to a pandemic. This is the most worrisome aspect of such studies, and the feasibility of conducting any particular study should be considered after a thorough examination of the balance between risks and benefits.

However, a review and analysis of the results of GOF research to date indicates that the

benefits to society are limited. In other words, the benefits have not been sufficiently proven to significantly outweigh the risks, but there is a minority view that the benefits will clearly outweigh the risks in the future[Ref]. (1) As for the mechanism of jumping the species barrier, which is shown above as the so-called "advantage of GOF research to create ePPPs," simulations based on computer models and specific analysis of genes in the relevant area are expected to produce sufficient information, and the advantage of daring to create ePPPs has not been proven. Therefore, the merit of creating ePPPs has not been convincingly demonstrated. In addition, (2) as for epidemic forecasting and surveillance, there is no evidence showing that ePPPs have contributed to the clarification of actual epidemics. As the most important benefits of scientific and technological progress in this respect are the rapid and mass sequencing of genomes and the advancement of their analysis systems, it is difficult to believe that the merits of GOF research outweigh these benefits. (3) When it comes to the selection of vaccine strains, it is nearly impossible to predict in advance, as pathogens can mutate rapidly. Even if the prevalent pathogen strain could be identified in advance, that itself cannot be used immediately as a vaccine as its efficacy can only be proven in actual clinical studies in the late stage. Therefore, as shown in our experience of COVID-19, the useful vaccine development technologies are (1) mRNA development technology, (2) recombinant virus vector technology, and (3) creation of inactivated vaccines based on epidemic strains, and there is very little evidence to justify the significance of creating ePPPs.

Taken together, we believe that there is little scientific evidence that the benefits outweighed the risks in GOF studies to create ePPPs. Therefore, the advantage of continuing such studies in the future seems very low. We also believe that continuing such studies is an inappropriate choice from the perspective of avoiding the associated risks.

Of course, we are clearly against restricting the freedom of scientific research and legitimate research based on the spontaneous ideas and intentions of researchers. It is desirable that science and technology be developed in a sound manner and applied in a way that contributes to society. From this standpoint, we believe that what should be promoted should be promoted, and that measures should be taken to ensure that the studies that are needed are properly governed.

Based on the above, we propose the following:

1. Establish a moratorium on GOF research that produces ePPPs for the time being, and consider banning research unless the significance of the research that should be conducted is well demonstrated.
2. For research involving the risk of infection, including GOF research to create ePPPs, the same measures should be taken regardless of whether the research is conducted or funded by a public or private institution.
3. Research using specific pathogens, regardless of whether it is GOF research to create ePPPs or not, carries risks. Therefore, - transparency and traceability should be ensured in the conduct of the research, while biosafety/biosecurity is adequately ensured.

Researchers and research facilities should be open to disclosure of all information as long as it does not interfere with patentability and originality of the research.

Our position on the GOF study to create the ePPP is as stated above, but we are sure that there are those who disagree with this position, and we sincerely hope that both sides can reach a common conclusion after a frank discussion in order to deal with this issue in the future. We are convinced that such open debate is the best way to ensure the future of necessary research and its effective management.

It is our sincere hope that the NSABB meeting will take the above proposals into full consideration, and that the discussions will proceed appropriately and result in a meaningful conclusion.

Reference

Shinomiya N, Minari J, Yoshizawa G, Dando M, Shang L. Reconsidering the need for gain-of-function research on enhanced potential pandemic pathogens in the post-COVID-19 era. Front Bioeng Biotechnol. 2022 Aug 26;10:966586. doi: 10.3389/fbioe.2022.966586. PMID: 36091454; PMCID: PMC9458934.

Submission Date: 1/24/2023

Name: David R. Gillum

Name of Organization: Arizona State University

Comment:

To Whom it May Concern:

Here are a few questions for Friday's NSABB meeting:

1. How do you define "likely moderately" and "highly transmissible" in the report?
2. What is the expected workload increase based upon these recommendations for an institution's biosafety professionals, compliance personnel, researchers, and others?
3. What is the expected cost to implement these recommendations at each institution?
4. Will there be funding provided to institutions to offset the increase in cost to implement this policy?
5. What would be the implications of combining the P3CO and DURC policies? For example, how would it impact NIH? How would it impact institutions?
6. Could there be some effort by NIH to quantify the impact of this policy, including the cost to implement and the cost to manage it over time?

Please feel free to contact me to discuss further.

Thank you,
David

David R. Gillum
Assistant Vice President and Chief Safety Officer
Environmental Health and Safety
Arizona State University

Additional Comment (attachment): None

Submission Date: 1/25/2023

Name: Daniel Blanco-Melo

Name of Organization: Fred Hutchinson Cancer Center

Comment:

To the National Science Advisory Board for Biosecurity,

While the COVID-19 pandemic will be remembered as a dark time in human history, it will also be remembered by how the scientific community raised up to the task and in record time produced a detailed understanding of what type of pathogen we were facing, how it was transmitted, how the body reacted to it, and how we could prevent its spread and ease the resulting disease. Although SARS-CoV-2 was a novel virus, the tools that allowed the timely delivery of knowledge, were built and refined in previous decades through basic biology research on other infectious diseases. Still, it is remarkable, that 10 days into 2020 we were able to know the entire sequence of the viral genome, and in a lapse of a few months we even had a validated efficient vaccine that has prevented millions of deaths worldwide.

Despite these successes, the unprecedented attention to the field of virology that the COVID-19 pandemic drew, has derived also in public concern about the safe conduct of research with human pathogens. While some narratives come from legitimate concerns and curiosity, the amplification of so called “fake news”, incomplete stories and individual political agendas, has resulted in public confusion about the safety of the biological research currently being performed, and driven requests for limiting, or even banning, some types of research, including those that I was praising previously.

Gain-of-function (GoF) research, defined as the genetic alteration of pathogens to change or enhance its biological functionality, is a valuable genetic tool used by scientists to understand essential biological and pathological processes, and even to develop much needed therapeutics against a variety of diseases. In fact, GoF research is behind remarkable discoveries that have enhanced human health – such as vector-based vaccines and oncolytic viruses for curing cancer – or even guided surveillance efforts to prevent future pandemics. While it might sound like extracted from a thriller movie, GoF research actually requires careful planning, it involves laborious work, and it is tightly regulated by rigorous policies from the U.S. government and most international publishers, in order to limit performing unnecessarily risky research or releasing information that could potentially be misused.

Therefore, the NSABB and scientific community must work together to build comprehensive policies that identify research of concern, consider the risks and benefits of such research, and establish safeguards to prevent any misuse. Thereby allowing scientists to keep innovating and enhance our ability to prepare for future viral threats.

Daniel Blanco-Melo, Ph.D.

Assistant Professor
Vaccine and Infectious Disease Division
Fred Hutchinson Cancer Center

Additional Comment (attachment): None

Submission Date: 1/25/2023

Name: Ryan Langlois

Name of Organization: University of Minnesota

Comment:

NSABB working group,

While I strongly support reasonable oversight on virology research I am concerned that this proposal is too broad and will cripple the field's ability to help prevent and respond to the next pandemic. One of the outlined DURC Policy Scope – Categories of experiments is particularly concerning: 5. Alter the host range or tropism of the agent or toxin. This would include "reverse zoonosis" studies where human viruses are put into animal models to test pathogenicity, antiviral drugs, vaccines, etc. This is also how some of the first live attenuated vaccines were generated, demonstrating that these approaches actually reduce, not increase, pathogenicity in people. I am not aware of any instance where this kind of research caused harm in humans. Hindering these kinds of low risk studies, which are vetted at the institutional level, will harm our capacity to fight future pandemics.

Sincerely,

Ryan A. Langlois, Ph.D.
McKnight Presidential Fellow
Associate Professor
Dept of Microbiology & Immunology
University of Minnesota

Additional Comment (attachment): None

Submission Date: 1/25/2023

Name: Christopher B. Brooke

Name of Organization: University of Illinois at Urbana-Champaign

Comment:

Dear NSABB working groups,

I am a faculty member at the University of Illinois, where my research group studies the evolution and pathogenesis of seasonal human influenza viruses. I am a strong supporter of responsible, community-informed review of potentially risky virology research and believe that oversight of this work should be updated as our understanding of biosafety risks evolves. That said, recommendation 10.1 in the January 2023 draft findings and recommendations of the NSABB working groups is likely to cripple the virology research endeavor in the United States, and along with it our ability to prevent and respond to future viral pandemics.

Recommendation 10.1 proposes to expand the group of agents and toxins subject to DURC oversight from the current list of 15 to include "any human, animal, or plant pathogen, toxin, or agent that is reasonably anticipated to result in one or more of the seven experimental effects" listed in Box 2. The problem with this is that **many of the categories of experiments listed in Box 2 are vaguely written and could easily be interpreted to include vast swaths of virology research that are of negligible risk**. Implementing this policy would massively expand the breadth of research that qualifies as potential DURC to include areas of research which pose no real public health or agricultural risk. Specific examples include:

Item 1. "Enhance the harmful consequences of the agent or toxin". "Harmful consequences" is an incredibly vague term that does not specify which host system it is in relation to. Many experiments may make an agent more cytotoxic or pathogenic in a given *in vitro* or *in vivo* model (and thus fitting the description) without actually increasing virulence in the host species of concern. For instance, adapting a human-origin virus to a mouse model will often "enhance the harmful characteristics of the agent" for a mouse, while generally decreasing expected harmfulness in the original human host.

Item 5. "Alter the host range or tropism of the agent or toxin". This language taken at face value would cover virtually any experiment where an agent is allowed to replicate in a host system other than its natural host *i.e.* the bulk of modern virology research. Almost any experiment where a virus is allowed to replicate in a new host system will result in a viral population with improved tropism for that system. In the vast majority of these cases, the potentially expanded host range will include *in vitro* or *in vivo* model systems that have negligible expectation of increasing pandemic risk. For example, this language would cover most work done with viruses in *in vitro* systems (where viruses are commonly grown in cell lines that originate in host species distinct from their natural host) as well as all historical live

attenuated vaccine development (which depended on alteration of tropism to lower virulence in the natural host).

While you can certainly imagine experiments in either of these categories that would be high risk and thus appropriate for elevated DURC review, as written these guidelines would necessitate classification of a huge number of studies with negligible risk as potential DURC. In practice this will cripple the virology research endeavor by imposing an enormous new regulatory and financial burden on investigators and institutions, the vast majority of whom are doing work with no real risk. **This will greatly hamper our ability to predict, prevent, and respond to future pandemics**.

The language should be rewritten to include only the specific types of agents known to pose pandemic risk and the types of experiments that could reasonably be expected to increase the ability of those agents to spread and cause disease in humans or other economically important hosts. This language should be written with input from experts in the evolution of cross-species transmission and virulence.

Thank you for your consideration.

Chris Brooke, PhD
Associate Professor of Microbiology
University of Illinois at Urbana-Champaign
Brookelab.org

Additional Comment (attachment): None

Submission Date: 1/25/2023

Name: Anice Lowen

Name of Organization: Emory University School of Medicine

Comment:

To whom it may concern:

I write in reference to the National Science Advisory Board for Biosecurity (NSABB) Meeting scheduled for 01/27/2023. I would like to offer the following written comments.

The draft recommendations propose a significant expansion of the scope of ePPP and DURC oversight. While appropriate safeguards on biomedical research are essential, I would like to emphasize to the board that requiring federal review of research on all pathogens, in addition to existing institutional review, will have a major impact on the pace of research progress. Our ability to respond rapidly to emerging viral threats will be negatively impacted. Regulations that are overly cumbersome will lead to unwarranted constraints on pandemic preparation and response could leave humanity more vulnerable to future disease outbreaks.

In addition, the phrase 'reasonably anticipated' is very problematic in that its interpretation is likely vary widely among individuals. This will lead to inconsistency in implementation across institutions and leave investigators and institutions open to criticism following publication of work that was deemed not to meet this bar upon either local or federal review.

Finally, I agree with draft finding no. 13: DURC and P3CO frameworks are largely redundant and should be streamlined into a single oversight framework to reduce the burden of review on investigators, institutions and the Government.

I thank the Board members for their consideration of these comments and for their service.

Anice Lowen

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Anice Lowen, PhD
Associate Professor
Department of Microbiology and Immunology
Co-Principal Investigator, Emory CEIRR
Emory University School of Medicine

Additional Comment (attachment): None

Submission Date: 1/26/2023

Name: Michael Imperiale

Name of Organization: University of Michigan

Comment:

I would like to submit the attached comments for consideration by the Board at tomorrow's meeting.

Thanks very much.

Mike
--
Michael J. Imperiale, Ph.D.
Arthur F. Thurnau Professor
Department of Microbiology and Immunology
University of Michigan
Editor-in-Chief, *mSphere*

Additional Comment (attachment):

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January 26, 2023

National Science Advisory Board for Biosecurity

Dear Colleagues:

I am writing to provide feedback on the *Proposed Biosecurity Oversight Framework for the Future of Science*.

In general, I think that the recommendations in this report are a step in the right direction. I can't help but notice that many of them sound very familiar to what we original members of NSABB proposed in our many reports in the 2000's, but which were not acted upon. For example, the 2007 Draft Framework did not propose to limit oversight to a specific list of agents; raised the issue of non-federally funded research; was not solely human pathogen-focused; and noted the importance of international cooperation.

I do have two concerns that I would like to raise about the current proposal.

The first is the analogy to the Belmont Report. I think this is ill advised. The oversight of human subjects research is a very different matter than the oversight of basic laboratory research. In addition, I strongly disagree with the proposal to modify Section III.4 of the P3CO policy to state "Risks that are not necessary to answer an important scientific question have been eliminated…" As we know, it often is not possible to eliminate all risks. Perhaps one can state that "Risks that are not necessary to answer an important scientific question have been appropriately considered and mitigated…."

My greater concern relates to the expansion of oversight to all microorganisms. While I do not disagree with this idea in principle, unless the types of experiments that do and do not require some type of review are clearly defined, this could lead to a lot of unnecessary review. In turn, research that is required to protect the world from pathogens and to contribute to US economic competitiveness will be slowed due to the presence of sand in the gears. I would note that this could have a huge impact on the field of synthetic biology, which is predicted to be a major contributor to the US bioeconomy in the near future. As the January, 2023 GAO report on Health Preparedness noted, the term "reasonably anticipated" is incredibly subjective. It will be even more problematic if, as it is proposed in the current NSABB document, additional responsibilities for review are imposed on institutions. There will be a lack of consistency among institutions unless very specific guidance and definitions are developed. In addition, I would surmise that many institutions do not have the appropriate expertise to determine what poses a risk. Thus, some sort of centralized review body will be necessary. The counterargument to having a centralized body, of course, is that it will definitely slow things down. This, too, was noted in the old NSABB reports. Thus, we have to have a clear delineation of what we are truly concerned about. "Reasonably anticipated" unfortunately does not cut it. I can tell you from my

experience on the ASM Responsible Publication Committee that this means different things to different people.

I would like to thank the current NSABB for its thoughtful work and tremendous efforts, and for the opportunity to provide these thoughts.

Sincerely yours,

Michael J. Imperiale, Ph.D.
Arthur F. Thurnau Professor

Submission Date: 1/26/2023

Name: Andy Pekosz

Name of Organization: Johns Hopkins University

Comment:

To whom it may concern,

As a virology researcher who has spent over 25 years investigating viruses that infect humans, I am writing to voice my extremely strong concerns over the NSABB recommendations that are being discussed today. I serve on my Institutional Review Entity for dual use research of concern and have participated in several government organized panels to discuss the biosafety and biocontainment needs for experiments involving H5N1 and 1918 influenza virus. My research has been primarily focused on viruses that are known human pathogens and circulate in annual epidemics (influenza A and B viruses, enterovirus-D68, SARS-CoV and SARS-CoV-2) but have also been involved in research on viruses that pose potential or emerging threats to humans. I am a fellow of the American Academy of Microbiology and a former President of the American Society for Virology.

My primary concern with these recommendations is the vague description of research that would fall under these guidelines. As described, virtually any research on microbes that cause human disease could be categorized as falling under these guidelines. Research on seasonal influenza transmission and evasion of preexisting immunity would fall under the areas of concern described in the document. The NSABB should take more time and effort to clearly describe the limited kinds of research that would require this higher level of scrutiny and approval to ensure that research that is critical to our understanding of known human pathogens that cause recurring infections are not caught up in these kinds of reviews, as it runs the risk of slowing and hampering our public health response to known human pathogens. I would also express my concern over the statement that implies investigators are inappropriately characterizing their work as being directly relevant to public health response or vaccine development to avoid additional biosafety scrutiny. This is a serious and strong allegation that needs to be supported by clear examples and evidence. In the absence of this evidence, the statement is simply inflammatory and sends the message that scientists should not be trusted.

I'll close by saying that I and my laboratory have always taken biosafety concerns very seriously and I certainly and strongly support additional clarification and transparency in the process of gaining approval for experiments that are focused on understanding how viruses evade preexisting immunity and maintain circulation in the human population. There are processes and procedures already in place that effectively do this but reassessing, streamlining and clarifying the process is something that should be done on a regular basis to ensure the process is working properly.

Regards,

Andrew Pekosz, Ph.D.
Professor and Vice Chair
W. Harry Feinstone Department of Molecular
Microbiology & Immunology
Johns Hopkins University
Bloomberg School of Public Health
http://www.jhsph.edu/faculty/directory/profile/1972/andrew-stanley-pekosz
Twitter: @andrewpekosz

Additional Comment (attachment): None

Submission Date: 1/26/2023

Name: James Alwine

Name of Organization: University of Pennsylvania School of Medicine

Comment:

Virology research is presently well regulated at the federal and local levels, thus I am bothered by the vagaries of the proposed oversight recommendations which appear to have been made with little or no consultation with virologists. The vagaries of the proposed regulations leave so much open and undefined that it is quite possible that, through pressures by anti-science groups, most viruses would eventually be swept into the category that gets increased oversight. This would greatly slow most virology research in the US; needlessly increase its cost and administrative burden, and make virology research unattractive for upcoming scientists who might have entered the field. Thus the greatest virology research enterprises in the world will be severely damaged. But recall the massive human and economic tolls caused each year by viral diseases of humans, animals and plants. The dismantled US virology enterprise would be unable to do research that might reduce these tolls. However, other countries would be able to, and the US would become beholden to others for pandemic detection and preparedness, vaccine development and supply, anti-viral drug development and basic virology knowledge. The economic costs and consequences of this scenario would be great, all resulting from ill-defined oversight. It is essential that pathogen research be well regulated but it must balanced, evidence-based oversight which maintains and expands much-needed virology research in the US.

James Alwine

Additional Comment (attachment): None

Submission Date: 1/26/2023

Name: Richard Webby

Name of Organization: St. Jude Children's Research Hospital

Comment:

To whom it may concern.

I would like to submit a written comment in response to the proposed Biosecurity Oversight Framework for to Future of Science to be discussed by the NSABB. This comment follows.

My comment relates to specific recommendation 2 that "Remove current blanket exclusions for research activities associated with surveillance and vaccine development or production. However, include and implement processes and procedures for urgent federal department level review and evaluation of ePPP research critical for public health or national security."
I would urge great caution in how this specific recommendation is implemented as it has tremendous capacity to negatively impact pandemic preparedness and the "future of science". One of the most acknowledged issues with implementing the current DURC and P3CO policies at the local level is lack of clarity (also identified in the recommendations). Should the current exemption for surveillance be removed and no detailed clarity provided on what aspects of surveillance would even fall under further review, the impact at the institutional level in many places will be a halt of these critical public health and scientific activities. Collection of samples from the field and further characterization in the laboratory underpins pandemic preparedness and response and should definitively not be considered a DURC or P3CO activity; I cannot imagine that this would be the intention of the committee. If the amended recommendations do not provide clarity to the Institutional Review Entity as to why surveillance activities would even need to be considered for further review the results will be damaging. I understand the recommendation to "include and implement processes and procedures for urgent federal department level review" but it is not the experiments that clearly reach the need for further review that concerns me. It is those activities that don't, but may be inadvertently caught up in institutional uncertainty.

Thank you

Richard Webby

Additional Comment (attachment): None

Submission Date: 1/26/2023

Name: Rebecca Dutch

Name of Organization: Unknown

Comment:

Dear NSABB members,

I am writing today out of concern for the policies being considered by the NSABB, especially related to the field of virology. We have faced a disastrous worldwide pandemic in the last few years driven by an emerging virus. Virologists have worked diligently for decades to understand the molecular details of infection by these pathogens, and to determine mechanisms to combat them. Virologists have also been warning of the wealth of potential pathogens that currently exist in nature. The diligent work of so many scientists is the reason the COVID pandemic was not worse than it was. Vaccines were rapidly developed which dramatically slowed the course of the pandemic, and the mRNA vaccines in particular absolutely drew off of the knowledge obtained from the study of previously known pathogens such as SARS and MERS. Antivirals were developed not long after, and again the knowledge obtained from years of study was instrumental.

We have faced multiplied emerging threats in the recent past - and will almost inevitably face more in the future. Careful and comprehensive research on a variety of pathogens is absolutely critical to ensure we are prepared. Enacting new policies that restrict critical classes of research is dangerous for all, and increases the risk that we will not be prepared for the next emerging virus. Decisions driven by unfounded beliefs that these pathogens were created by man, and not nature, are extremely troubling. Man likes to believe that we are in control of nature - but we are not. Nature has mechanisms to generate a wide variety of pathogens, and the very best thing we can do is to be as prepared as possible to meet the challenge.

Rebecca Dutch

Additional Comment (attachment): None

Submission Date: 1/26/2023

Name: Randy Albrecht

Name of Organization: Mount Sinai School of Medicine

Comment:

The NSABB findings and recommendations draft report, Proposed Biosecurity Oversight Framework for The Future Of Science, provides a detailed assessment of the two oversight frameworks governing biomedical research with enhanced potential pandemic pathogens (PPPs) and Dual Use Research of Concern (DURC). Development and implementation of a single regulation that provides clear oversight of biomedical research, regardless of funding source, with PPPs and DURC, including clear articulation of the federal, institutional, and investigator responsibilities, would be a positive outcome of this review process. However, implementation of some of the nineteen recommendations may impart unintended restrictions on biomedical research in pandemic preparedness and response to emerging infectious diseases, including zoonotic diseases. This review process should address the potential negative impact of these recommendations and current frameworks on public health risk assessment activities for emerging infectious diseases, including zoonotic diseases. It is unclear how the proposed recommendations will shorten the timeline of the review and determination process for research involving PPPs or DURC and how funding agencies may incorporate those pertinent recommendations into their review processes for research grant and contract applications.

Thank you for this opportunity to provide comments on these draft recommendations.

Randy A. Albrecht

Additional Comment (attachment): None

Submission Date: 1/26/2023

Name: Tom Inglesby, Anita Cicero, Jaspreet Pannu, Marc Lipsitch, David Relman

Name of Organization: *Assorted (refer to attachment)*

Comment:

Dear colleagues,

Thank you for the opportunity to provide public comment. Please find attached a letter responding to the NSABB document "Proposed Biosecurity Oversight Framework for the Future of Science" recently posted on the NIH website.

I will also be giving brief remarks (at 1:56pm Eastern) about this response during the public comment segment of tomorrow's (Jan 27) NSABB meeting.

With best regards,
Tom Inglesby

Tom Inglesby, MD
Director, Johns Hopkins Center for Health Security
Professor, Environmental Health and Engineering
Johns Hopkins Bloomberg School of Public Health
Joint Appointment, Medicine, Johns Hopkins School of Medicine

Additional Comment (attachment):

Response to the NSABB Document

"Proposed Biosecurity Oversight Framework for the Future of Science"

January 26, 2023

Dear NSABB members,

We are writing in response to the NSABB document **"Proposed Biosecurity Oversight Framework for the Future of Science"** recently posted on the National Institutes of Health (NIH) website. In early July 2022, we and 29 other signatories (the 'Signatory Group') submitted a document titled *Recommendations to Strengthen the US Government's Enhanced Potential Pandemic Pathogen Framework and Dual Use Research of Concern Policies* to the NSABB, NIH, and White House. In September, a subset of this group submitted this letter in response to your preliminary draft report.

The purpose of this letter is to commend recommendations made in the new NSABB draft document, including significant improvements since the September draft. It is also to express continued concern about remaining policy gaps that we believe should be addressed in the final NSABB report to the US government (USG).

We commend the NSABB for its recommendations to the USG to:

- ***Modify the definitions of potential pandemic pathogens (PPP) and enhanced potential pandemic pathogens (ePPP)*** to place the focus on what can be reasonably anticipated regarding the resulting pathogen, and to include transmissible pathogens that have low or moderate virulence, as well as less transmissible pathogens that have higher virulence, while focusing on the reasonably anticipated end state rather than the approach.
- ***End the exclusion for surveillance and vaccine-related work.***
- ***Articulate specific roles, responsibilities, and expectations for all institutions*** involved in the proposed research, including requiring local entities to conduct ePPP reviews before submitting for USG review and requiring the same level of oversight throughout the course of the research (not only at the start).
- ***Develop principles and guidelines*** applicable to substantiating the claims that:
    1. There are no feasible, scientifically sound alternative methods of obtaining the benefits sought in the research in a manner that poses less risk.
    2. Unnecessary risks have been eliminated and an overall assessment of remaining risks finds they are justified by the potential benefits to society.
- ***Share a summary of key determinants and decisions*** resulting from USG review.
- ***Designate a USG office with adequate technical and financial support*** to run this oversight and evaluation process.
- ***Consider developing similar frameworks for pathogens*** that could pose severe threats to human health or food security via impact on animals and/or plants.

Even with these many important recommendations made in the **"Proposed Biosecurity Oversight Framework for the Future of Science"** document, we are seriously concerned the document does not yet address several of the most important recommendations from our July document, which can be summarized as:

- ***Within the ePPP Framework, establish oversight of sequence information*** about ePPPs, the risks related to computational methods for designing PPPs, and biosafety measures related to the synthesis of ePPPs, which would address the information hazards that are created as part of this work.
- ***Distinguish between practical benefits and unsupported claims*** of benefit.
- ***Improve transparency throughout the approval process*** by using a model such as Registered Reports to allow for the public to see risk-benefit assessments and any dissenting views prior to the research commencing.

Fundamentally, we also remain concerned that the new NSABB draft recommendations do not spell out who decides, and at what stage, which proposals need to be subject to department-level review. We note that only three projects have been referred to the Department of Health and Human Services (HHS) for department-level review in the lifetime of the existing ePPP Framework. This is a period during which, for example, experiments were being performed on mpox virus that some in the community considered potential ePPP work, (https://www.science.org/content/article/u-s-weighs-crackdown-experiments-could-make-viruses-more-dangerous) even after it was clear that this virus in its naturally occurring form was capable of global spread.

Likewise, during the same period, government funds partially supported experiments on recombinant SARS-CoV-2 that, likewise, were judged by some experts to constitute ePPP work (https://www.science.org/content/article/was-study-created-hybrid-covid-19-virus-too-risky). The fact that these experiments did not get reviewed under the ePPP Framework is evidence that the existing guidelines are inadequate. We remain strongly concerned that while the changes proposed in the current NSABB draft document are big steps forward, there may still be too many loopholes exempting research that should be reviewed within this Framework.

NSABB should strongly advise the USG to ensure that oversight of this work will encompass all research falling within the scope of the policy, including research such as the recent concrete examples above.

Along these lines, we have concerns about one new stipulation that was added to the new NSABB draft document—Recommendation 1 now states that this policy only applies to research that "likely poses a severe threat to public health, the capacity of public health systems to function, or national security." In practice, this shifts the responsibility to the government program manager for determining whether the proposed research poses a severe public health threat at the start of the process, instead of where that judgment should reside, which is at the department-level review at the end of the review process. It is not clear why this new stipulation was added.

In addition to the above concerns, there are other challenges in current USG policy not yet addressed in the NSABB's **"Proposed Biosecurity Oversight Framework for the Future of Science."** To that end, we urge the NSABB to recommend both new and revised USG policy do the following:

- ***Articulate the risks that must be considered*** in the ePPP Framework process, including accident, deliberate misuse, and insider threat.
- ***Define the process for the "responsible communication of results."***
- ***Expand the stakeholders*** involved in the review and approval processes and recuse those whose agency is funding or participating in the research.
- ***Broaden the ePPP Framework to apply to non-federally funded research.***

- ***Require all USG agencies to implement*** the ePPP Framework.
- ***Strengthen USG outreach to other governments*** to catalyze ePPP Framework and Dual Use Policy development.
- ***Expand the types of experiments*** included in USG Dual Use Policy.

The recommendations noted above are highly important elements of a strong and clear governance framework for ePPP research and dual use research of concern (DURC) experiments. Incorporating these recommendations into the final NSABB document will help ***diminish the risk*** that US science could inadvertently initiate epidemics or pandemics while ***minimizing disruption*** of scientific work that does not pose this risk; ***clarify the scope and decision-making*** process; and ***increase transparency*** around US policy and decision-making on these issues.

We remain very hopeful that as the NSABB considers their current draft document and this additional feedback, these concerns will be addressed in the final recommendations to the USG. We are greatly appreciative of the NSABB's careful consideration of these issues and value the importance of the constructive impact they will have on US policy.

Sincerely,

Tom Inglesby, MD
Anita Cicero, JD
Jaspreet Pannu, MD
Johns Hopkins University

Marc Lipsitch, DPhil
Harvard University

David Relman, MD
Stanford University

Submission Date: 1/26/2023

Name: Jeremy Kamil

Name of Organization: Louisiana State University Health Sciences Center Shreveport

Comment:

To Whom It May Concern,

I am writing today to enter my comments concerning the recommendations that were put forth in the January 2023 draft report from the NSABB, entitled *Proposed Biosecurity Oversight Framework for the Future of Science*.

I am concerned that the report fails to do an adequate cost-benefit analysis weighing the risks to our nation's pandemic readiness of enacting the recommendations it puts forward.

For example, in 2015 Dr. Vineet Menachery and co-authors from the Baric laboratory at University of North Carolina Chapel Hill, published a research article in Nature Medicine entitled, "*A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence*" (PubMed Central PMCID: PMC4797993). This work, which was funded by various NIH / HHS grants and which relied on so-called "gain of function" approaches, presciently warned the world of an imminent risk from SARS-like coronaviruses. Indeed, had the world better heeded this warning, for example by convening political bodies to pressure China to enforce its own already existent bans on the sale of live wild animals in its "wet markets," the COVID-19 pandemic may have never happened.

My overarching concern is that enacting the NSABB recommendations will have a large, net negative unintended consequence: important work like that of Menachery et al. will become so restricted and delayed by cumbersome approval processes, that it will not get done in the first place. The ultimate effect of this increased oversight and additional regulations will be to deny ourselves a fair warning about imminent microbial threats and health risks that we should be paying more attention to. There are dozens of pre-emergent and emergent microbial pathogens that pose serious risks to humanity, and research shows that the risks of these only is increasing with climate change, population growth, and increasing overlap between human-controlled habitats and those of wildlife.

Amidst a highly politicized environment surrounding the origins of COVID-19, there's an air of regulatory "*mission creep*" regarding oversight of biological experiments on viruses, which is exemplified in many of the "findings" and "recommendations" found in the NSABB report. I know that I speak not only for myself but also for many others in the virology community – most of whom do not work on potential pandemic pathogens or DURC agents. I strongly fear that if the full slate of NSABB recommendations end up becoming enshrined in U.S. HHS policy, we will only end up further saddling talented U.S. scientists with unnecessary and cumbersome paperwork and regulations, which are largely redundant to and in many cases duplicative of

existing regulatory frameworks. It is my view that most of the recommendations put forth in the Jan 2023 NSABB draft report will have little-to-no ultimate effect other than to slow down critical scientific progress in research that has already proven itself essential to identify pre-emergent risks and hazards of viruses in nature.

Instead, we need to do a better job communicating the rigor of existing frameworks. Indeed, many policy makers and members of the public are unaware that all research on viruses, bacteria and other pathogen infectious agents at U.S. institutions that accept federal funding is already subjected to extensive and rigorous oversight, starting with the issuance of permit from the local institutional biosafety committee, all the way up to the level of funding agency review and pre-publication peer-review. Further, research involving Potential Pandemic Pathogens (PPP), "enhanced" PPP (ePPP) and DURC agents already includes additional regulatory frameworks.

There also seems to be little admission or realization in the NSABB document that the most pressing threats of PPP and ePPP come from pre-emergent and emergent pathogens in nature. Microbial evolution in nature includes a vast, unthinkably large number of entirely legally unregulated events occurring all the time in viruses, fungi and bacteria that colonize humans, livestock, and wildlife outside of controlled laboratory environments.

To effectively contend with the ongoing and growing threat that microbes pose to human health and our economies, we need to do more to streamline a set of meaningful but simple-to-follow regulations for practical, achievable, and reasonable oversight of biological research on pathogens, not add paperwork and bureaucracy for performative and/or political purposes.

Any efforts to enact the NSABB recommendations needs to consider the practicality and potential negative effects on research activities that have a proven track record of supplying scientific progress to identify threats and develop countermeasures. In this spirit, I will now point to two specific recommendations from the Jan 2023 NSABB draft report that I find particularly concerning and problematic. I list them here in order of relevance and my level of concern.

· Recommendation #2 is particularly troublesome, and in my view, illogical and counterproductive. It reads:

"*Remove current blanket exclusions for research activities associated with surveillance and vaccine development or production. However, include and implement processes and procedures for urgent federal department level review and evaluation of ePPP research critical for public health or national security*."

CONCERN. This recommendation, if enacted as written, disincentivizes and may make impractical important ongoing efforts being undertaken by various scientists and U.S. agencies (such as USAMRIID) and partners (WHO) to monitor for pre-emergent and emergent biological threats and to develop countermeasures. These are vital and urgent efforts that merit blanket

exclusion, and which already involve oversight and extensive safety precautions. More specifically, this regulation does not identify what precise sorts of activities under this rubric that are potentially problematic in the first place, and if so, what should and should not be excluded. Nor does the report include a cost-benefit analysis of the real-world effects of enacting the proposed recommendations.
PROPOSED SOLUTION: Remove this recommendation or re-write it with a much clearer scope of specific surveillance activities and types of vaccine development projects that ought to fall under the new regulations/ and be subjected to enhanced oversight, justifying why they should require additional regulation and how this is a net benefit over the cost to pandemic preparedness.

· Recommendation #1 is far too vague. It reads:

"*Amend USG P3CO policy to clarify that federal department-level review is required for research that is reasonably anticipated to enhance the transmissibility and/or virulence of any pathogen (i.e., PPPs and non-PPPs) such that the resulting pathogen is reasonably anticipated to exhibit the following characteristics that meet the definition of a PPP:*
• Likely moderately or highly transmissible and likely capable of wide and uncontrollable spread in human populations; and/or
• Likely moderately or highly virulent and likely to cause significant morbidity and/or mortality in humans;
And, in addition
• Likely to pose a severe threat to public health, the capacity of public health systems to function, or national security.

CONCERN. This recommendation, as written, is far too vague and subjective. Encompassing "non-PPPs" and using the term "*reasonably anticipated*" to define its scope of affected pathogens and pathogen-related research activities. (Indeed, elsewhere in the report, the very well-defined scope of DURC policy is presented as a strength for its clarity in helping focus regulatory efforts appropriately). Recommendation #1, if enacted, could have a chilling effect on health-related research. For example, anti-tumor interventions, including highly efficacious FDA approved ones that can cure patients of melanoma (e.g., Talimogene Laherparepvec, "TVEC") have relied on modified human viruses to activate immune responses against tumors. Newcastle Disease Virus, an avian paramyxovirus, is being developed as a vaccine vector and an anti-cancer treatment. The problem with the vague wording exemplified within this recommendation is that research to develop new life-saving therapies that harness the infectious and immune-modulating or activating features of viruses to protect human health might be nipped in the bud at the earliest stages of conceptualization because researchers will simply decide that it is not worth the effort and the inevitable delays to obtain the approvals needed. Even once the approvals are obtained, additional reporting requirements will mean more time in the office filling out forms and reports, rather than doing research and making scientific progress.

PROPOSED SOLUTION. "*reasonably anticipated"* needs to be replaced with a comprehensive Table listing the specific pathogens and activities concerning those pathogens that would fall within the scope of any new regulations, similar to the DURC Policy Scope table shown on page 8. Any pathogens and activities encompassed by the proposed amendment to USG P3CO should be well justified in the report, and subjected to a rational and rigorous cost-benefit analysis for their potential to limit pandemic preparedness as well as advances in biotechnology relevant to human health (new vaccine vectors, anti-cancer therapies, et cetera)

The Jan 2023 NSABB draft report includes a lovely figure (see page 25), *Figure 1: Conceptual approach to oversight of research that raises biosafety and biosecurity concerns as described in this report*. This type of clean regulatory framework is reasonable. However, "*reasonably anticipated*" needs to be much better defined, in a manner as clear as the current DURC policy scope shown on in Box 1 on page 8 of the Jan 2023 NSABB draft report. Efforts to add to existing biosafety regulations and requirements seems misguided if it fails to adequately consider how effective the existing set of biosafetly, PPP, ePPP, and DURC regulations actually are. Any revision to the regulations governing U.S. taxpayer funded research on pathogens ought to integrate with and streamline current review practices. Additionally, HHS / U.S. policy ought to implement only those NSABB recommendations that appropriately balance the potential for negative unintended consequences on research progress and pandemic preparedness against any desired effects or goals sought by those proposing to increase oversight and implement new regulations.

In closing, I would like to remind those considering the viability and practicality of the NSABB recommendations that viruses and other microbes are infinitely more abundant in nature than in laboratory environments, and it is from nature that the greatest threats remain. There are no permits required for a virus in a bat's gut to recombine with another, potentially resulting a gain-of-function offspring with pandemic potential. There are no biosafety committees regulating people exposed to spores or respiratory droplets on a subway train. To effectively protect ourselves from the ongoing and increasing threats that microbes pose to human health and economic stability, we must facilitate and support biological research on these pathogens. Existing U.S. regulatory frameworks already do an excellent job assuring that biological research activities within the U.S. and in collaborating laboratories in other countries are done in a safe and responsible manner. Any changes to these policies must be thoughtfully considered not only for their potential to directly improve safety and biosecurity but also for their potential to deprive us of much needed progress in the areas of pandemic preparedness and human health research.

Thank you,

Jeremy P. Kamil, Ph.D.
Associate Professor, Department of Microbiology and Immunology
Associate Director, Center of Excellence for Emerging Viral Threats
Louisiana State University Health Sciences Center Shreveport

Additional Comment (attachment):

January 26, 2023

To Whom It May Concern,

I am writing today to enter my comments concerning the recommendations that were put forth in the January 2023 draft report from the NSABB, entitled *Proposed Biosecurity Oversight Framework for the Future of Science*.

I am concerned that the report fails to do an adequate cost-benefit analysis weighing the risks to our nation's pandemic readiness of enacting the recommendations it puts forward.

For example, in 2015 Dr. Vineet Menachery and co-authors from the Baric laboratory at University of North Carolina Chapel Hill, published a research article in Nature Medicine entitled, "*A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence*" (PubMed Central PMCID: PMC4797993). This work, which was funded by various NIH / HHS grants and which relied on so-called "gain of function" approaches, presciently warned the world of an imminent risk from SARS-like coronaviruses. Indeed, had the world better heeded this warning, for example by convening political bodies to pressure China to enforce its own already existent bans on the sale of live wild animals in its "wet markets," the COVID-19 pandemic may have never happened.

My overarching concern is that enacting the NSABB recommendations will have a large, net negative unintended consequence: important work like that of Menachery et al. will become so restricted and delayed by cumbersome approval processes, that it will not get done in the first place. The ultimate effect of this increased oversight and additional regulations will be to deny ourselves a fair warning about imminent microbial threats and health risks that we should be paying more attention to. There are dozens of pre-emergent and emergent microbial pathogens that pose serious risks to humanity, and research shows that the risks of these only is increasing with climate change, population growth increased and increasing overlap between human-controlled habitats and those of wildlife.

Amidst a highly politicized environment surrounding the origins of COVID-19, there's an air of regulatory "*mission creep*" regarding oversight of biological experiments on viruses, which is exemplified in many of the "findings" and "recommendations" found in the NSABB report. I know that I speak not only for myself but also for many others in the virology community – most of whom do not work on potential pandemic pathogens or DURC agents. I strongly fear that the full slate of NSABB recommendations end up becoming enshrined in U.S. HHS policy, we will only end up further saddling talented U.S. scientists with unnecessary and cumbersome paperwork and regulations, which largely redundant to and in many cases duplicative of existing regulatory frameworks. It is my view that most of the recommendations put forth in the Jan 2023 NSABB draft report will have little-to-no ultimate effect other than to slow down critical scientific progress in research that has already proven itself essential to identify pre-emergent risks and hazards of viruses in nature.

Instead, we need to do a better job communicating the rigor of existing frameworks. Indeed, many politicians and member of the public are unaware that all research on viruses, bacteria and other pathogen infectious agents at U.S. institutions that accept federal funding is already subjected to extensive and rigorous oversight, starting with the issuance of permit from the local institutional biosafety committee, all the way up to the level of funding agency review and pre-publication peer-review. Further, research involving Potential Pandemic Pathogens (PPP), "enhanced" PPP (ePPP) and DURC agents already includes additional regulatory frameworks.

There also seems to be little admission or realization in the NSABB document that the most pressing threats of PPP and ePPP come from pre-emergent and emergent pathogens in nature. Microbial evolution in nature includes a vast, unthinkably large number of entirely legally unregulated events occurring all the time in viruses, fungi and bacteria that colonize humans, livestock, and wildlife outside of controlled laboratory environments.

To effectively contend with this ongoing and growing threat that microbes pose to human health and our economies, we need to do more to streamline a set of meaningful but simple to follow regulations for practical, achievable, and reasonable oversight of biological research on pathogens, not add paperwork and bureaucracy for performative and/or political purposes.

Any effort to enact the NSABB recommendations needs to consider the practicality and potential negative effects on research efforts that have a proven track record of supplying scientific progress to identify threats and develop countermeasures. In this spirit, I will now point to two specific recommendations from the Jan 2023 NSABB draft report that I find particularly concerning and problematic. I list them here in order of relevance and my level of concern.

- Recommendation #2 is particularly troublesome, and in my view, illogical and counterproductive. It reads:

  "*Remove current blanket exclusions for research activities associated with surveillance and vaccine development or production. However, include and implement processes and procedures for urgent federal department level review and evaluation of ePPP research critical for public health or national security*."

CONCERN. This recommendation, if enacted as written, disincentivizes and may make impractical important ongoing efforts being undertaken by various scientists and U.S. agencies (such as USAMRIID) and partners (WHO) to monitor for pre-emergent and emergent biological threats and to develop countermeasures. These are vital and urgent efforts that merit blanket exclusion, and which already involve oversight and extensive safety precautions. More specifically, this regulation does not identify what precise sorts of activities under this rubric are potentially problematic in the first place, and if so, what should and should not be excluded. Nor does the report do a cost-benefit analysis of the real-world effects of enacting this regulation.

PROPOSED SOLUTION: Remove this recommendation or re-write it with a much more clear scope of specific surveillance activities and types of vaccine development projects that would fall under the new regulations/ and be subjected to enhanced oversight.

- Recommendation #1 is far too vague. It reads:

  "*Amend USG P3CO policy to clarify that federal department-level review is required for research that is reasonably anticipated to enhance the transmissibility and/or virulence of any pathogen (i.e., PPPs and non-PPPs) such that the resulting pathogen is reasonably anticipated to exhibit the following characteristics that meet the definition of a PPP:*

  • Likely moderately or highly transmissible and likely capable of wide and uncontrollable spread in human populations; and/or
  • Likely moderately or highly virulent and likely to cause significant morbidity and/or mortality in humans; And, in addition
  • Likely to pose a severe threat to public health, the capacity of public health systems to function, or national security.

CONCERN. This recommendation, as written, is far too vague and subjective. Encompassing "non-PPPs" and using the term "*reasonably anticipated*" to define its scope of affected pathogens and pathogen-related research activities. (Indeed, elsewhere in the report, the very well-defined scope of DURC policy is presented as a strength for its clarity in helping focus regulatory efforts appropriately). Recommendation #1, if enacted, could have a chilling effect on health-related research. For example, anti-tumor interventions, including highly efficacious FDA approved ones that can cure patients of melanoma (e.g., Talimogene Laherparepvec, "TVEC") have relied on modified human viruses to activate immune responses. Newcastle Disease Virus, an avian paramyxovirus, is being developed as a vaccine vector and an anti-cancer treatment. The problem with vague wording exemplified within this recommendation is that research to develop new life-saving therapies that harness the infectious and immune-modulating or activating features of viruses to protect human health might be nipped in the bud at the earliest stage because researchers will decide that it is not worth the effort and to contend with the inevitable delays to obtain the approvals needed. Even once the approvals are obtained, additional reporting requirements will mean more time in the office filling out forms and reports, rather than doing research and making scientific progress.

PROPOSED SOLUTION. "*reasonably anticipated"* needs to be replaced with a comprehensive Table listing the specific pathogens and activities concerning those pathogens that would fall within the scope of any new regulations, similar to the DURC Policy Scope table shown on page 8. Any pathogens and activities encompassed by the proposed amendment to USG P3CO should be well justified and subjected to a rational and rigorous cost-benefit analysis for their potential to limit

pandemic preparedness as well as advances in biotechnology relevant to human health (new vaccine vectors, anti-cancer therapies, et cetera)

The Jan 2023 NSABB draft report includes a lovely figure (see page 25), *Figure 1: Conceptual approach to oversight of research that raises biosafety and biosecurity concerns as described in this report*. This type of clean regulatory framework is reasonable. However, "*reasonably anticipated*" needs to be much better defined, in a manner as clear as the current DURC policy scope shown on in Box 1 on page 8 of the Jan 2023 NSABB draft report. Efforts to add to existing biosafety regulations and requirements seems misguided if it fails to adequately consider how effective the existing set of biosafetly, PPP, ePPP, and DURC regulations actually are. Any revision to the regulations of U.S. funded research on pathogens ought to integrate with and streamline current review practices, and HHS / US policy ought to implement only those NSABB recommendations that appropriately balance the potential for negative unintended consequences on research progress and pandemic preparedness, against any desired effects or goals in practice of adding more oversight.

In closing, I would like to remind those considering the viability and practicality of the NSABB recommendations that viruses and other microbes are infinitely more abundant in nature than in laboratory environments, and it is from nature that the greatest threats remain. There are no permits required for a virus in a bat's gut to recombine with another, potentially resulting a gain-of-function offspring with pandemic potential. There are biosafety committees regulating people exposed to spores or respiratory droplets on a subway train. To effectively protect ourselves from the ongoing and increasing threat that microbes pose to human health and economic stability, we must facilitate and support biological research on these pathogens. Existing U.S. regulatory frameworks do an excellent job assuring that biological research activities within the U.S. and in collaborating laboratories in other countries are done in a safe manner. Any changes to these policies must be thoughtfully considered not only for their potential to directly improve safety and biosecurity but also for their potential to deprive us of much needed progress in the areas of pandemic preparedness and human health research.

Thank you,

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Submission Date: 1/27/2023

Name: John Purdy

Name of Organization: Pacific University Oregon

Comment:

Public Comments regarding the NSABB Meeting on 1/27/2023 and draft recommendations.

I commend the board for thoroughly reviewing and providing their initial recommendations. I have studied several viruses for over 20 years as a basic scientist, and my opinions are informed by my decades of experience.

The work done by NSABB will be impactful. We must acknowledge that nothing will be risk-free. Instead, we must find a balance between the benefits and risks, aiming to maximize the benefits and minimize the risk. Additionally, we must acknowledge that reducing, severely hampering, and stopping research would potentially be the greatest risk of all. Unquestionably, some of this research is risky by nature, and the scientists performing this research know this far better than most. However, doing no research is much riskier to the broader public, as it would leave us unprepared for what will come.

The scientists doing this research should be commended too for taking on this challenging work, providing much-needed benefits to all of us.

I have read the draft recommendations and agree that revisiting the current policy and updating it to reflect changing science is important. Additionally, the policy should reflect the advances and new understandings that we have gained recently through the significant research of many scientists. I write today to express my concerns regarding some of the findings and recommendations in the draft proposal that may leave us unprepared and at much greater risk when the next pandemic occurs. My greatest concerns are:

Regarding Phase 2 Findings: Finding 8): The draft states, “the policy scope limits the evaluation of the framework’s success to only a small fraction of the life sciences research enterprise” as justification for “an expansion of policy scope (beyond the 15 agents/toxins)”. However, the draft itself is evidence that evaluation of the framework can be successfully undertaken without an ambiguous expansion to all work with pathogen and non-pathogen microbes. To me, this represents an unsubstantiated justification for policy expansion. Without empirical scientific evidence to justify an expansion, the recommended policy changes may further limit research needed to prepare for or prevent future pandemics while providing little to no benefit in reducing risk.

Regarding Recommendation 2. This recommendation seeks to limit and slow all activities associated with surveillance and vaccine development or production through a lengthy, undefined review process. This change may delay or altogether block the ability to prevent

future pandemics. Moreover, it may limit our ability to reduce the harm a future pandemic has on lives, the economy, and national security. The recommendation may also reduce the development of knowledge necessary to inform public health policies and reduce the ability of local, regional, state, and national governing bodies to respond appropriately to rapidly changing pandemics.

Recommended changes may limit the development of new or improved treatments for all infections. A shared goal of many pathogen research programs is to create novel or improved antimicrobial therapies or drugs. Essential to developing these compounds is an evaluation of a pathogen's ability to develop resistance to the investigational treatment or compound and a comparison of drug-resistance development to a standard-of-care therapy (if available). Given the broad nature of the recommendations in the draft, all such research could be halted, limited, or blocked. This would leave us unprepared for the next pandemic. Moreover, it may hinder the development of new or improved treatments for non-pandemic infections that occur in plants and animals, including humans. An essential tool for new discoveries—that, as an example, may lead to a new antibiotic to multidrug-resistant staph (MRSA) or antiviral to herpesviruses—may be lost due to policy. Without better clarification, this could weaken our public health systems, food supplies, national security, and economic stability.

In closing, I encourage greater consideration, clarification, and discussion of the draft recommendations before moving forward with policy changes. Virus evolution in humans and other animals does not pause nor follow any government policies regarding research. We must remain vigilant in surveying potential pandemics and developing the knowledge and tools to respond rapidly to persistent and pandemic pathogens. We must ensure that heated, passionate language does not unscientifically tip the balance of maximizing benefits while minimizing risks, leaving us at greater risk for future pandemics. We have the capacity to watch pandemics unfold on a global scale over a rapid period. The question is: Will we build the capacity to respond appropriately or prevent future pandemics to save lives, protect national security, and secure economic and societal gains? Building that capacity will depend on current and future research.

Sincerely,
John Purdy, PhD

Additional Comment (attachment): None