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Dear Dr. Osterholm,

I have read carefully your letter regarding the March 29–30 meeting of the National Science Advisory Board for Biosecurity (NSABB). Your concerns warrant a full response, and I would like to address the specific points in your letter.

First, you state, "…the Board was requested by the USG to reconsider our previous decision recommending the redaction of both…manuscripts before publication." I am concerned that you seem to have misunderstood the purpose of the March 29–30 NSABB meeting. It is important to be very clear on this point—the NSABB was not asked to reconsider its November 2011 recommendations about the original two manuscripts. Those recommendations were based on information available at the time, and they will always stand as NSABB recommendations. When the manuscripts were revised to reflect additional data and clarifications of key scientific points, the NSABB was asked to review the revised manuscripts. This charge was related to, but distinct from the tasking in the fall of 2011. Specifically, the Board was charged with considering the additional information and clarifications, as yet unpublished epidemiological information presented during the meeting, and security information presented in a classified briefing. With those additional considerations in mind, the NSABB was to assess the dual use research implications of the two unpublished, revised manuscripts; consider the risks and benefits of communicating the research results; and develop findings and recommendations regarding whether or not the information should be communicated, and if so, to what extent. This was clearly stated in the charge to the NSABB, which was presented by the NIH Director, Dr. Francis Collins, on the first day of the NSABB meeting.

Second, you assert, "the agenda and speakers for the March 29 and 30th NSABB meeting as determined by the OBA staff and other USG officials was designed to produce the outcome that occurred. It represented a very 'one sided' picture of the risk benefit of the dissemination of the information in these manuscripts. The agenda was not designed to promote a balanced reconsideration of the manuscripts." You are of course entitled to your opinion in this regard, but as noted above, the agenda was not designed to produce any specific outcome other than a rigorous scientific discussion of the manuscripts and any dual use implications. We invited additional influenza experts to inform the NSABB discussions, as well as to provide contextual epidemiologic information that was presented at the World Health Organization (WHO) meeting in February and considered by attendees at that meeting to be highly relevant and helpful to the discussions. In addition, I would note that a draft version of the agenda was circulated to Board members on March 21, and we modified the agenda to address comments from NSABB members. NSABB staff and I have checked our email and did not find any feedback from you about the agenda.

I would further note that I am not aware that any of the Federal officials involved in the planning of the NSABB meeting had a particular outcome in mind; we were naturally very interested in what the NSABB would ultimately recommend, but there was no "right answer" toward which we sought to steer the committee. The NSABB's decisions about communication of the manuscripts, while of considerable interest to the Government, has more direct and immediate implications for the journal editors than it does for current Federal activities. By that I mean that, regardless of the NSABB's recommendations about communication of the information in the manuscripts, the Federal Government would still continue its policy development activities regarding oversight of dual use research.

Third, you state, "I also believe that this same approach in the future will mean all of us, including life science researchers, journal editors and government policy makers, will just continue to 'kick the can down the road' without coming to grips with the very difficult task of managing DURC and the dissemination of potentially harmful information to those who might intentionally or unintentionally use that information in a way that risks public safety." I agree with you that it is important that the larger issue be addressed—how to communicate dual use research of concern (DURC) responsibly—but I believe you are conflating the Board's very specific tasking about the two manuscripts with the larger issue for which international discussion is needed. The March 29–30 meeting was never intended to be an international discussion of the broad issue of communication of DURC. It was for the NSABB to discuss and make recommendations regarding the two revised manuscripts.

With regard to the larger issue of how to communicate DURC responsibly, as you know, the NSABB has a number of highly relevant activities underway. For example, the NSABB Working Group on Global Engagement, of which you are a member, is focused on broader issues, including recommending the criteria for identifying "threshold-crossing" DURC, the need for international strategies for oversight and communication, and other pressing challenges. In addition, the NSABB Working Group on Journal Review Policies is focused on working with scientific journal editors to raise awareness of practices for identifying and addressing the responsible

communication of dual use research of concern. As reported at the NSABB meeting, the WHO is planning additional international discussions regarding the responsible management of DURC, and the U.S. Government is continuing its efforts to develop a secure mechanism for disseminating sensitive scientific information to those with a legitimate need to know. And finally and most importantly, as you know, the U.S. Government is actively implementing a policy framework for the oversight of Federally funded DURC, as evidenced by the formal Federal policy announced on March 29, 2012. In addition, as discussed at the NSABB meeting, the U.S. Government is currently developing a companion policy for local, institutional oversight of DURC that will require institutions receiving Federal funding for life sciences research to conduct reviews and risk assessments on the research that they are proposing or conducting. This draft policy will be published for public comment. Together, these policies will help ensure comprehensive oversight of ongoing and future cases of Federally funded DURC.

Fourth, you assert, "There was no objective review provided by a disinterested subject matter expert that addressed the current state of the art regarding the proliferation and use of reverse genetics technology that can incorporate the methods and results presented in the current manuscripts to allow those who would not have the ready expertise or resources to more easily repeat these experiments." As noted at the outset, the NSABB itself is composed of subject matter experts who are selected based on their ability to offer impartial and objective advice to the U.S. Government on issues such as these. The Board has issued reports on synthetic genomics and on synthetic biology, which indicates that members have knowledge of the current state of the art regarding the proliferation and use of reverse genetics technology. Also, during the NSABB meeting, there was a lengthy discussion about the complex issue of whether the information is immediately and directly enabling. The majority of the NSABB members judged that the findings were not immediately and directly enabling for those with intent to do harm. This was evident in the Board's vote, and this decision and its rationale are recorded in the Board's recommendations to the U.S. Government.

Fifth, on a related matter, you write, "...the voice of an important group of senior influenza researchers not doing similar mutation/transmission work was not heard regarding this issue. I personally tried to have their voices represented at the meeting. They were not invited." As noted above, we did not receive any suggestions from you regarding additional experts to invite to the meeting. One of our expectations for NSABB voting members is that they interact with their colleagues, raise awareness of issues with which the NSABB is grappling, and bring to the table the perspectives and concerns of their colleagues and communities. As director of one of the five NIH-supported Centers of Excellence in Influenza Research and Surveillance, you are in an ideal position to act as a liaison to the influenza research community. Your reading at the meeting of the very same statement included in your letter to me allowed the Board to take this perspective into consideration during its discussions. Your spokesmanship on behalf of the individuals who have communicated with you was helpful, and we appreciate your efforts in this regard.

Sixth, you note, "The Board received no formal or informal presentation from those on the front lines of H5N1 animal surveillance and control. Specifically, no one with H5N1 virus surveillance and control expertise from either the Food and Agriculture Organization (FAO) or the World Organization for Animal Health (OIE) were invited to participate." I would note that during the

meeting, the Board heard from *ex officio* members representing the U.S. Department of Agriculture, and the Assistant Director-General for Health Security and Environment of the World Health Organization. It was noted that the full publication of this research might not, by itself, improve surveillance, but constitutes an important step toward developing better surveillance, which was recorded in the Board's recommendations.

Seventh, you express dismay that "...Dr. Smith was able to present the work on the population-based mutational changes in H5N1 viruses without an opportunity for others in the influenza field to provide commentary. Since Dr. Fouchier was a coauthor of the work, it hardly represented an unbiased view of H5N1 virus genetics." Many others have a different view of this, as indicated by the many positive comments at the meeting regarding Dr. Smith's presentation. The work he presented was very relevant and helpful because it utilizes the mutational data from both manuscripts to provide greater understanding of the evolution of wild-type H5N1. These findings emphasized the urgency of openly accessible research into H5N1 (please note that Dr. Kawaoka is also a coauthor on the Smith work).

Eighth, you avow, "We need look no further than the reemergence of H1N1 in 1977, after a 20-year absence from global circulation. Our group has been actively investigating the return of H1N1 in 1977, and based on that work we are convinced it leaked out of a Russian lab that was working on a live-attenuated H1N1 virus vaccine. Again, none of this information was addressed in the risk assessment overview." You made this point during the NSABB meeting, and thus it was taken into consideration by the Board during its deliberations. Again, setting aside the contentious origins of the 1977 H1N1 outbreak, we expect NSABB members to raise such points that inform NSABB deliberations and appreciate that you did so.

Ninth, you observe, "The authors of the [Science and Nature articles on H5N1 surveillance] interviewed a number of global experts in the area of influenza countermeasures; they concluded there was no immediate benefit to countermeasure development or production as a result of the availability of the mutation data. At no time was this information presented to the Board by a disinterested expert." Like others, I would posit that it is not knowledge of the mutations *per se* that hold benefit, but rather that these mutations help shed light on certain epitopes—and their biological properties—that will be important in understanding in the broader sense how to design effective countermeasures or predicting how a virus could evolve to become transmissible among mammals. Without the open communication of this research, such progress may not be possible. This concept was addressed in the Board's recommendations.

Tenth, you note, "Any decisions that the NSABB makes with regard to the influenza issue may possibly have far-reaching and yet unrecognized implications, like the 1918 virus situation." I agree with that sentiment, and note that when the NSABB is asked to make recommendations on an issue, it is with the understanding that they can only do so based on information available at the time. We can only ask that the NSABB make thoughtful, defensible recommendations in good faith and based on current understanding at the time of its deliberations.

At the meeting, Dr. Fauci, Director of the National Institute of Allergy and Infectious Diseases, noted that there have been very positive outcomes from the full and open communication of the

manuscripts on reconstruction of the 1918 influenza virus. For example, as reported in the literature, reconstruction and study of the 1918 pandemic influenza virus already have significantly contributed to our understanding of the emergence, transmissibility, and pathogenicity of this virus and provided critical information to help prepare for the emergence of other influenza viruses. As well, exploring the significant role of the host immune response to the 1918 virus in disease progression has led to new insights into novel anti-inflammatory and immunomodulatory therapies to treat severe influenza infections. Mutations associated with its pathogenicity and host adaptation helped strengthen our response to the 2009 H1N1 influenza pandemic and have provided critical insights into how influenza viruses switch hosts and cause pandemics. Evolutionary studies with the 1918 genome have led to greater understanding of the genetic relationships between the 1918 pandemic and all subsequent pandemic viruses. In addition, the 1918 HA crystal structure is helping inform universal vaccine development and monoclonal antibody studies. This important research on the 1918 influenza virus has broadened our knowledge of seasonal and pandemic influenza viruses as illustrated by hundreds of follow-on publications that build on the original information. Just as importantly, the research was conducted over the past 15 years with appropriate biosafety and biosecurity oversight and without negative consequences.

Eleventh, you state, "One of the most disturbing aspects of the meeting was the security briefing on the evening of March 29th. It was one of the most incomplete and, dare I say, useless classified security briefings I've ever attended." Although commenting on the specifics of that classified briefing is not permitted, it is important to note that it was planned by intelligence officials at the Office of the Director of National Intelligence. The briefers were intelligence experts from multiple agencies and, as you might recall, were open to questions and responded thoughtfully to questions from the Board members. You also expressed the concern that this briefing had a "substantial impact" on the thinking of other members of the NSABB. Members of the NSABB have attended numerous security briefings in the past, and, I think it is fair to say, have the ability to judge the usefulness of this information for themselves. And, in the judgment of many with whom I spoke, the briefing was thorough and helpful.

Finally, I would like to acknowledge some of the very important issues that were raised during the NSABB meeting and that were taken into consideration by many of the members in formulating their votes. For instance, it was explained that the Government is exploring the feasibility of developing a mechanism for controlled access to sensitive scientific information for those with a legitimate need to know, in cases where certain details are redacted from a manuscript, and this would be a way for the full information to reach relevant communities. However, the Government noted that there were complex legal and practical issues still to be addressed and thus such a mechanism was not currently available for communicating information in the H5N1 manuscripts under consideration at the March 29–30 NSABB meeting. There was also discussion of the international framework for virus sharing recently negotiated by the WHO and concerns that the framework could be endangered if the manuscripts were redacted. Redaction also carries with it the danger that the U.S. could be perceived as withholding vital public health information from the regions of the world most at risk of an H5N1 outbreak. Participants also discussed the potential for broad negative consequences to the field of influenza research if the papers are not published in full, e.g., the potential to discourage researchers and funders from pursuing this line of public

health research. These were all very important perspectives and legitimate considerations that informed many of the NSABB members' decisions.

In conclusion, I want to thank you again for your comments. These are exceptionally complex issues that are bound to generate differences of opinion and judgment. I respect your opinions and perspectives on the meeting, but I do believe that some of them were based in part on a misunderstanding of the facts. I hope that this letter has served to clarify the facts and highlight other aspects of the discussion that were critical to the Board's recommendations.

Respectfully,

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cc: NSABB members