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BIOLOGICAL SECURITY: THE RISK OF DUAL-USE RESEARCH

HEARING

BEFORE THE

COMMITTEE ON HOMELAND SECURITY AND GOVERNMENTAL AFFAIRS UNITED STATES SENATE

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THURSDAY, APRIL 26, 2012

U.S. SENATE,
COMMITTEE ON HOMELAND SECURITY
AND GOVERNMENTAL AFFAIRS,
Washington, DC.

The Committee met, pursuant to notice, at 10:06 a.m., in room SD–342, Dirksen Senate Office Building, Hon. Joseph I. Lieberman, presiding.

Present: Senators Lieberman and Collins.

OPENING STATEMENT OF CHAIRMAN LIEBERMAN

Chairman LIEBERMAN. The hearing will come to order.

Good morning, and thanks very much to our really distinguished panel of witnesses. We use the word "distinguished" around here very easily, but it actually does relate to this panel and I thank you for being here.

If I may begin by looking back a bit, in 1851, a revolution in medicine already underway was crystallized in a letter Louis Pasteur wrote to a friend, "I am on the edge," he said, "of mysteries and the veil is getting thinner and thinner." Thanks to the work of Pasteur and succeeding generations of scientists, the mysteries of the microbial world have slowly been revealed and we are all a lot healthier and living a lot longer as a result. Childhood diseases like polio and measles have, in many ways, been vanquished. Scientists were able to identify the acquired immunodeficiency syndrome (AIDS) virus, which helped lead to treatments. And according to one of our witnesses today, the real possibility of a cure for AIDS is in sight.

The last global pandemic, the Spanish Flu pandemic, which killed on a massive scale, at least 50 million people, was almost a century ago. I remember this because it deprived me of ever knowing one of my grandmothers, my paternal grandmother who died as a young woman in New York in that pandemic.

But in addition to all the medical miracles that were underneath that veil Pasteur began to peel back, there were, of course, also dangers. Research that could lead to cures, extending life for millions, also could kill many if a rogue pathogen were released either by accident or because it fell into what I will call evil hands. And it is this paradox of dual-use research that we gather together today to consider at this hearing.

Last fall, the world was shaken by the news that two research teams, working independently had been able to engineer a new

strain of the H5N1 virus, which we know as Bird Flu, that could easily infect humans. Epidemiologists have long feared that if the H5N1 virus ever made the jump from a virus mostly confined to birds to one easily transmitted among humans, it could swiftly cause a pandemic. The mortality rate for the few reported cases in humans who have been infected is as high as 60 percent. By contrast, the Spanish Flu, which I mentioned earlier, had a mortality rate of about 2 percent.

The researchers that I referred to, based both at Erasmus University in the Netherlands and at the University of Wisconsin, announced that they were going to publish the results of their studies in the journal, *Science and Nature.* This set off what I would call a global ethics debate in the scientific community about whether to publish or not publish these results, and if the experiments, which were funded by the National Institutes of Health (NIH), should have been undertaken at all.

On the one hand, there are those who say that getting this information out could help other scientists better understand the mutant strain so they could prepare for a possible pandemic by looking for natural mutations and developing vaccines and medications. The fact that these two research teams were able to create this new strain from existing genetic material means that nature could create it, as well. In fact, many scientists said that that was quite likely.

But given the lethality of the virus, others argued that publishing the results would create a huge security risk because it would offer a blueprint for a deadly biological weapon to rogue states or terrorists, and, of course, that is where this Committee's interest is drawn because of our responsibility for homeland security.

In a recent speech at a biological weapons conference in Geneva, Secretary of State Clinton warned that al-Qaeda in the Arabian Peninsula had, in fact, issued a call for "brothers with degrees in microbiology or chemistry to develop a weapon of mass destruction." And, of course, there is also a danger that the manufactured strain might somehow escape, so to speak, from the laboratory, which is something we have worried about in the past.

Last December, at the request of the Department of Health and Human Services (HHS), the National Science Advisory Board for Biosecurity (NSABB), was asked to review the H5N1 research papers. The NSABB concluded that more needed to be known before the research was made public and they asked the editors of *Science and Nature* to delay publication.

Last month, after further review, the NSABB withdrew its objections and voted unanimously to allow the University of Wisconsin study to be published, and by a divided vote of 12–6 to allow the Netherlands study to be published with some revisions and clarifications.

One of the things that apparently influenced the Board's decision was the revelation that the modified strains of H5N1 had become less lethal. But as the members of the panel know, I am sure, that decision has drawn criticism from Dr. Michael T. Osterholm, Director of the Center for Infectious Disease Research and Policy at the University of Minnesota and an NSABB Board member himself. In

a letter to the NIH, he wrote that the NSABB had deliberately ignored the voice of scientists who believed publication of the H5N1 research was dangerous, and I quote from his letter. "I believe there was a bias toward finding a solution that was a lot less about a robust science and policy-based risk-benefit analysis and more about how to get out of this difficult situation." He then added, "We cannot just kick the can down the road without coming to grips with the very difficult task of managing," and I know he was referring to dual-use research. So this is a serious charge, which I hope as the morning goes on the panel will respond to.

The publish or not publish debate continued earlier this month during a 2-day conference of the world's leading scientists convened by the Royal Society in London. One point I learned that most of the attendees seemed to agree on is that we need to put in place better systems to track this kind of research at each experimental stage rather than waiting until it is ready for publication to make decisions about what can be revealed. That is another question that I hope our panelists will discuss today.

Although this particular controversy about publication appears to have been resolved, it is going to recur and, as Dr. Osterholm said, we cannot just kick the can down the road and deal with it on an ad hoc basis. What systems to monitor dual-use research that could produce dangerous results were in place at the time these experiments were begun? What new systems are being in place now? Are more needed? And how do we balance these against our obvious valuation of the valuing of the question for knowledge, of free scientific inquiry?

Etched into the National Academy of Sciences headquarters wall are the words of Einstein, one of Einstein's many phases that are quoted often, "The right to search for truth implies also a duty. One must not conceal any part of what one has recognized to be true." But, of course, this matter before us this morning raises another question that is relevant, which is what if peeling away nature's veil, in Pasteur's term, unleashes dangers to the world?

Those are difficult questions to balance, and again, I repeat that we ask them here in this Committee because of the direct connection between the scientific work and the homeland security of the American people, which it is our first responsibility to protect. I really look forward to your testimony and the question and answer period, and again, I thank you for being here.

Senator Collins.

OPENING STATEMENT OF SENATOR COLLINS

Senator COLLINS. Thank you, Mr. Chairman.

It has been almost a century since the 1918 Spanish influenza virus infected one-fifth of the world's population, killing more than 50 million people and claiming some 600,000 American lives. Yet virulent strains of influenza are still a major threat.

The H1N1 strain, more commonly known as the Swine Flu, claimed more than 18,000 lives during the 2009 outbreak and exposed gaps in our preparedness capabilities for response to a global pandemic, especially in the development, production, and distribution of life-saving vaccines.

In 2008, this Committee held a hearing on the report by the Commission on the Prevention of Weapons of Mass Destruction, which examined the security of biological pathogens on the select agent list. The testimony by the Chairmen of the Commission, former Senators Bob Graham and Jim Talent, helped to raise awareness on the issue of biosecurity and the need to ensure that deadly pathogens and the research carried out on them are contained in secure lab facilities.

This Committee has also held numerous hearings on the Nation's efforts to prevent, prepare for, and mitigate the impact of a pandemic influenza outbreak. In 2009, the Administration's failure to ensure that the government was prepared to rapidly distribute vaccines was and remains a cause for great concern.

Preparedness also requires investing in critical life sciences research to expand our knowledge base and technologies to help us better respond to the next potential global pandemic. Such a pandemic could be even more communicable than the 1918 influenza virus or as virulent as the Avian Flu virus. The World Health Organization (WHO) has documented 576 human cases of Avian Flu infection worldwide since 2003, 339 of those cases resulted in death.

Recently, research funded by the National Institutes of Health and conducted in Wisconsin and the Netherlands resulted in genetic changes to a strain of Avian Flu that allowed its airborne transmissibility. The NIH-funded researchers planned to publish their full findings in two academic journals. Now, publication, peer review, and replication of findings are obviously important steps in a vigorous scientific process. But others have expressed concern that the publication of the methodology and some of the data could help create a road map for terrorists and others seeking to further modify the virus into a bio-weapon. That is why a government advisory board, the National Science Advisory Board for Biosecurity, recommended in late December that partial information be withheld from publication.

Late last month, however, the Board—with some dissenters—reversed course, and is now advocating for the full publication of the research done in Wisconsin as revised, and the publication of a revised paper on the research performed in the Netherlands. The decision and its reversal have been part of a larger debate within the scientific and national security communities and there are important arguments being made on both sides. When the American people pay for scientific research intended for the common good, they have a right to expect that their money will not be used to facilitate terrorism.

These are not hypothetical threats. Before he was killed, Anwar al-Awlaki reportedly sought poisons to attack the United States. Adding to these concerns, the new leader of al-Qaeda has a medical background. Therefore, he may have an even greater interest in pursuing chemical and biological terrorism.

At the same time, there is a legitimate concern about government censorship that could chill academic freedom and scientific inquiry or even limit the sharing of information necessary to save lives or improve public health. Recently, NIH released a new policy for the oversight of dual-use research of concern. This policy is in-

tended to improve our awareness of current and proposed dual-use research of concern and provide some guidelines for mitigating the associated risks. This new policy, however, is only the beginning of what must be a straightforward dialogue among science, health, national security, and government experts and leaders in order to promote scientific research while protecting the safety of Americans and others around the world.

I look forward this morning to hearing and reviewing the testimony of our witnesses about these challenging issues and how we can strike the right balance.

I do want to apologize that I will, however, have to leave early due to a markup in the Appropriations Committee that begins at 10:30, but I will certainly review the transcript of this hearing.

Thank you, Mr. Chairman.

Chairman LIEBERMAN. Thank you, Senator Collins, for that thoughtful statement. I am sure whether it is at this particular hearing, Appropriations, or others, you will be watching out for the budgets of NIH, the Department of Homeland Security (DHS), and others that may be recipients on the panel.

Senator COLLINS. Absolutely.

Chairman LIEBERMAN. That is your record, I know.

Our first witness is Dr. Anthony Fauci—really a national hero, at least a hero of mine and I am sure others—Director of the National Institute of Allergy and Infectious Diseases at NIH. I really appreciate that you are here today and we look forward to your testimony now.

TESTIMONY OF ANTHONY S. FAUCI, M.D.,[1] DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, NATIONAL INSTITUTES OF HEALTH, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Dr. FAUCI. Thank you very much, Mr. Chairman and Senator Collins. Thank you for the opportunity to testify today on the NIH mission of performing biomedical research for the purpose of preparing for and responding to naturally emerging and reemerging infectious diseases and the relationship of this type of research to biological security.

As you mentioned in your statement, the issue at hand is the ongoing threat of the emergence of an H5N1 pandemic influenza and the research that was supported by the NIH to address this threat. The publication of the results of such research in the form of the two manuscripts that you mentioned has focused considerable public attention on the issue of dual-use research, namely research that is directed at providing new information critical to the public health, but at the same time has the potential for malevolent applications.

My written testimony is submitted for the record, and in my few minutes of time, I will highlight just a few important aspects of this issue.

First, the public health challenge. Seasonal influenza is an ongoing threat to public health worldwide and is among the leading global causes of death due to infectious diseases. Each year, influ-

[1] The prepared statement of Dr. Fauci with attachments appear in the Appendix on page 34.

enza causes more than 200,000 hospitalizations and up to 49,000 deaths in the United States and up to a half-a-million deaths globally. Yet influenza has animal reservoirs, especially in birds, and these viruses can undergo extensive genetic changes and jump species, resulting in an influenza virus to which humans are highly vulnerable.

Such an event can and historically has led to global disasters, such as the one you mentioned, the prime example being the 1918 global influenza pandemic that killed up to 100 million people worldwide and caused enormous social and economic disruption. There is a clear and present danger that we will have another influenza pandemic, since these viruses continue to circulate in the world and are constantly evolving toward pandemic capability, as we have seen in 1957, 1968, and 2009.

Over the last decade, a highly pathogenic H5N1 influenza has emerged among chickens. Rarely, the virus spreads to humans. Since 2003, approximately 600 confirmed cases have occurred in humans in more than a dozen countries shown in red on this poster.[1] Nearly 60 percent of those reported cases have resulted in death. Should the virus mutate to transmit more efficiently to and among people, a widespread influenza pandemic could ensue.

Indeed, nature itself is the most dangerous bioterrorist, and even as we meet today, H5N1 and other influenza viruses are naturally mutating and changing with the potential of a catastrophic pandemic. This is not a theoretical danger. It is a real danger.

For decades, NIH has supported basic influenza research included on transmissibility, host adaptation, and virulence. The goal is to anticipate what the virus is continually trying to do on its own in the wild and to prepare for it. Such goals were pursued by the NIH-funded scientists Kawaoka and Fouchier and could have important positive implications for pandemic influenza prediction, prevention, diagnosis, and treatment.

Kawaoka and Fouchier constructed variants of H5N1 avian influenza in order to identify which genetic mutations might alter the transmissibility of the virus. In their studies, they employed a standard influenza animal model, namely the ferret. This poster shows the basic design of the experiments,[2] in which the virus was modified to allow for aerosol transmission from one ferret to another.

I might point out that one of the causes of the public misunderstanding was the widespread belief that the virus that was transmitted by aerosol from one ferret to another actually killed the ferrets when, in fact, that was not the case.

We feel that these studies provide critical information and it was important to determine if H5N1 virus that has this enhanced transmissibility would remain sensitive to existing anti-influenza drugs and vaccines. In addition, and importantly, knowledge of the genetic mutations that facilitate transmission may be critical for global surveillance of emerging influenza viruses.

Yet since transmissibility of a virulent virus was increased, this constitutes dual-use research of concern (DURC), which is shown

[1] The poster referenced by Dr. Fauci appears in the Appendix on page 48.
[2] The poster referenced by Dr. Fauci appears in the Appendix on page 50.

on this poster.[1] If a particular research experiment is identified as DURC, that designation does not necessarily mean that such research should not be published, nor should it even be prohibited in the first place. However, it does call for us, as you mentioned, to balance carefully the benefit of the research to the public health, the biosafety and biosecurity conditions under which the research is conducted, and the potential risk that the knowledge gained from such research might fall into the hands of those with ill intent.

In this regard, the National Science Advisory Board for Biosecurity was asked to advise the U.S. Government on the publication of these manuscripts. You will hear in detail from Dr. Paul Keim, the Chair of that group, about the Board's deliberations. Importantly, the public attention and concern generated by this issue has triggered a voluntary moratorium or pause on this type of research on the part of the influenza research community as well as a fresh look at how the U.S. Government handles DURC, as manifested by a formalization of a government-wide policy to address the issue.

This policy, which was released on March 29, strengthens and formalizes ongoing efforts in DURC oversight and is described in my written testimony. The ultimate goal of the NIH in its embrace of this new policy is to ensure that the conduct and communication of research in this area remain transparent and open at the same time as the risk-benefit ratio of such research clearly tips towards benefitting society.

The public, which has a stake in the risks as well as in the benefits of such research, deserves a rational and transparent explanation of how these decisions are made. The upcoming dialogue related to this policy certainly will be informative and, hopefully, productive in its goal of benefiting the public with the fruits of such research while ameliorating the associated risks. Thank you.

Chairman LIEBERMAN. Thanks very much, Dr. Fauci. That was an excellent introduction to the topic and I look forward to asking you some questions.

Next, Dr. Daniel M. Gerstein, Deputy Under Secretary for Science and Technology at the U.S. Department of Homeland Security, obviously sharing with the Committee the concern about whether this research represents a real threat to our homeland security, and if so, what we should do about it. Thanks so much for being here, and we welcome your testimony now.

TESTIMONY OF DANIEL M. GERSTEIN, PH.D.,[2] DEPUTY UNDER SECRETARY FOR SCIENCE AND TECHNOLOGY, U.S. DEPARTMENT OF HOMELAND SECURITY

Mr. GERSTEIN. Thank you. Good morning, Chairman Lieberman and Senator Collins. I thank you for the opportunity to testify today regarding dual-use life science research of concern.

My testimony today will describe both Department of Homeland Security mechanisms for addressing and mitigating dual-use concerns arising from internal life sciences research that DHS funds or performs as well as DHS involvement in U.S. Government and

[1] The poster referenced by Dr. Fauci appears in the Appendix on page 51.
[2] The prepared statement of Mr. Gerstein appears in the Appendix on page 53.

other efforts to address security concerns arising from the life sciences research.

As the Department considers the DURC issue, several principles help guide our thinking. First, DURC is an extremely complex issue for the scientific research and development community, balancing our Nation's need to excel in science and exploration of robust technologies with ensuring our Nation's security by preventing the misuse of such technology.

Second, almost all research conducted today in bioscience and biotechnology contains some degree of dual-use application.

Third, dual-use concerns must be addressed at a variety of different levels, from research funded by governments, to research funded privately, to experimentation done by individual scientists.

And finally, there are both domestic and international dimensions to the DURC issue, as the recent H5N1 papers have clearly demonstrated.

DHS performs research which might be considered DURC through a variety of different mechanisms, including our internal laboratories, such as the National Biodefense Analysis and Countermeasures Center (NBACC), and Plum Island Animal Disease Center (PIADC). We also sponsor and collaborate with other departments. Additionally, we provide funding to colleges and universities, primarily through our DHS Centers of Excellence Program.

One vignette that demonstrates the degree to which dual-use research is both ongoing and critical to the DHS mission is the development of a recombinant foot-and-mouth (FMD) disease vaccine. The recombinant vaccine components are being developed through our DHS Center of Excellence at Texas A&M. The material is then shipped to Plum Island, where it is used in challenge tests employing live FMD virus. At Plum Island, DHS and the U.S. Department of Agriculture are working shoulder to shoulder in this effort. Once approved for licensure, a commercial company will produce the vaccine. This cross-cutting project demonstrates the importance of collaborative efforts in dual-use research.

DHS's primary objective in funding activity in the life sciences is to meet our homeland security mission. We, therefore, exercise control of the information where necessary through non-publication or non-disclosure mechanisms. Research conducted or funded by DHS in the areas of biological and chemical defense undergo particular scrutiny and high-level departmental review because of the potential to raise concerns regarding security, nonproliferation, and treaty compliance.

At DHS, our approach to dual-use research is multi-dimensional. At the lowest levels, project managers are trained to understand and assess their programs for possible dual-use implications. The National Science Advisory Board for Biosecurity, definition of DURC embodied in the NSABB's seven experiments of concern serves as the basis for this understanding. These same criteria have been identified for use in the new Federal-wide DURC policy.

The DHS Compliance Assurance Program Office (CAPO) reviews projects that are to be conducted. This review divides potential projects into tiers based on whether they include NSABB experiments of concern, raise perceptions of noncompliance with arms control agreements, utilize select agents or toxins, have the poten-

tial to generate or reveal national security vulnerabilities, or provide information on threat agent production or dissemination.

At the highest levels of the Department, our Compliance Review Group (CRG), chaired by our Deputy Secretary with full participation across the staff, reviews all DURC with a particular eye toward ensuring compliance with the Chemical Weapons Convention and Biological Weapons Convention (BWC).

DHS routinely contracts for life science research that involves use of select agents and toxins or that require special biosafety provisions. In all cases, we ensure that contracts contain clauses to ensure conformity with applicable laws, regulations, and internal policies. In addition, research contracts for life sciences work typically provide for DHS to object to publication or disclosure. Further, depending on the type of proposed publication or disclosure, the information to be released must go through an internal review process. In the unlikely event that sensitive or classified material is produced from research projects funded through grants to academia, DHS requires grant recipients to create information protection plans which detail how the information would be identified and secured.

Now, I have been discussing the internal management of DURC within DHS. Let me now turn briefly to the broader DURC issue. DHS has been an extremely active participant in the formulation of the U.S. Government policy on the dual-use research, including the March 29 government policy for DURC oversight. We are in complete agreement that strengthening DURC oversight and establishing regular reviews of U.S. Government funded or conducted research is both necessary and a responsible approach.

However, even with the kind of internal DHS oversight policies described previously and the U.S. Government-wide policy on oversight of U.S. funded life sciences research, DHS believes that security-related concerns to DURC cannot be entirely resolved by formal U.S. Government policies. The international nature of life sciences research, coupled with the explosion in biotechnology funded by private sources, means that much of the DURC being conducted is not under direct U.S. Government control. Advances in the life sciences will undoubtedly create technological capabilities that will be of tremendous benefit to humankind but will also require careful stewardship, including development of appropriate regulations and policies, as well as continued emphasis on strong bio-risk management programs that emphasize biosafety, biosecurity, and bioethics.

In working through this issue, we must find ways to mitigate risk associated with the potential malicious use of DURC while at the same time allowing for open and unfettered innovation by our Nation's scientists and laboratories. At the end of the day, the DURC issue comes down to a risk-benefit evaluation of whether the balance is in favor of sharing the information for the good of humankind for public health, medical, or biotechnology advancement versus the potential for misuse.

Ultimately, the international life sciences community must appreciate the DURC problem and internalize these concerns while developing and conducting research. In this regard, the H5N1 pa-

pers have served as a necessary wake-up call for the life sciences community.

Thank you for giving us the opportunity to testify today and we look forward to your questions.

Chairman LIEBERMAN. Thanks, Dr. Gerstein.

Just clarify for the record, and for me, what the role of the Department of Homeland Security is with regard to dual-use research happening outside of DHS grantees.

Mr. GERSTEIN. Well, Senator, we sit as part of the interagency body that deliberates, and so we have a strong voice. And in fact, as I am sure we will talk more about later, the March 29 policy actually reflects much of the work that we have been doing previously in fulfilling our Biological Weapons Convention requirements. We made use of the NSABB's seven experiments of concern. We have always looked at the select agent program to make sure that we are in accordance with the requirements and the reporting requirements. So we do that tiered process in order to make sure that experiments do fall in full compliance with the BWC.

What we have done, though, is because of the alignment of the March 29 policy and the work that we have done previously, we essentially have a leg up on the implementation of the March 29 policy.

Chairman LIEBERMAN. And just to take this one step further, the board on which you sit, is this to determine government-wide policy or also to approve and evaluate particular research projects?

Mr. GERSTEIN. These are internal boards that are designed to look at the Department's experimentation, the projects that we are to be conducting.

Chairman LIEBERMAN. And then, finally, just give us a sense, and I do not think you have to get into too much detail here, about how widely dual-use research projects are being carried out or funded in the Federal Government. In other words, the natural place to think about it is NIH, but I presume DOD is also funding projects, etc.

Mr. GERSTEIN. Well, Senator, I would like to stick to my Department and just tell you what we are doing in the Department of Homeland Security. Through our review process, our Compliance Review Group looks at a total of about 200 projects that fall into what we call Tier One, just regular experiments that do not rise to the level of concern. In the Tier Two, ones that could perhaps have some issues with perception——

Chairman LIEBERMAN. Right.

Mr. GERSTEIN [continuing]. We do 12 to 15 experiments. And then in the highest category, we do 5 to 10 experiments. So a total of about 225 experiments per year, of which all run through our Compliance Review Group process.

Chairman LIEBERMAN. And those are all funded within DHS?

Mr. GERSTEIN. They are, yes.

Chairman LIEBERMAN. So maybe, Dr. Fauci, you are the one to turn to to give us for the record a kind of broader sense of how widely dual-use research is either being done in Federal agencies or funded by Federal agencies.

Dr. FAUCI. So that is a very good question, Mr. Chairman, and it is important, as you did yourself, to distinguish between dual-use research and dual-use research of concern.

Chairman LIEBERMAN. Right.

Dr. FAUCI. Almost any time you even go near a microbe, it is dual-use research. If you are talking about dual-use research of concern, just for this purpose, as part of the implementation of the March 29 government-wide policy, we did an inventory of what we do both with our own scientists at the National Institute of Allergy and Infectious Diseases (NIAID) as well as the external extramural grantees and contractors.

And just to give you some examples, when we did an inventory of what we do mostly on our Bethesda campus and in our Rocky Mountain campus, there were 404 intramural projects that could be dual-use plus 147 manuscripts and none were found to be dual-use research of concern. When we did the extramural inventory of all of the grantees—there were 381 grantees or contractors—10 of those grants were designated as DURC. Seven of them were in influenza, one in anthrax, one in plague, and one in botulism. So out of 381, there were only 10, and those are the ones we are now going through the process that is delineated very carefully in the new policy. So that is the scope of what we are doing at NIAID.

Chairman LIEBERMAN. That is very helpful. And just generally, am I right to assume there may be dual-use research projects of concern, for instance, funded by the Department of Defense?

Dr. FAUCI. I would hesitate to make a statement about the Department of Defense, but we collaborate a lot with them——

Chairman LIEBERMAN. Yes.

Dr. FAUCI [continuing]. And yes, I cannot imagine that they are not doing some.

Chairman LIEBERMAN. Good enough.

Dr. FAUCI. But probably a really small amount. But they clearly are doing some.

Chairman LIEBERMAN. So most is probably coming through NIH?

Dr. FAUCI. Right.

Chairman LIEBERMAN. Thanks very much.

Next, Dr. Paul Keim, Acting Chairman of the aforementioned National Science Advisory Board for Biosecurity. We thank you very much, Dr. Keim, for being here, and please proceed with your testimony now.

TESTIMONY OF PAUL S. KEIM, PH.D.,[1] ACTING CHAIRMAN, NATIONAL SCIENCE ADVISORY BOARD FOR BIOSECURITY, NATIONAL INSTITUTES OF HEALTH, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. KEIM. Chairman Lieberman, thank you for holding this hearing on "Biological Security: The Risk of Dual-Use Research." I am Paul Keim, the Acting Chair of the National Science Advisory Board for Biosecurity. I appreciate the opportunity to speak to you about dual-use research and in particular about the Board's activities and our recent evaluation of two scientific papers concerning the H5N1 influenza virus.

[1] The prepared statement of Mr. Keim appears in the Appendix on page 59.

It has been recognized for many years that science and technology can be used for both good purposes and bad. It is this two-sided coin that we refer to as dual-use research. The problem is that all biological research can be construed as having potential bad applications as well as their good ones.

The NSABB created a new term, dual-use research of concern to distinguish normal research from that with exceptionally high potential to be misused. The parameters defining DURC would include the magnitude of any danger and the immediacy of any threat as balanced against the overall benefits of the work.

Over the last 8 years, the Board has advised the U.S. Government on best practices and policy approaches for research communication, personnel reliability standards, codes of conduct, and international engagement for issues associated with DURC. The Board has recognized that good policy needs to protect us from scientific misuse and protect the scientific enterprise from being overburdened with unnecessary regulation. Both are essential for our country to be safe, productive, and remain a global leader.

The National Science Advisory Board for Biosecurity is comprised of well respected scientists, lawyers, infectious disease experts, scientific editors, and public health experts. We have an 8-year track record of protecting academic freedom while seeking policy recommendations that will minimize the misuse of biological sciences research.

With that in mind, recognize the significance for the Board to unanimously recommend against the publication of two scientific papers in November 2011 due to their potential to be misused. The U.S. Government asked the Board to review two NIH-funded studies reporting mutations that allowed a highly dangerous bird flu virus to transmit from one ferret to another. By a split vote, the Board instead recommended to the government that key elements of the studies not be published and that only redacted papers were acceptable for general distribution.

These recommendations were based upon the Board's finding that if this avian influenza virus acquires the capacity for human-to-human spread and retained its current virulence, the world could face a pandemic of significant proportions. We found that the potential risk for public harm to be of unusually high magnitude.

The Board has published its recommendations to the U.S. Government along with its rationale. Importantly, we pointed out that an international discussion was needed amongst multiple societal components to develop policy in this arena of high-consequence DURC. I would further note that in the few months since our recommendations were released, there has been a flurry of U.S. and international meetings to discuss the risks and benefits of these experiments.

The research issues and policy consequences are now commonly known and being debated. This continuing global conversation is important for the scientific endeavor and for our biosecurity.

In late March 2012, the U.S. Government tasked NSABB with reviewing revised versions of the two original manuscripts. This was coupled with a face-to-face meeting such that the Board could hear directly from the investigators about their research. In this meeting, the Board received non-public information about the risks

and benefits of the research from the international public health and research community as well as from the U.S. Government intelligence community.

In a classified briefing from national intelligence counsel and National Counterterrorism Center representatives, the Board heard an assessment of the risk for misuse and of the global political ramifications associated with these papers. The details of these briefings are classified, but I can tell you that many of the Board were left with the impression that the risk of misuse did not appreciably increase with full publication, and there is a high likelihood of undesirable political consequences to not publishing.

In addition, the U.S. Government has recently issued new policy guidelines targeting high consequence DURC. This was based upon the NSABB's own definition of DURC and seven categories of experiments that warrant special consideration and targeting particular high-consequence pathogens.

It is in this context that the Board arrived at different recommendations for the revised manuscripts. One paper was unanimously recommended for full publication while the other was recommended by a split vote of 12–6. In balancing the risks against the benefits of the revised manuscripts in the context of additional information and new U.S. Government policy, the Board shifted its position.

In my opinion, the split vote is highly significant and signals that the Board still believes that there is great potential for misuse of information generated by these types of experiments. The majority of the Board members voted for publication, but they were clearly still troubled by this research and its potential to be misused. It is fair to say that the Board believes that these types of experiments will arise again and that these issues are not fully settled. As one Board member noted, we have only kicked this can down the road and will be dealing with it again in the future.

It is critical that we establish policy that intensely monitors high potential DURC research from cradle to grave in order to protect us from misuse, but also to free low-potential DURC research from onerous regulations. We must be careful that we do not destroy the scientific enterprise as we try to protect against misuse of some research. Thank you.

Chairman LIEBERMAN. Thanks very much, Dr. Keim.

Let me just ask you, while the phrase is in my mind, what did you mean when you said or referred to undesirable political consequences from not publishing?

Mr. KEIM. This information was conveyed in a classified briefing and we cannot talk about it in detail, but there are many international collaborative projects here in public health to try to control, predict, and understand influenza pandemics. Some of those political agreements are very fragile, and I think that it is fair to say that not releasing this information was seen by the intelligence community as having a detrimental effect upon those fragile relationships.

Chairman LIEBERMAN. Understood. Thank you.

Our final witness is Dr. Thomas Inglesby, Chief Executive Officer and Director, Center for Biosecurity, University of Pittsburgh Medical Center. Welcome back.

TESTIMONY OF THOMAS V. INGLESBY, M.D.,[1] CHIEF EXECUTIVE OFFICER AND DIRECTOR, CENTER FOR BIOSECURITY, UNIVERSITY OF PITTSBURGH MEDICAL CENTER

Dr. INGLESBY. Mr. Chairman, thank you for the chance to speak to you today. My name is Tom Inglesby. I am the Director for the Center for Biosecurity of University of Pittsburgh Medical Center. I am an infectious disease physician by training, and over the last two decades, I have seen many patients with influenza die despite excellent medical care in American hospitals.

For many years, my Center colleagues and I have been studying avian pandemic flu and the public health actions that need to be taken to protect us from those challenges, and like all of you, I am deeply concerned that H5N1 is a major global threat.

I have been opposed to the publication of the revised Fouchier manuscript. The breakthrough in that work was making H5N1 transmissible through the air between ferrets. Just as wild type H5N1 kills ferrets when instilled into their tracheas, this engineered virus also kills ferrets the same way. So there is no evidence that I have seen publicly presented that this engineered virus would have less virulence in humans than wild type H5N1 infection would.

Were this virus to cause a human infection, it could acquire new, unpredictable virulence properties. So if this work were replicated after publication and if it led to human infection following accident or misuse, we cannot rule out the chance that it would lead to high case fatality in a spreading epidemic difficult to stop with quarantine, vaccine, or antivirals. As you noted, there are others in the scientific and public health communities who share this concern.

That said, I appreciate that a deliberative process has taken place in the last 6 months. The majority of NSABB members, the U.S. Government agencies, and the journal, *Science and Nature,* have decided that this work should be published. I am concerned about this, but I recognize this decision has been made. So now it is time to look ahead and anticipate the future of H5N1 mammalian transmissibility research, which scientists are now poised to pursue. Here are some brief thoughts on benefits and risks of further pursuing this line of research.

Will further engineering H5N1 mammalian transmissible viruses help improve surveillance? In my view, in the short term, it is unlikely. Genetic mutation data is not widely collected in avian flu surveillance systems. Very few sequences are analyzed in real time. Even if we could identify experimental mutations in birds in real time, the prescribed response would still be the same: Culling of infected birds, all flocks, regardless of the mutations of the virus. Until we have a surveillance system in place that collects far more genetic sequence, does so in time frames that are meaningful, and have predictive value sufficient to lead to additional action in the field, this action seems unlikely to practically improve surveillance. Nor is this research necessary to making H5N1 vaccine for reasons I explain in my written testimony.

What could go wrong with mammalian transmissible H5N1? Could an accident occur? Biosafety at modern labs is generally ex-

[1] The prepared statement of Dr. Inglesby appears in the Appendix on page 63.

cellent. Accidents are uncommon, and most pathogens have little capacity for societal spread. But the accidental escape of an engineered mammalian transmissible H5N1 could result in catastrophe. Although it is uncommon, accidents do happen. In 1977, H1N1 caused a mini-pandemic, probably from a lab escape. Nine years ago, during the severe acute respiratory syndrome (SARS) outbreak, there were at least three incidents in which researchers working in Biosafety Level 3 (BSL-3) or BSL-4 labs in Singapore, Taiwan, and China accidentally infected themselves with SARS. I am not meaning to single out laboratorians for criticism. Mistakes are made by all types of professionals, doctors, pilots, rocket scientists, all of us, because we are human. We have to factor the possibility of human error, surprise, and accidents into our calculations of the risk of this research.

Can we assure this research will not be replicated and deliberately misused? No. We can hope no potential adversary will have the competence or the intention to pursue this, but we cannot accurately predict the chances this work will be replicated by a malevolent or disaffected scientist somewhere in the world, or a terrorist group or a Nation State.

What happens if a mammalian transmissible H5N1 starts to spread? Seasonal flu infects 10 to 20 percent of the world every year, as much as a billion people or more. The case fatality rate of wild H5N1 in the WHO database is nearly 60 percent, as you indicated. So if a strain of H5N1 with that fatality rate were engineered to spread like seasonal flu, hundreds of millions of people's lives would be at risk. Even a strain 100 times less lethal would place at risk millions of people's lives.

So what should be done about H5N1 mammalian transmissible research going forward? First, I would extend the moratorium that Dr. Fauci discussed. The reasons many experts agreed with the moratorium are still valid. Before proceeding, we should have more confidence this research will lead to practical benefits, and we should look for other ways to study transmissibility that do not require engineering mammalian transmissible strains. If this work is allowed to continue, we should limit it to the smallest number of labs. My understanding is that the United Kingdom and Canada have indicated their concern by deciding this work can only be performed in BSL-4 labs. We should have these discussions in an open, transparent way that includes the scientific and public health communities.

Second, let us decide if there are red lines that should not be crossed. For example, should increased lethality be engineered into mammalian transmissible strains in order to understand virulence? Should other avian flu strains be engineered for mammalian transmissibility? Should transmissible H5N1 strains be engineered to make them resistant to vaccines or antivirals so we can understand the genetics of those problems? We should decide now if there are any uncrossable lines.

And third, the United States should continue to strengthen its pandemic preparedness efforts. Priorities should include the capacity to manufacture flu vaccine on a large scale—a universal flu vaccine and new antivirals—and better surveillance and culling of in-

fected flocks. Preparing for pandemic and avian flu is critically important.

Let me turn to the policy for DURC that was recently announced. This policy is a good step towards addressing the kinds of issues raised by the H5N1 controversy. The success of the policy will depend on how it is implemented. In my written testimony, I provide recommendations for success of the policy and I will highlight four of them here.

First, implement effectively at the local level. Scientists, their institutions, and their institutional biosafety committees will be crucial to the success of this policy. This is new territory for them, so training and education will be key. They will also need new members, new resources, and a clear process for elevating concerns.

Second, learn from experience. This process will need to evolve as we learn. I understand that the NIH review of the portfolio found that 10 experiments warranted further risk management. It would be a valuable learning tool for the science community to understand these 10 cases. What caused the concerns? How were risks mitigated? I think this could be done in an unidentified way to protect the scientists.

It would also be useful to learn as much as we can from the H5N1 risk assessment and risk management process. How were risks assessed? How were conflicts of interest managed? How did the process ensure all relevant judgments were considered and data seen? Going forward, the success of the DURC policy will depend on these issues.

Third, attend to the regulatory burden. This new policy will add another process to be navigated by a scientific community that is already heavily regulated. We have to make sure we do not impose such a regulatory burden that scientists cannot continue their important work. And so to this end, I would recommend asking the National Academies to examine the effects of existing policy and regulatory burdens on U.S. scientists.

And last, reaffirm the role of NSABB. It deserves a lot of credit for its work. NSABB members have done substantial public service. They have prepared valuable dual-use guidelines and spent a great deal of energy, intellect, and time on this H5N1 debate. An independent and strong NSABB should have an important role in DURC policy implementation going forward, and I hope that the NSABB will rarely be in the position of getting invited into the process after manuscripts have been submitted. I think we all agree in this room that the risk assessment and management process should happen early in the research process.

To conclude, scientists who research influenza and other infectious diseases are working to improve our understanding of biology and to better the world. The United States needs to continue supporting entrepreneurial and talented scientists with the best ideas. At the same time, we need to acknowledge there are rare situations where the consequences of an accident or misuse are so serious that special processes are needed to manage the risk to the public, and this new DURC policy is a good step in that direction.

Chairman LIEBERMAN. Thanks, Dr. Inglesby.

When we hear about accidental escape of pathogens from laboratories, we get alarmed. Talk a little more about it. Does that normally happen?

Dr. INGLESBY. No.

Chairman LIEBERMAN. Because the example you have stated, the infection of workers or personnel in the labs——

Dr. INGLESBY. Yes. In all the cases that I mentioned and in other cases, that is typically the way that an infection would escape a lab. A laboratorian would get infected. Usually when laboratorians are infected, though, they do not spread it to anybody else.

Chairman LIEBERMAN. Right.

Dr. INGLESBY. So the risk really is primarily to the person working in the laboratory. It is rare for the laboratorian to pose a risk outside the lab.

Chairman LIEBERMAN. Right. Dr. Fauci, I assume that all the regulations, both before and after March 29, were intent on limiting the possibility of exposure to personnel?

Dr. FAUCI. Definitely, Mr. Chairman. In general, definitely. And specifically, in the two cases that we are discussing as prototypes here today, the two laboratories, one in Wisconsin and one at Erasmus University, were very highly qualified, inspected multiple times, and given a rating of "meet or exceed" the standards for the kinds of protection we are talking about.

Chairman LIEBERMAN. Good. Dr. Keim, let me ask you first about the two laboratories that were the subject of this concern. To the extent that you can, why was the ultimate decision unanimous in the case of Wisconsin and then mixed in the case of Erasmus University?

Mr. KEIM. The underlying science and approaches that each laboratory took for doing these experiments were different. While the two studies lumped together a lot in our discussions, they were distinct. We viewed Dr. Yoshihiro Kawaoka's approaches as having a greater biological control of the risks. It is one of the aspects that we have instituted routinely in biosafety experiments in the United States, where these types of experiments are performed in a biological context that would be less dangerous. For example, if we do an experiment where we add a novel gene or biological property to an organism, we prefer to do it with a pathogen that has been disarmed, or attenuated, to lessen the risk.

And so in distinguishing the two research groups and their scientific approaches, the biggest difference is that one worked on a biological platform, the H1N1 virus that was viewed as less risky, and not as virulent than the other one. In contrast, taking the wild type H5N1 avian influenza virus, the raw material from nature, and then directly changing the transmissibility on that genetic platform was viewed as a potentially very risky experiment.

Chairman LIEBERMAN. And if I understand, that difference had more to do with the scientific decisions of each team as opposed to differing levels of safety standards that they were operating under in their respective institutions or countries.

Mr. KEIM. Yes. As Dr. Fauci has already pointed out, both institutions were heavily regulated, heavily reviewed, and both exceeded the current requirements for biological safety that are required to perform these types of experiments.

Chairman LIEBERMAN. Dr. Keim and Dr. Fauci, I want to give you an opportunity to respond to the dissent in the letter which was, I gather, originally a confidential letter and then was leaked, from Michael Osterholm in his criticism of the NSABB decisions.[1] And to some extent, Dr. Inglesby expressed some concern about the decision.

Dr. Keim, please begin.

Mr. KEIM. So first off, we are a Board of almost 25 highly qualified individuals and we rarely agree 100 percent on anything.

Chairman LIEBERMAN. It sounds like Congress. [Laughter.]

Mr. KEIM. I know.

Chairman LIEBERMAN. Although we may not be highly qualified. [Laughter.]

Mr. KEIM. I must say that we actually embrace this dissent, we use it and we actually cherish the different members and their differing opinions. This is true for this particular example, as well.

I believe that this letter that was meant for an internal constructive criticism process, and to help us to understand in a retrospective fashion what we had done and what we had just come through as a board. As such, I view it as a very constructive type of communication. It was unfortunate that it was leaked and it became part of the public dialogue. The public nature of the ensuing debate has made it harder to have a constructive and proactive type conversation.

That aside, many of the things that he said are worth carefully examining. One point made in the letter is that there was a bias in the witness list. I think that is true. The primary briefers that were brought to the hearing, were, in fact, the investigators themselves. They are inherently biased with an easily identifiable conflict of interest. They wanted their work published in these prestigious journals. In addition, we brought in a third investigator who has been collaborating with two primary research groups. His report and work was on how you use the mutation information for surveillance purposes. Again, this was an individual who would like to see their work published and, it can be argued, that they would see the benefits far clearer than the risks.

However, I do not think this is of great concern, Mr. Chairman. The Board is comprised of experienced scientists and what we routinely do in our profession is look at scientific data and critically examine other scientists' work. And so the biases that were inherent in those types of witnesses, I think, were not a problem for us. In fact, I think, that we dealt with the briefers' conflict of interest very well. We had ample opportunity to ask very tough questions of the investigators. Dr. Ron Fouchier, for example, was in front of us for over 2 hours with lots of intense questioning about his work. In the end, I think that those inherent biases were something the Board could and did deal with quite well.

One part of Dr. Osterholm's letter criticized the intelligence briefing. This was a classified briefing that was presented by the U.S. Government intelligence community. Most of the Board members came into the briefing as academic scientists and we pretty much had to take this assessment on faith. We could not examine the

[1] The letter referenced by Senator Lieberman appears in the Appendix on page 76.

data or assumptions and had to assume that the assessments of the risks and the political consequences were fact. This is an environment where the Board is perhaps a little bit naive and did not have the capability to look behind these assessments in a critical fashion. The briefing was held at the "secret" level before we were told that the supporting information was at a higher level of classification. The intelligence community briefers were quite confident, and suggested to us that the risks of publishing these papers were minimal while the political consequences of not publishing were great. I think that this briefing had a great effect upon individual Board members' deliberations and our ultimate decisions. Dr. Osterholm's criticism of the briefing is hard for me to evaluate. I think that summary-type classified briefings may be unavoidable. At some level, all advisory boards will be faced with accepting such an evaluation at face value.

The March 29 and 30 Board meeting was never set up to be a point-counterpoint debate but rather a fact finding endeavor with heavily emphasis on the researchers themselves. So we did not have time in the 6 hours to hear from every witness in the world. But we did succeed in hearing the most important witnesses, even if they were inherently biased.

Chairman LIEBERMAN. Interesting. So if you had it to do over again——

Mr. KEIM. Absolutely, I would do many things different, Mr. Chairman. For one, I would make sure that DURC review was being performed long before it ever came to the Board. We were brought these papers under a very tight timeline back in October, 2011.

Chairman LIEBERMAN. Right.

Mr. KEIM. In retrospect, the amount of effort it took to review this science was too large for the time line we were on.

The process and the number of hours we put into reviewing these two papers was massive. It is clear that the new government policy for identifying DURC early in the research cycle is going to be critical for moving much of this evaluation early on, before it is submitted for publication.

Chairman LIEBERMAN. Yes, that is a very important point. I mean, I agree with you that the dissent, even to some extent the bias, is not of itself of concern, particularly in scientific debate and discussion. But, obviously, from a homeland security point of view, we are concerned about the impact. Am I right that you are essentially, to the best of your ability, providing assurances that information is not going to be released in the two studies, particularly in the Fouchier study, that would significantly increase the risk of deliberate or accidental release of H5N1?

Mr. KEIM. The Board was pretty confident in the case of the Kawaoka paper and the vote was unanimous. In the case of the Fouchier paper, it was a split vote. The vote was 12–6 and there were strong feelings on both sides.

In this type of an advisory Board process, each of us had to weigh the evidence and it was not black and white. There were great uncertainties in this research. A relatively small number of ferrets were actually used in these experiments making the data less than definitive in some cases. Our understanding the biological

properties of these viruses is not 100 percent certain. In the end, the 18 Board members had to weigh the evidence as best they could.

And I will tell you, you will not find a better group of people to do this. This Board is extremely qualified and capable to do this assessment. We worked very hard at understanding the risks and benefits, but were not unanimous and came to a split vote on the Fouchier paper.

Chairman LIEBERMAN. Dr. Fauci, do you want to respond to the Osterholm complaints, and to some extent, to Dr. Inglesby's concerns?

Dr. FAUCI. Sure. Well, with regard to the letter, as you probably know, because I am sure that your staff or you have a copy of the letter, there were several issues that were brought up in there. I have to say that I agree with many of the things that Dr. Keim said in the sense of this is a strong Board, a really good Board. We have worked with them for a long time and I do not think they are going to be significantly influenced by what they might perceive as a bias. So if they did, I believe, as Dr. Keim has done in the past, if you have an issue with something, you bring it up.

The letter was sent to the Executive Secretary of the NSABB, who is at NIH, Dr. Amy Patterson. We have responded on a point-by-point basis to everything in that letter, so we would be more than happy to make that response available to you so that you could see the point-by-point discussion.

Again, there were important issues about looking forward. There were several things in there that I must say, quite frankly, Mr. Chairman, that I actually disagree with, one of which was the concern about the security briefing. I have a great deal of trust in the Director of the National Intelligence to tell us what we need to know. So that is just one example.

The idea, as you mentioned, about the picking of people who would be on the agenda, we did not get any indication from Dr. Osterholm of people that he wanted to see there that were not there.

So rather than go tit for tat on that, I can just say that I think the general principles that were brought up by Dr. Keim, I totally agree with. I just have to say for the record that I disagree with many of the things in his letter.

Chairman LIEBERMAN. No, I appreciate that directness and I thank you for it.

Do you have a reaction to Dr. Inglesby's suggestion that the moratorium should be extended, and if so, for how long?

Dr. FAUCI. I totally agree with Dr. Inglesby about an extension of the moratorium. The real critical issue is for how long.

Chairman LIEBERMAN. Right.

Dr. FAUCI. This is a voluntary moratorium, and I think that is something that the public needs to understand. This is a voluntary moratorium on the part of the scientific community.

Chairman LIEBERMAN. Right.

Dr. FAUCI. I had discussions with the influenza scientists and encouraged them and actually, to their credit and to the discussion that Dr. Keim himself had in the NSABB, this was something that they agreed upon. Exactly when to call it off, we are very actively

involved in pushing forward the principles and the implementation of the March 29 government-wide DURC policy. That is going to have an important impact on when we can feel comfortable that we can then go on, as long as people understand both the principles and the implementation mechanisms of how you address DURC. Several of the labs that are involved understand that now. We need to make sure that is broadly understood. So I definitely agree with that.

I just want to make one point——

Chairman LIEBERMAN. Go ahead.

Dr. FAUCI [continuing]. Of minor disagreement, if you want to call it that, with what my esteemed colleague, Dr. Inglesby, says. If we only looked at the short-term benefit of research, we would not do a lot of research at the NIH because you very often have a situation where it is incremental and you build up into something that really becomes important. So although I understand the point that is being made, if you look at what immediate benefit those mutations are going to have right now, sure, you can say that there is not a lot of surveillance capabilities of high sequencing, etc. But the incremental accumulation of knowledge is one of the fundamental principles that the NIH research agenda is built upon.

So I think there is a little bit of a disagreement on that. I do not think you need to have an absolute immediate benefit for research to be ultimately important to do and to publish.

Chairman LIEBERMAN. Do you want to respond?

Dr. INGLESBY. Yes. Well, actually, I completely agree with what you just said, so I do not think we disagree on that. I agree that fundamental research into understanding biological principles is critical and it is a critical part of the science mission. I think this is just one very specific and rare example where I think the bar for whether to proceed with this line of research should be beyond a deeper fundamental understanding of biology.

In general, I completely agree that the test for basic science should not be whether it has practical benefits in the next year. But in this case, a lot of the proponents of the research have been arguing for urgent practical benefit, and in my view, I just have not seen a compelling case for that.

Chairman LIEBERMAN. It is not worth it.

This leads me to ask you, Dr. Fauci, and anybody else who wants to answer—and in some sense, it is a question at the margins—when considering future research that would be seen as DURC, can you imagine instances in which you would conclude that research should not be undertaken under any circumstances?

Dr. FAUCI. I do. I think it would be scientific hubris for scientists to say we can do anything that we want to do, regardless, just for the curiosity of it, for understanding it. So I do think there are some experiments that would better not be done. I think that would be a very rare situation, Mr. Chairman, I mean, you can fantasize about ridiculous and dangerous experiments just for the sake of doing it. Those, we do not even bother with. But in the realm of trying to keep up with something that is a clear and present danger of happening in nature itself—that is the critical thing that we are dealing with here and that is the reason why we agree so

much on it, and yet all of us at the table know that this is a delicate issue.

If you are doing something in an experimental fashion that you might be pushing the envelope of creating something that would give you some information but it is not really addressing any danger, then I think that is very ill advised to go there. But when you have a situation where nature itself is already doing some of the things that you are trying to stay ahead of, that is when you really have to seriously consider it.

The short answer to your question, the principles of the new government-wide DURC policy that we put out on March 29 actually put that into the consideration. So when you look at the number of experiments that you can do—there are now seven classic experiments, that if they come up, you have to decide if you have a risk mitigation for that particular result or experiment.

One of the risk mitigations very well may be to not do the experiment. So it really falls very nicely into the answer to your question. It is built into the new government-wide DURC policy, that is, in fact, an option.

Chairman LIEBERMAN. So I presume that this is not an area where you can draw a very clear red line, right? In other words, what you have described are the standards adopted in the policy, and particularly with regard to risk mitigation, and that in a given case, the decisionmakers might decide that in the interest of risk mitigation, the research simply should not be conducted.

Dr. FAUCI. It is essentially a continual evaluation of risk-benefit.

Chairman LIEBERMAN. Right.

Dr. FAUCI. And you take each individual case and you look at it, and it could turn out that, clearly, the risk and our ability to mitigate the risk might be such that it is just not worth doing.

Chairman LIEBERMAN. Dr. Gerstein, from a homeland security point of view, talk to us a little about whether you think that there ought to be clearer red lines here or whether this is an area of scientific inquiry where it is simply impossible to state a red line unless you see it in a particular proposal for a research project of concern.

Mr. GERSTEIN. Well, Senator, I agree exactly with what Dr. Fauci said. I think there are some experiments that should not be done. In fact, that is actually the intent of the Compliance Review Group——

Chairman LIEBERMAN. Right.

Mr. GERSTEIN [continuing]. Looking at the NSABB seven experiments and looking at the type of pathogens we routinely work with in this sort of threat analysis and characterizations that we do. So we look at these very hard. We make sure that all of them are needed. We make sure that we are doing them in the safest possible ways, in the appropriate facilities. But at the end of the day, we recognize that DHS needs to look at some of these different capabilities and assess what sort of threats they pose.

Still, we are doing them in the highest containment. For the Department, we do most of our internal work in our facilities, the Fort Detrick facility, NBACC, and then the Plum Island facility, PIADC. So we are very keen on that.

Chairman LIEBERMAN. We have talked so far about the U.S. Government response to this challenge of dual-use research of concern, but, obviously, scientific research is global, and in this case one team is in Wisconsin, and one team is in the Netherlands. So help the Committee understand for the record, what is the state of the discussion of standards internationally? Are there international scientific bodies that are moving to adopt standards such as the March 29 U.S. policy? Are there national standards being adopted in individual countries throughout the world? What is happening, because obviously we are talking here about a fear, in one sense, of a global pandemic. So if something wrong happens in a laboratory halfway around the world, it could still affect the lives of people here in the United States.

Dr. FAUCI. Let me take a shot at that, Mr. Chairman.

Chairman LIEBERMAN. Please.

Dr. FAUCI. It is very interesting, because this gets into what we refer to as the culture of responsibility, a global culture of responsibility. Back in the 1970s when the revolution in DNA technology took place globally, but fundamentally here in the United States, scientists got together—it is strikingly similar to the challenges that we are facing now—and came up with what we ultimately have right now, the DNA Recombinant Advisory Committee (RAC).

And although that only pertains when you talk specifically about government-funded research here in the United States, what has happened is that the fundamental principles, the codes of conduct, and the culture of responsibility that was engendered by the discussions back in the 1970s regarding recombinant DNA technology, without any capability of enforcing it globally, essentially permeated the global approach towards recombinant DNA technology. So although we did not have any enforcement capability, it became something that was widely shared throughout the world.

Now, other countries, including the Netherlands right now, are addressing in a very serious manner how they are going to approach this because it was one of their scientists. But this is also going on in the United Kingdom, in France, and places like that. So what we hope and what we envision is that as a result of this, there will be a culture of responsibility that even though we do not have the carrot and the stick of funding and withdrawing funding, that these kinds of principles will actually be implemented throughout the world. We are all hoping for that, and I actually have confidence that it will.

Chairman LIEBERMAN. Good. Dr. Gerstein, I know that Secretary Janet Napolitano and people in the Department now are developing ongoing relations with homeland security departments or comparable departments around the world. Is there discussion of this particular concern in those international meetings?

Mr. GERSTEIN. Senator, there is. We have had a number of bilaterals, for example, in the Directorate of Science and Technology (S&T). We have 12 nations with whom we have bilateral discussions.

Chairman LIEBERMAN. Right.

Mr. GERSTEIN. And we have had these discussions. The nations feel very similar to us, but there is not all good news as far as this is concerned, and I would take you back to the Biological Weapons

Convention. Some interesting things come out when you look at that.

There is a London-based Verification, Research, Training, and Information Center (VERTIC), and in one analysis they did a couple of years ago, they discovered that very few nations of the 87 that they surveyed even had laws or definitions of what a select agent is, and they did not have laws against developing, stockpiling, or storing biological material. And the news does not get any better when you talk about export control measures.

So it highlights the fact that we may be working very hard in this country and we may put in place the proper provisions, but it is important that we do the international outreach, especially into some of the countries that may not have the same sense of the life science issue and the DURC issue that we do.

Chairman LIEBERMAN. Yes, Doctor.

Dr. INGLESBY. Can I just add to the good news side of the story.

Chairman LIEBERMAN. Yes.

Dr. INGLESBY. First of all, I think the H5N1 debate, as painful as it has been in the last 6 months, has been somewhat useful internationally because people are all paying attention to this issue. So I think that one good consequence of this has been enlightenment or awakening in many places in the world which were not paying attention to this.

The second point is at a science meeting 2 weeks ago when this question came up and there was concern that private foundations would not follow the lead of the U.S. Government in the new policy, a representative from one of the most important science foundations stood up and said, let me make very clear, if the U.S. Government is going to pursue this policy, we absolutely intend to follow it ourselves, and I imagine that others will.

And the third point of good news was an article published in the journal *Nature* yesterday, one of the most important science journals in the world, said that the United States is taking an important leadership position on this DURC policy and that other nations should follow suit.

So there are some indications that maybe this will move in a direction where other people are doing similar things.

Chairman LIEBERMAN. Well, that is encouraging.

Let me go to a different aspect of the DURC policy which interested me, which is that it requires departments and agencies to report to the White House National Security Staff in the next several months on their current DURC projects and on risk and mitigation measures. The National Security Council (NSC) staff is probably larger than most people think, but it is still relatively small for the range and responsibilities it is given, particularly those on the NSC staff that work on biosecurity and bioterrorism issues. And I wonder whether you have a sense of how the information is going to be used to support oversight of such research and whether any of you expect your agencies and/or the NSABB will be asked to support the oversight that the White House National Security Staff is charged with carrying out here. Maybe I will start with you, Dr. Gerstein.

Mr. GERSTEIN. Well, Senator, that would be somewhat speculative. I would just like to take you back to the deliberations to date.

We have used those deliberations to better understand what has gone on with the papers. We have been briefed on the science. We have been briefed on the policies, the issues that have surfaced. And I think what has come out of the March 29 White House-led effort is a good first start. What we expect is that this will continue, that this is not an end point, so to speak, but it is the beginning of a process that we will continue to look and try to ensure that our policies with regard to DURC are as good as they can be to ensure national security, but also homeland security as well as ensuring scientific work goes on unfettered. So in that regard, we are very hopeful.

It is a reporting requirement. All departments and agencies are submitting to that. And we have not come up with the next step, so to speak, in trying to finalize the policy. This has generated, though, incredible discussions across the interagency where departments are getting together and discussing how they are handling it. We received several phone calls to see how we were dealing with our university grants program and the language that we have inserted that provides us at least a stop-gap measure should it be necessary to ensure that publication of certain materials would not proceed.

So this has actually been a very positive outcome, I think, across the government.

Chairman LIEBERMAN. Good. Dr. Keim, do you anticipate that the NSABB may be asked to help the White House in these reviews?

Mr. KEIM. We do whatever the Administration asks us to do and we do not do anything they do not. [Laughter.]

Chairman LIEBERMAN. A good standard. Thank you for that.

Dr. Fauci, do you want to comment on that at all?

Dr. FAUCI. Well, I actually agree with what Dr. Gerstein said. If you look carefully at the DURC policy—the part about within 60 days to give an inventory, within 90 days to determine how you are going to do risk mitigation—that was really the first cut at making sure we know what is going on right now. I think this is going to be an evolving process. Ultimately, we are going to try and make sure that when you get down to the local level of the institutional biosafety committees, a lot of the kinds of monitoring that will be done will be essentially automatic by well-trained people.

Chairman LIEBERMAN. I agree.

Let me ask this question. In your testimony, Dr. Fauci, you discussed NIH-funded efforts to develop a universal influenza vaccine, and Dr. Inglesby highlights the ongoing efforts to develop vaccines focused on H5N1. I wonder whether the findings of these kinds of studies will lead NIH and other organizations that fund vaccine research to increase the priority that you are placing on these kinds of research efforts?

Dr. FAUCI. The answer is a resounding yes. There are a couple of ways of getting rid of this problem. One of them, I think, Dr. Inglesby mentioned in his testimony, certainly in some discussions we have had, is to just kill the chickens that have H5N1 and make sure that we just get rid of the reservoir. That is very difficult to do because you have countries that are not necessarily interested for economic and other reasons.

The other thing is to have available countermeasures that actually work really very well. The idea of getting a universal influenza vaccine is not only going to be very important for seasonal influenza, so we do not have to keep chasing each year getting the right combination and matching it with what is circulating out there, but also, it is a major countermeasure against the emergence of a pandemic.

So we are putting a considerable amount of effort, and we have had some very encouraging scientific advances over the past year and a half to 2 years on understanding much better the type of immune response that you need to induce in an individual to cover virtually all strains. We are not there yet, but this is something that we see as the light at the end of the tunnel. It is always risky to predict when you are going to get a vaccine for whatever, but unlike it was a few years ago, we now see that we have the scientific mechanisms and wherewithal that we are on the road to developing a universal flu vaccine.

Chairman LIEBERMAN. Well, that is tremendously encouraging, and, of course, that is exactly the kind of work even in a budget-constrained atmosphere that I hope we will find adequate funds for.

Do you want to comment at all on that, Dr. Inglesby?

Dr. INGLESBY. I would say that it is extremely encouraging. It is exciting. If we had a universal flu vaccine, it would change the risk equation for everything we have talked about today in the realm of influenza. So I would just strongly support the efforts that are going on at NIH by the industry on that.

Chairman LIEBERMAN. I have a final question, which is the kind of question, I must say for the benefit of staff, that my friend and colleague from Delaware, Senator Carper, would normally ask if he were here. Incidentally, I learned a lot from the testimony today and, overall, I am reassured by the government policies that have been put into effect. Even at the far end that we have set up a decisionmaking process that considers and values risk mitigation and says, in some cases, it may be that there will be a decision that research should not proceed because it is impossible to adequately mitigate the risks.

So the question Senator Carper would ask, I believe, if he were here, is if you were a member of the Committee, is there anything more that we, with our primary concern about homeland security, ought to be either asking the government to do or doing ourselves, either by way of encouraging regulation or, in the extreme, some kind of legislation? Dr. Inglesby.

Dr. INGLESBY. I do not see at this point any legislative or regulatory proposal that would substantially improve the situation. I do think it is very useful to have oversight like this on the development of the new policy because I think there are a lot of things along the way that are going to be challenging. I think, for example, understanding the criteria for risk assessment and how we manage those risks is going to be very important. I think the composition and responsibilities of the NSABB will be very important.

So asking reasonable questions of the government about how this new DURC policy is working as it evolves is very important, and I think, in particular, paying attention to the very specific case of

H5N1 mammalian transmissibility research. While the decision has been made to move on to publication for this experiment—which I am concerned about—I think the next issue is going to come up relatively soon unless there is a change in course. I think that will come up again, so I think you just have to pay attention to that.

Chairman LIEBERMAN. Thank you. Dr. Keim.

Mr. KEIM. I would just reiterate what Mr. Davis just said, that how the new policy is implemented is going to be very key. One important role that the NSABB has played is that we are an independent body. We are non-government.

Chairman LIEBERMAN. Right.

Mr. KEIM. And I think it is very important that we have "external eyes" as a part of this new policy's implementation. There are inherent conflicts of interest between the funding agencies and the investigators, and the investigators themselves. While the board has infectious disease researchers, we were outside the small influenza research community and we were independent of the funding agencies. We are able to look at this problem in a way that is unique, and I think that is an important part to what needs to happen in the future.

Chairman LIEBERMAN. I agree. Dr. Gerstein.

Mr. GERSTEIN. Thank you, Senator. Well, I will go back to the original remarks I made, that I think it is a very complex issue. It requires balancing outcomes. We do not want to do something precipitously that is going to have a deleterious effect on the science. On the other hand, we have a very important mission in Homeland Security that we must ensure is well served.

We do have to avoid red lines because the minute you put out a red line, somebody is going to figure out a way to cross it. And so the best way to do it is through very thoughtful, very judgmental type bodies like the NSABB that has played an extraordinarily important role in getting us through these two papers and understanding what was going on with those papers. So it really does come down to a matter of judgment.

On the direct question, do we need legislation right now or regulations, I would say the Executive Branch has a lot of work to do to work through the policies. As we talked about, the March 29 government policy is a first step. We are making great headway. We are continuing those deliberations. We are learning from each other. We think in DHS we have a lot of good policies that we have implemented. We are sharing those to the maximum extent possible.

So I would like to put down a marker that says that perhaps later, after we have had some more time working through the March 29 policy and adding more meat to the bones, that we come and consult with Congress on this very critical issue.

Chairman LIEBERMAN. That makes sense. I hope you will do that. Dr. Fauci.

Dr. FAUCI. Yes. Mr. Chairman, I do not see any immediate legislative issue that would be appropriate at this point. But I think when you asked, if I were on the Committee, what would I do, I think what you just did today was really a very important thing. That is really very beneficial to this difficult process that we are

going through, particularly with the new policy and trying to get it right and implemented right.

And the fact that an important Committee like this Committee, with yourself as Chairman, is actually interested in the subject, is looking at us—we know that we will come back to you sometime, and maybe soon, to just give you follow-up about how we are progressing on the implementation of this policy. So you have already done something, I think, that is very important and valuable to us, because not only here in the United States, but globally, people are aware that the U.S. Senate and this Committee are interested in this problem, and that adds a degree of seriousness to it which we appreciate.

Chairman LIEBERMAN. Well, I appreciate you saying that, and that clearly is our intention. So let us agree we will keep in touch. As you know, we want the benefits of scientific inquiry. We need them. We also need to mitigate risk, and I think the policy that we have now is clearly aimed at doing exactly that. So we will follow it to see how it is going. Maybe we will come back again and do one more hearing toward the end of the year.

But I thank you very much for the work you did on your prepared testimony, which will be entered into the record of the hearing, and for the testimony this morning. We are going to leave the record of the hearing open for 15 days for any additional questions or statements.

With that, I thank you very much and the hearing is adjourned.

[Whereupon, at 11:36 a.m., the Committee was adjourned.]

APPENDIX

Opening Statement for Chairman Joseph Lieberman
Homeland Security and Governmental Affairs Committee
"Biological Security: The Risk of Dual-Use Research."
Washington DC
Thursday, April 26, 2012

Good morning. In 1851, a revolution in medicine already underway was crystallized in a letter Louis Pasteur, one of the fathers of microbiology, wrote to a friend: "I am on the edge of mysteries and the veil is getting thinner and thinner."

Thanks to the work of Pasteur and succeeding generations of scientists, the "mysteries" of the microbial world have slowly been unraveled and we all live in a healthier world for it. Childhood diseases, like polio and measles have been all but vanquished. Scientists were able to identify the AIDS virus, which helped lead to treatments and – according to one of our witnesses today – a cure is in sight.

And the last global pandemic that killed on a massive scale – the Spanish flu, which killed at least 50 million people – was almost a century ago.

But for all the medical miracles that lie underneath that veil Pasteur began to peel back, there also lie dangers. Research that can lead to cures extending life for millions can also kill by the millions if a rogue pathogen were released either by accident or by falling into the wrong hands.

And it is this paradox of "dual-use" research we consider with today's hearing.

Last fall the scientific world was rocked by the news that two researchers working independently had been able to engineer a new strain of the H5N1 virus – also known as bird flu – that could easily infect humans. Epidemiologists have long feared that if the H5N1 virus ever made the jump from a virus mostly confined to birds to one easily transmitted among humans it could swiftly cause a deadly pandemic.

The mortality rate for the few reported cases in humans who have been infected is as high as 60 percent.

By contrast, the Spanish flu had a morality rate of about 2 percent and the Great Plague that devastated Medieval Europe had an overall death rate of about 40 percent.

The researchers, based at Erasmus University in the Netherlands and at the University of Wisconsin, announced they were going to publish the results of their studies in the journals "Science" and "Nature" respectively.

This set off a global ethics debate in the scientific community about whether to publish or not publish these results – or if the experiments, funded by the National Institutes of Health, should have been undertaken at all.

On the one hand, there are those who say that getting this information out there could help other scientists better understand the mutant strain so they could prepare for a possible pandemic by watching for natural mutations and developing vaccines and medications.

After all, the fact that these two research teams were able to create this new strain from existing genetic material means that nature could create it as well. In fact, many scientists thought that was likely.

But given the lethality of the virus, others argued that publishing the results create huge security risks by offering a blueprint for a deadly biological weapon to rogue states or terrorists.

In a recent speech at a biological weapons conference in Geneva, Secretary of State Hillary Clinton warned that al Qaeda in the Arabian Peninsula has issued a call for – I quote: "Brothers with degrees in microbiology or chemistry to develop a weapon of mass destruction."

And there is also a danger that the manufactured strain might somehow escape from the laboratory as others have in the past.

In December, at the request of the Department of Health and Human Services, the National Science Advisory Board for Biosecurity – or NSABB – was asked to review the H5N1 research papers.

The NSABB concluded that more needed to be known before the research was made public and they asked the editors of "Science" and "Nature" to delay publication. Both magazines agreed.

Last month, after further review, the NSABB withdrew its objections and voted unanimously to allow the University of Wisconsin study to be published and 12 to 6 to allow the Netherlands study to be published with some revisions and clarifications.

One of the things that influenced the board's decision was the revelation that the modified strains of H5N1 had become less lethal.

But that decision has drawn criticism from Dr. Michael T. Osterholm, director of the Center for Infectious Disease Research and Policy at the University of Minnesota and an NSABB board member.

In a letter to the National Institutes of Health he wrote that the NSABB had deliberately ignored the voice of scientists who believed publication of the H5N1 research was dangerous.

"I believe there was a bias toward finding a solution that was a lot less about a robust science- and policy-based risk-benefit analysis and more about how to get us out of this difficult situation," Osterholm wrote.

We can't just "kick the can down the road without coming to grips with the very difficult task of managing [dual use research of concern]."

The "publish or not publish debate" continued earlier this month during a two-day conference of the world's leading scientists held at the Royal Society in London.

One point that most of the attendees seemed to agree on is we need to put in place better systems to track this kind of research at each experimental stage rather than waiting until its ready for publication to make decisions about what can be revealed.

And that's what I want our panelists to talk about today. Although this particular issue appears to have been resolved, it's going to recur and we can't just "kick this can down the road" and deal with it on an ad hoc basis when it happens again.

What systems were in place to monitor dual use research that could produce dangerous results at the time these experiments were begun? What new systems are being put in place? Are more needed? And how do we balance these against the quest for knowledge, which means free scientific inquiry.

Etched into the National Academy of Sciences headquarters are the words of Albert Einstein who said: "The right to search for truth implies also a duty; one must not conceal any part of what one has recognized to be true."

But what if peeling away nature's veil reveals a Pandora's box that could unleash new waves of disease upon the world?

These are tricky questions and I want to thank the expert panel – who I will introduce shortly – for joining us today to help us hold this much-needed conversation.

Statement of
Senator Susan M. Collins, Ranking Member
Homeland Security and Governmental Affairs Committee

Biological Security: The Risk of Dual-Use Research
April 26, 2012

It has been almost a century since the 1918 Spanish influenza virus infected one fifth of the world's population, killing more than 50 million people and claiming some 600,000 American lives. Yet virulent strains of influenza are still a major threat.

The H1N1 strain, more commonly known as the swine flu, claimed over 18,000 lives during the 2009 outbreak, and exposed gaps in our preparedness capabilities for response to a global pandemic, especially the development, production, and distribution of life-saving vaccines.

In 2008, this Committee held a hearing on the report by the Commission on the Prevention of Weapons of Mass Destruction, which examined the security of biological pathogens on the Select Agent List. The testimony by Commission chairmen, former Senators Bob Graham and Jim Talent, helped raise awareness on the issue of biosecurity and the need to ensure that deadly pathogens, and the research carried out on them, are contained in secure lab facilities.

The Committee has also held numerous hearings on the nation's efforts to prevent, prepare for, and mitigate the impact of a pandemic influenza outbreak. In 2009, the Administration's failure to ensure the government was prepared to rapidly distribute vaccines was, and remains, a cause for great concern.

Preparedness requires investing in critical life sciences research to expand the knowledge base and technologies to help us respond to the next potential global pandemic. Such a pandemic could be even more communicable than the 1918 influenza virus, or as virulent as the Avian Flu Virus.

The World Health Organization has documented 576 human cases of Avian Flu infection worldwide since 2003. 339 of these cases resulted in death. Recently, research funded by the National Institutes of Health and conducted in Wisconsin and the Netherlands resulted in genetic changes to a strain of Avian Flu that allowed its airborne transmission.

The NIH-funded researchers planned to publish their full findings in two academic journals. Publication, peer review, and replication of findings are important steps in a vigorous scientific process.

But others have expressed concern that the publication of the methodology and some of the data could help create a roadmap for terrorists and others seeking to further modify the virus into a weapon. That's why a government advisory board -- the National Science Advisory Board for Biosecurity -- recommended in late December that partial information be withheld from publication.

Late last month, however, the Board -- with some dissenters -- reversed course, and is now advocating for the full publication of the Wisconsin research paper as revised, and the publication of a revised paper on the research performed in the Netherlands.

The decision and its reversal have been part of a larger debate within the scientific and national security communities, and there are important arguments being made on both sides.

When the American people pay for scientific research intended for the common good, they have a right to expect that their money will not be used to facilitate terrorism.

These are not hypothetical threats. Before he was killed, Anwar al-Awlaki reportedly sought poisons to attack the U.S. Adding to concerns, the new leader of al Qaeda has a medical background; therefore he may have an even greater interest in pursuing chemical and biological terrorism.

At the same time, there is legitimate concern about government censorship that could chill academic freedom and scientific inquiry - or even limit the sharing of information necessary to save lives or improve public health.

Recently, NIH released a new policy for the oversight of "dual-use research of concern." This policy is intended to improve our awareness of current and proposed dual-use research of concern, and provide some guidelines for mitigating the associated risks.

This new policy, however, is only the beginning of what must be a straight-forward dialogue among science, health, national security, and government experts and leaders in order to promote scientific research while protecting the safety of Americans and others around the world.

I look forward to reviewing the testimony of our witnesses about these challenging issues.

Testimony
Before the
Committee on Homeland Security and
Governmental Affairs
United States Senate

Dual Use Research of Concern: Balancing Benefits and Risks

Statement of
Anthony S. Fauci, M.D.

Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health
U.S. Department of Health and Human Services

For Release on Delivery
Expected at 10:00 a.m.
April 26, 2012

Mr. Chairman and members of the Committee:

I am pleased to have the opportunity to discuss with you recent events related to two manuscripts, as yet unpublished, reporting research results from studies focused on H5N1 avian influenza transmissibility (spread from one animal or person to another) and pathogenesis (ability to cause disease). These manuscripts have drawn global attention and led to important and intense discourse, both in the scientific community and in the media, about the need for, appropriateness of, and conditions under which "dual use research of concern", or DURC, is conducted and its results communicated to the scientific community as well as to the public. In my testimony, I will provide an overview of dual use research, as well as the chronology of these scientific manuscripts, which have garnered unprecedented attention by the U.S. Government, the international scientific and security communities, and the public. While concerns about dual use research are not new, the Administration continues to take oversight of such research very seriously and has recently strengthened procedures to mitigate any potential risks arising from DURC as scientific progress continues.

The National Institutes of Health (NIH), part of the Department of Health and Human Services (HHS), is the Nation's premier agency for the conduct and support of biomedical research. The National Institute of Allergy and Infectious Diseases (NIAID), which I direct, is the lead component of NIH for research on biodefense against terrorist attacks with pathogenic microbes or toxins and naturally occurring emerging and re-emerging infectious diseases including seasonal and pandemic influenza. In this regard, NIAID conducts and supports

basic research on microbiology and immunology; applied research, including the development of medical countermeasures for the diagnosis, treatment, and prevention of emerging infectious diseases; and clinical research to evaluate experimental drugs and vaccines. For example, NIAID leads NIH efforts to develop a "universal" influenza vaccine designed to protect people against multiple strains of seasonal and pandemic influenza without the need for an annual vaccination. Such a vaccine would potentially save millions of lives and be of great global economic benefit.

Dual use research is research that ultimately could yield new information critical to the development of technologies needed to improve public health, such as vaccines, diagnostics, and therapeutics, but also has the potential for malevolent applications if used by people with intent to do harm. In the biomedical research community, we remain mindful that much infectious diseases research may inherently have the potential for dual use.

A smaller portion of biological research has a greater potential for yielding knowledge that could be used for harm. This subset of dual use research is known as "dual use research of concern," or DURC. DURC is research that, based on current understanding, can be *reasonably anticipated* to provide knowledge, information, products, or technologies that could be *directly* misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security. Categories of research that should be closely scrutinized for DURC potential include experiments that, for a specific

group of agents and toxins: (a) enhance the harmful consequences of an agent or toxin, (b) disrupt the effectiveness of an immunization against an agent or toxin, (c) confer resistance to clinically useful prophylactic or therapeutic interventions against an agent or toxin, (d) increase the stability or transmissibility of an agent or toxin, (e) alter the host range of an agent or toxin, (f) enhance the susceptibility of a host population to an agent or toxin, and (g) generate or reconstitute an eradicated or extinct agent or toxin[1].

Because of NIAID's lead Federal role in supporting and conducting biodefense and emerging infectious diseases research, it can be expected that NIAID has funded and will fund some measure of DURC within its research portfolio. If a particular research experiment is identified as DURC, that designation does not necessarily mean that such research should be prohibited or avoided or not widely published. To the contrary, we must balance carefully the benefit of the science to public health, the biosafety and biosecurity conditions under which the research is conducted, and the potential risk that the knowledge gained from such research may fall into the hands of individuals with ill intent. Recently, a clear example of the need to weigh this balance arose with the NIAID-supported H5N1 influenza transmissibility studies conducted by Dr. Yoshihiro Kawaoka at the University of Wisconsin and Dr. Ron Fouchier at

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[1] United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern. March 29, 2012: http://oba.od.nih.gov/oba/biosecurity/pdf/united_states_government_policy_for_oversight_of_durc_final_version_032812.pdf

Erasmus Medical Center in The Netherlands. I will describe for you the context within which this research was conducted.

The Threat of Influenza

Seasonal and pandemic influenza is an ongoing threat to public health worldwide and is among the leading global causes of death due to infectious diseases. According to the Centers for Disease Control and Prevention (CDC), each year, seasonal influenza causes more than 200,000 hospitalizations and up to 49,000 deaths in the United States. Throughout the world, seasonal influenza causes three million to five million cases of severe illness each year, and an estimated 250,000 to 500,000 influenza-related deaths, according to the World Health Organization (WHO). In addition to the annual threat that seasonal influenza poses, influenza viruses can undergo extensive genetic changes, sometimes resulting in the emergence of a novel influenza virus to which the human population is highly susceptible and which is readily transmissible among humans. The emergence of such pandemic influenza viruses is unpredictable; however, the consequences can be severe. The 1918-1919 global influenza pandemic was catastrophic, killing between 50 and 100 million people worldwide and causing enormous social and economic disruption.

In the last decade, the public health community has closely monitored the emergence of highly pathogenic H5N1 avian influenza. This virus circulates in birds and has, on occasion, spread to humans who, in almost all cases, have had direct contact with infected birds. Since 2003, the WHO reports that

approximately 600 confirmed cases of H5N1 influenza have occurred in humans in more than a dozen countries. Nearly 60 percent of these reported cases have resulted in death. The grave concern over the high mortality rate associated with the H5N1 virus has, to this point, been balanced by the apparent inability of the virus to transmit efficiently from human to human. However, should this virus mutate to transmit more efficiently among people, while retaining its ability to cause disease, it would create the potential for a widespread influenza pandemic

NIAID Research on Influenza

For decades, NIAID has supported basic influenza research to investigate pathogenesis, viral evolution, host immune response to the virus, adaptation of the virus to the host, and the complex factors affecting transmissibility of influenza within and among species. Results from such basic research lay the foundation for more precise surveillance of emerging new viruses as well as the design of new diagnostics, drugs, and prevention tools, and are applicable to seasonal epidemic and pandemic strains alike. For example, basic research on the molecular structure of the influenza virus has led to advances in the development of improved influenza vaccines. Recently, NIAID researchers demonstrated that a "prime-boost" gene-based vaccination strategy could activate the immune system and lead to broadly neutralizing antibody responses against a range of influenza viruses, signaling that we are getting closer to a universal vaccine that could protect people against multiple strains of seasonal and pandemic influenza viruses.

A critical goal of influenza research is to understand how pandemic influenza viruses emerge. In this regard, it is important to conduct research to address host adaptability to viruses, transmissibility within and among species, and the effect of these processes on pathogenesis. These are among the questions investigated by Drs. Kawaoka and Fouchier and their colleagues in the highly publicized studies that we are discussing today. Elucidation of the mechanisms by which genetic mutations and other changes occur and may lead to an influenza pandemic could have important implications for influenza outbreak prediction, prevention, diagnosis, and treatment. For example, it would be important to determine if a virus that has enhanced transmissibility in animal models would remain sensitive to existing anti-influenza drugs and be inhibited by the immune responses elicited by existing vaccines. In addition, knowledge of a particular genetic mutation or set of mutations that facilitates influenza transmission in humans may be crucial for use in global surveillance of emerging pandemic influenza viruses.

H5N1 Studies and DURC

The process of genetically manipulating organisms, such as bacteria and viruses, and then identifying and analyzing the positive or negative effects of these mutations on biological functions has historically been central to infectious diseases research. Such experiments have helped to identify molecular targets on pathogenic microbes and have led to the development of currently available

products, such as vaccines for influenza, polio and chicken pox virus, as well as a newer vaccine for smallpox (MVA) and therapeutics for hepatitis C.

Using standard molecular biology and virology techniques, Drs. Kawaoka and Fouchier constructed variants of H5N1 avian influenza viruses in order to identify which genetic mutations might alter the transmissibility of the virus as well as determine their effect on pathogenicity. In their studies, these investigators employed a standard influenza animal model, the ferret. The ferret is a useful, though imperfect, model of human influenza. Though the results of scientific experiments in ferrets cannot always be directly extrapolated to humans, they are the best model available to study transmissibility and pathogenicity of influenza viruses as they might apply to humans.

Drs. Kawaoka and Fouchier submitted manuscripts to the journals *Nature* and *Science*, respectively, in which they described the increased transmissibility in ferrets of the H5N1 viruses modified in their laboratories. NIAID scientific program staff, who had been informed of the results in the manuscripts, recognized that the results of these studies might constitute DURC and referred the manuscripts to the NIH Office of Biotechnology Activities, the office that manages the National Science Advisory Board for Biosecurity (NSABB). The NSABB is an independent Federal advisory committee chartered to provide advice, guidance, and leadership regarding biosecurity oversight of dual-use research to all Federal departments and agencies with an interest in life sciences research.

Review of H5N1 Studies

In November 2011, the NSABB completed a review of the Kawaoka and Fouchier manuscripts and, in December 2011, recommended that the general conclusions summarizing the novel outcome of the studies be published due to the importance of the findings to the public health and research communities, but that the manuscripts should not include the methodological and other experimental details that could enable replication of the experiments. The NSABB also recommended a rapid and broad international discussion on dual-use research policy concerning H5N1 influenza. Lastly, the NSABB discussed the possibility of a voluntary moratorium on broad communication of such results NIH and HHS responded quickly, accepting the recommendations and delivering them to the authors and the journals who agreed to consider the recommended redaction on the condition that the government develop a mechanism for restricted circulation of non-redacted manuscripts. The influenza research community led by the two authors in question also responded by initiating a voluntary moratorium on H5N1 influenza transmissibility studies.

On February 16 and 17, 2012, the WHO held an international non-decisional and non-binding meeting to discuss the issues related to the H5N1 influenza research. Drs. Kawaoka and Fouchier presented additional data related to the manuscripts, and Dr. Fouchier clarified data in his original manuscript.

A summary of the main points of the discussion reflects that, from a public health perspective, publishing the full manuscripts at a later date was preferable

to publishing in redacted form, and emphasizes the importance of biosafety and biosecurity measures and enhanced communication of the balance of the risks versus benefits of such research.

At the request of NIH, Drs. Kawaoka and Fouchier submitted revised manuscripts for review by the NSABB. With the further clarification of the data and methodology provided in the revised manuscripts, consideration of new non-public epidemiological information, and a security briefing on H5N1 influenza, the NSABB recommended that the revised manuscripts be published in full. The NSABB members concluded that the clarified data do not appear to provide information that would immediately enable misuse of the research in ways that would endanger public health or national security. According to the NSABB, "new evidence emerged that underscores the fact that understanding specific mutations may improve international surveillance and public health and safety."

DURC Oversight

Beyond the Kawaoka and Fouchier manuscripts, we remain deeply mindful of the potential risks of DURC. We must continually examine and balance the immediate and long-term benefit of the critical research for the public health with the risk that the conduct of certain types of DURC and/or the broad communication of the findings might enable a bioterror attack or accidental release of a microbe. NIH plays a role— which we take very seriously— in assessing whether the potential benefits of DURC outweigh the risks, and in mitigating any such risks.

The review and oversight of NIAID research is a dynamic process that occurs in multiple steps to ensure that the research we conduct and support is based on a sound scientific rationale, is relevant to our mission to conduct research in immunology and infectious diseases to improve health and alleviate suffering, and is conducted safely with minimal risk to the researchers and community. Through internal research portfolio reviews and with input from outside experts, NIAID develops research agendas that outline research priorities and highlight important research opportunities. As with all NIH research grants and contracts, research applications and proposals for individual projects are peer-reviewed by external and internal subject matter experts and advisors for scientific merit and public health relevance. Once research is initiated, NIH-supported investigators submit annual research progress reports, which are reviewed by NIH scientific program staff. Institutional Biosafety Committees, with oversight from the NIH Office of Biotechnology Activities, provide review of recombinant DNA research and pertinent biosafety measures at the institutional level where such research is conducted. For domestic research on Select Agents and toxins, the CDC and the U.S. Department of Agriculture provide biosafety and biosecurity oversight through site visits, personnel screening, security checks, and biosafety, biosecurity, and training compliance. The screening of personnel is done in partnership with the Department of Justice. For NIAID-supported research on Select Agents and toxins outside of the United States, NIAID has executed an agreement for CDC to perform similar site visits and assessments. Both the Wisconsin and Dutch laboratories have been

inspected multiple times and have been found to be in compliance with recommended biosafety and biosecurity practices. Finally, as I mentioned above, the NSABB provides advice and guidance on DURC to NIH and other Federal agencies that conduct, support, or have an interest in life sciences research, including reviewing specific DURC at the request of NIH, as was the case with the Kawaoka and Fouchier manuscripts.

Enhancing Federal Oversight of DURC

Concurrent with the recent focus on the Kawaoka and Fouchier studies, the U.S. Government has formalized a policy for the oversight of DURC. This policy, which was released for internal U.S. Government use on March 29, 2012, strengthens ongoing efforts in DURC oversight and establishes regular review of U.S. Government-funded or -conducted research on certain high-consequence pathogens and toxins for its potential to be DURC. The policy requires that Federal agencies assess the potential risks and benefits of such DURC projects and determine whether risk is generated by access to the information, products, or technologies resulting from the research. Based on this assessment, the Federal agency, in collaboration with the institution or researcher conducting the research, must develop an appropriate risk mitigation plan or take other actions if it is determined that the risk cannot be adequately mitigated.

Conclusion

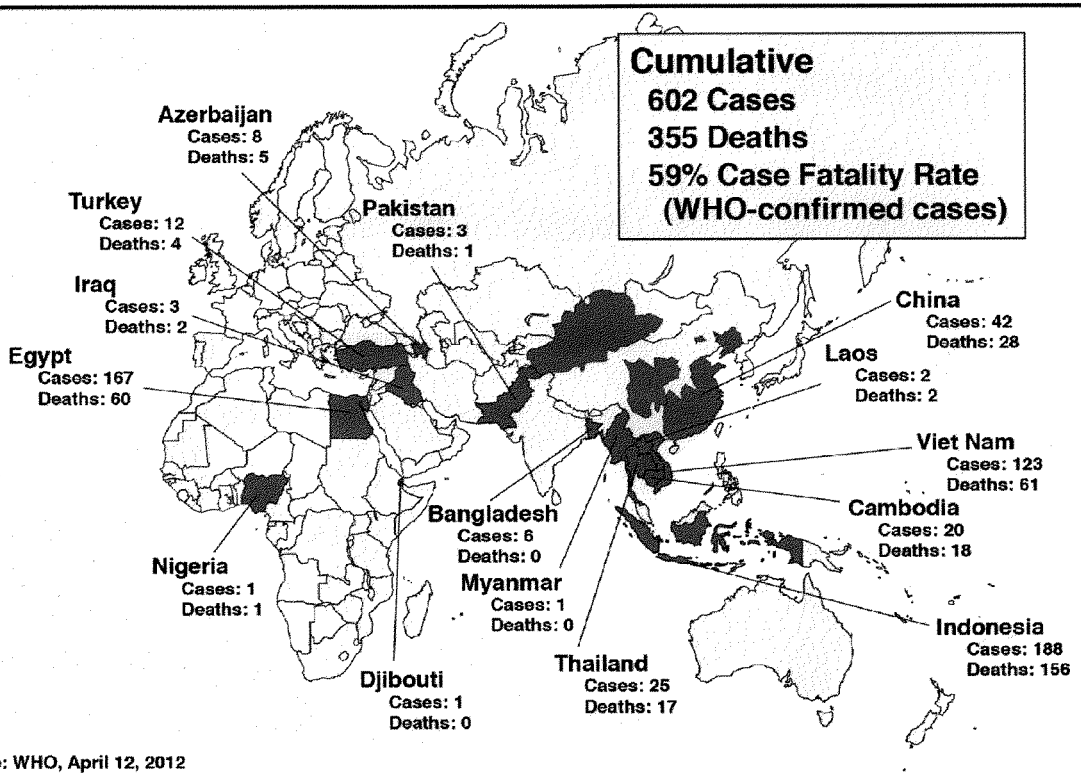
The NIAID-supported research by Drs. Kawaoka and Fouchier on the transmissibility of H5N1 remains important to global health. Although concerns about the potential dual use applications of their studies brought much global attention to this research, when complete information about these studies became available and data were clarified, the NSABB determined that the benefit of communicating the results of these studies outweighed the risk of potential misuse of the information in the manuscripts.

We are committed to addressing concerns about DURC in order to maintain public confidence in the biomedical research enterprise and its critical contributions to public health and national security. The new U.S. Government policy on DURC oversight will strengthen existing processes to further ensure that we fully assess the benefits and risks of DURC, mitigate potential risks where they exist, and communicate responsibly about the importance of such research and the safety and security of its conduct.

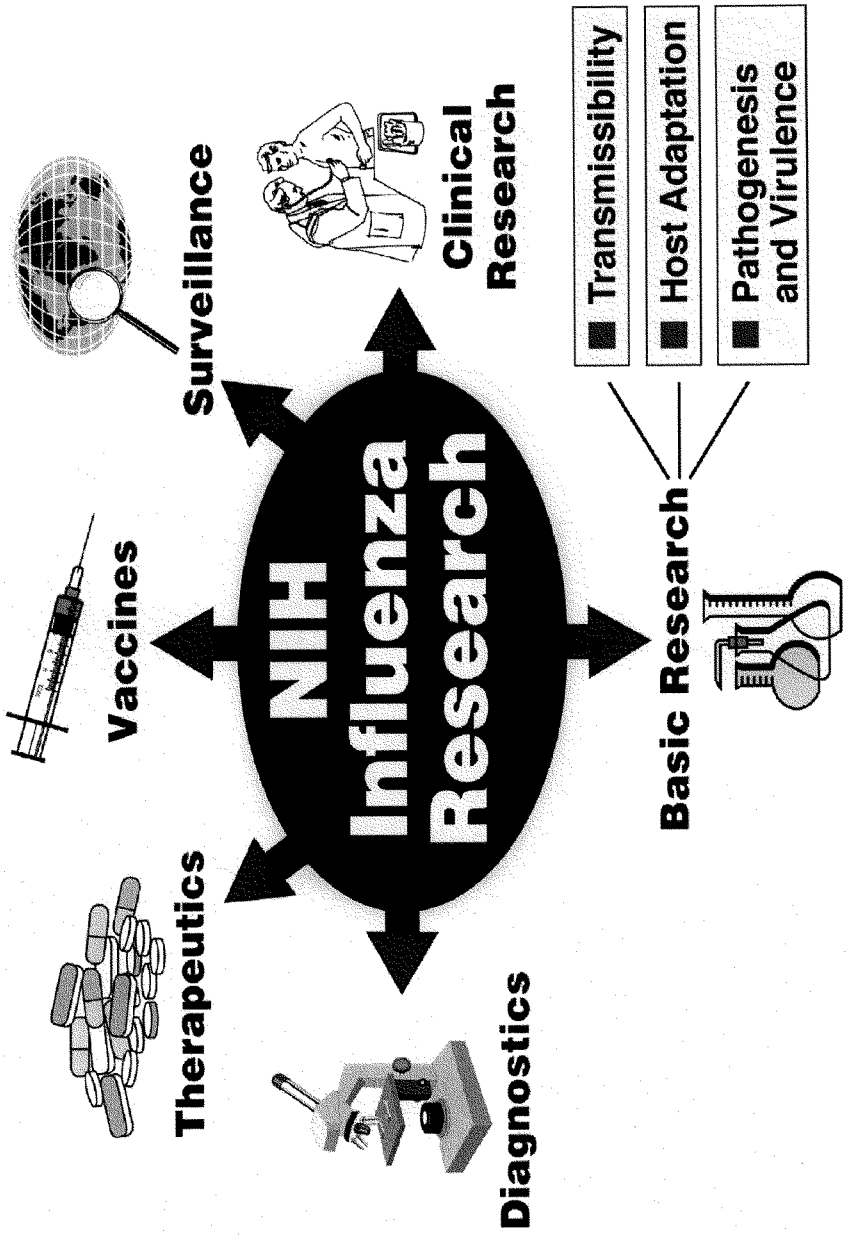
The Threat of Influenza

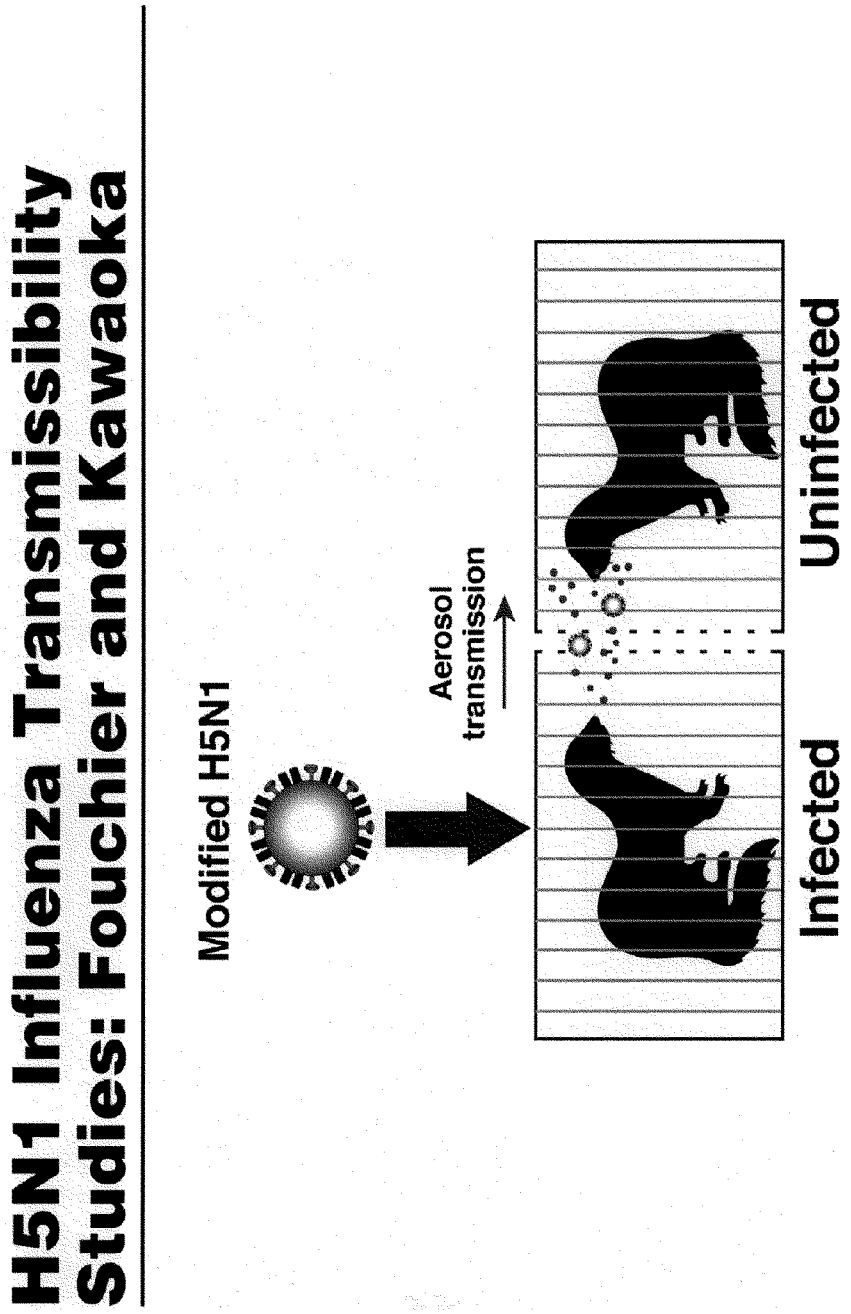
- Seasonal Influenza – annual burden:
  - USA
    - up to 49,000 deaths
    - more than 200,000 hospitalizations
    - $27 billion in medical costs plus lost earnings
  - Global - 250,000 to 500,000 deaths
- Pandemic Influenza
  - 1918, 1957, 1968, and 2009
  - 1918 "Spanish Flu" pandemic caused 50 to 100 million deaths worldwide

H5N1 Cases/Deaths Worldwide Since 2003



Source: WHO, April 12, 2012

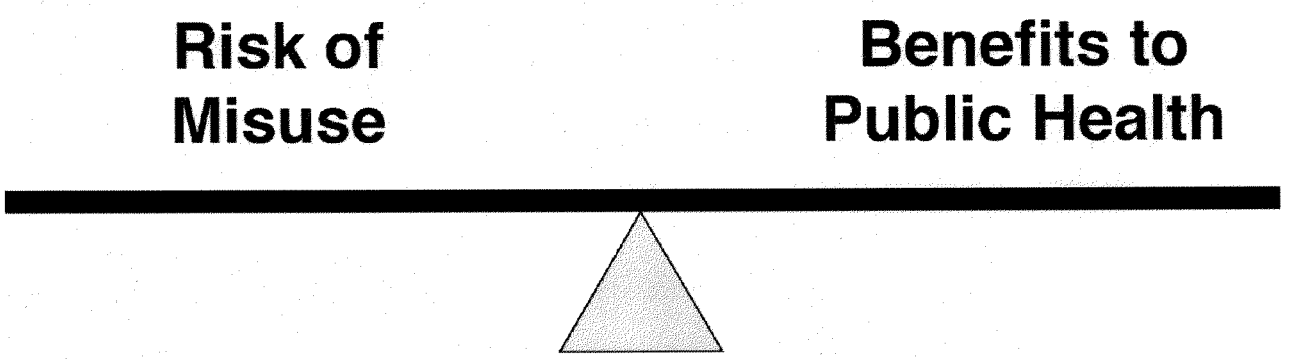

NIH Influenza Research
Surveillance
Clinical Research
Vaccines
Therapeutics
Diagnostics
Basic Research
Transmissibility
Host Adaptation
Pathogenesis and Virulence


H5N1 Influenza Transmissibility Studies: Fouchier and Kawaoka
Modified H5N1
Aerosol transmission
Infected
Uninfected

Dual Use Research of Concern (DURC) - Definition

Life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technology that could be directly misapplied to pose a significant threat with broad potential consequences to public health, safety, agricultural crops and other plants, animals, environment, materiel, or national security.

DURC: A Delicate Balance*



*USG Policy for Oversight of Life Sciences DURC – March 29, 2012

Testimony of Daniel M. Gerstein, Ph.D.
Deputy Under Secretary for Science and Technology
U.S. Department of Homeland Security

U.S. Senate
Committee on Homeland Security and Government Affairs
Biological Security: The Risk of Dual-Use Research?
April 26, 2012

Good morning Chairman Lieberman, Ranking Member Collins, and distinguished members of the Committee. I thank you for this opportunity to testify today regarding the Department of Homeland Security (DHS) activities to address the security concerns raised by dual use life science research of concern (DURC). DURC is defined by the U.S. government as research conducted for legitimate purposes that, based on current understanding, might reasonably be anticipated to provide knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential consequences for public health and safety, agricultural crops and other plants, animals, the environment, or national security.

My testimony today will describe both DHS mechanisms for addressing and mitigating dual use concerns arising from intramural life science research activities that DHS funds and/or performs as well as DHS's involvement in U.S. government and other efforts to address security concerns arising from life science research and technology development. It should be noted that DHS's review process is very specific to its mission, and that the National Security Staff is overseeing a process to assess improvements and consistency in DURC policies across the entire Federal government. This has recently resulted in the creation of a United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern policy released a month ago.

As we consider the DURC issue, several principles help to frame our thoughts. First, DURC is a complex issue for the scientific research and development community, balancing our Nation's need to excel in science and exploration of robust technologies with ensuring our Nation's security by preventing the misuse of such technology." Second, almost all research conducted today in bioscience and biotechnology contains some degree of dual-use application, even if the research scope does not require DURC oversight. Third, addressing dual use concerns must be a shared responsibility, as research occurs at a variety of levels from the research funded by governments to research funded privately to experimentation done at institutions and by individual scientists. Finally, there are both international and domestic dimensions to DURC issue.

DHS Funded and/or Conducted Dual Use Research of Concern (DURC)

DHS performs research, some of which might be considered DURC, at several locations, including our internal laboratories such as the National Biological Analysis and Countermeasures Center (NBACC) and the Plum Island Animal Disease Center (PIADC). We also sponsor and collaborate with other departments including the Department of Defense's (DoD) Defense Threat Reduction Agency (DTRA), Health and Human Services (HHS), United States Department of Agriculture, and the Department of Energy (DOE), including their laboratories such as the Sandia National Laboratories (SNL) and Lawrence Livermore National

Laboratory (LLNL). Additionally, we also provide funding to colleges and universities, primarily through our DHS Centers of Excellence (COE) program. The first-rate, cutting edge scientific research and development ongoing in these efforts is crucial to DHS fulfilling its homeland security mission; they contribute to our understanding of threats and vulnerabilities, help guide development of detection and diagnostics tools, and lead to the development of standards for preparedness and response, as in the case of our "white powder" standard for response to screening and testing for a potential anthrax attack.[1]

DHS's primary objective in funding technical activity in the life sciences is to meet our homeland security mission. We therefore exercise strong control of the information to avoid or deter misuse of critical information through non-publication or non-disclosure mechanisms. DHS routinely contracts for life science research that involves use of select agents and toxins, or that require special biosafety provisions; in all cases, we ensure that contracts contain clauses to ensure conformity with applicable laws, regulations, and internal policies. In addition, DHS contracts for life sciences research typically provide for the right for DHS to object to publication or disclosure. Further, depending on the type of proposed publication or disclosure, the information to be released must go through an internal review process including, but not limited to, review by the DHS Science and Technology (S&T) Offices of Security, Foreign Disclosure, and Corporate Communications. In the unlikely event that sensitive or classified information is produced from research projects funded through grants to academia, DHS requires grant recipients to create information protection plans which detail how this information would be identified and secured.

A foundational element of the internal DURC review process is the S&T's Compliance Assurance Program Office, or CAPO, which reports directly to the Deputy Under Secretary of the S&T Directorate. The CAPO provides a multidimensional review of DHS's research programs for compliance with treaties, laws, regulations, and policies regarding applicable arms control agreements, export control regulations, and requirements for biological select agents and toxins, biosafety and biosecurity, and animal care and use. S&T CAPO facilitates DHS's management of DURC through a review and approval process which has evolved to include important best practices.

The process for identification and selection of a potential DURC program starts at the program manager level. DHS program managers propose a program of work to the leadership for review of the technical feasibility, impact, and potential benefits. DHS program managers are instructed about the applicable requirements inherent in their programs and provided with a checklist of areas with relevant points of contact within CAPO to facilitate the compliance process. For projects involving biological and/or chemical agents, data calls are held to make sure all project databases are current and that projects are being reviewed for DURC and other issues as appropriate. S&T leadership also reviews and approves these programs with support from the S&T CAPO, the Office of the General Counsel, the S&T Office of Security, and the S&T Privacy Office.

[1] Two voluntary consensus standards published in Oct 2010 by ASTM International provide guidance for initial response to suspected biothreats and a standard sample collection method (E2770-10 and E2458-10, respectively).

Research projects conducted or funded by DHS in the areas of biological and chemical defense undergo particular scrutiny and high-level Departmental review because of their potential to raise concerns regarding security, nonproliferation, and treaty compliance. After CAPO flags research for further review, approval is determined by the Department's Compliance Review Group, or CRG, which is chaired by the DHS Deputy Secretary with participation of the Under Secretary for Science and Technology, the General Counsel, and the Assistant Secretary for Policy as permanent members and the Chief Medical Officer and the Under Secretary for Intelligence and Analysis as advisory members. This review ensures compliance with the Chemical Weapons Convention (CWC) and the Biological and Toxin Weapons Convention (BWC).

In preparing for the meeting of the CRG, each project is reviewed in the context of its use of select agents and toxins and as well as the National Science Advisory Board for Biosecurity (NSABB)'s definition of Dual Use Research of Concern (colloquially known as the NSABB Seven Experiments of Concern). Of note, these same criteria have been identified for use in the new U.S. government DURC policy. In reviewing the projects, the CAPO divides potential projects into three tiers based whether they include any NSABB "experiments of concern," raise perceptions of noncompliance with arms control agreements, utilize select agents or toxins, have the potential to generate or reveal critical national security vulnerabilities, or enable information on agent production or dissemination. Any research scope modifications proposed after initial authorization are reviewed and must be reauthorized. Biological and chemical research defense projects that involve experiments of concern that have not been reviewed and authorized by DHS leadership, may not be initiated or conducted.

For internal DURC compliance, the CAPO has established management controls employing compliance, classification and export control reviews. Compliance reviews at laboratories serve to ensure DHS biological research conforms to applicable biosafety and biosecurity regulations and guidance. This assurance is achieved through collecting relevant facility and project level documentation, conducting site visits, and performing laboratory inspections in accordance with a Memorandum of Understanding between DHS, the Centers for Disease Control and Prevention (CDC), and the Department of Agriculture Animal and Plant Health Inspection Service (USDA APHIS).

The Classification Review Panel, or CRP, ensures compliance with relevant classification authorities. Projects identified through the compliance process as raising potential need for classification are subject to review by the CRP. The CRP is co-chaired by the Director of Security at S&T and the S&T Compliance Assurance Program Manager and is attended by DHS technical subject matter experts, security experts, and legal counsel. The CRP uses the "Chemical and Biological Defense Security Classification Guide" of October 2010, which articulates with specific levels of classification and controlled unclassified protections, in making recommendations to the Under Secretary for Science and Technology regarding whether classification is required.

The S&T Export Control Group conducts reviews to ensure compliance with all applicable export control laws and regulations and seeks licenses as appropriate for any DHS exports or imports, especially those in support of international cooperative research activities.

DHS also employs internal controls to confront insider concerns. Biorisk management is an important part of managing the DURC issue. The elements of our biorisk management include biosafety, biosecurity and bioethics. Additionally, DHS personnel are provided with annual security and counterintelligence training, including training on insider threats. DHS also monitors researcher access to DHS facilities and sensitive information technology systems through security clearances and personnel suitability screening to manage levels of access to these facilities and sensitive technology systems.

A variety of different legal instruments are available to government agencies to fund research. DHS selects the best instrument for achieving desired research results and tailors it to specifically address issues such as mission requirements, information security, deliverables, and government control of the research activity. As an example, since grants in general do not afford the government much control over how research is performed, DHS includes non-standard grant terms in its research grants and cooperative agreements to capture any unintended security vulnerabilities created during the research. These terms require grant recipients to immediately notify DHS if sensitive information or products are created or discovered during the course of research. DHS generally does not provide grant recipients sensitive information (i.e., information that is deemed "for official use only") and only uses grants to fund those projects that are appropriate to the level of government oversight and control that grants provide. In the rare circumstance where DHS does provide sensitive information to performers under grants or cooperative agreements, performers are bound by non-disclosure provisions. Research that requires more stringent government oversight and direction than a grant can provide is typically conducted pursuant to a contract.

It is essential for accomplishing the DHS mission to stay at the forefront of science and technology development to support biosecurity. In some case, this entails maintaining active engagement with international researchers and U.S. academic research institutions that draw on the world's brightest students and researchers. DHS weighs the need for government oversight and control in determining which activities should be performed in government laboratories and which ones are appropriately done in academic settings or with international partners.

DHS Active in DURC Issues Across the Federal Government

As the National Academy of Sciences recognized in its landmark 2004 study *Biotechnology Research in an Age of Terrorism,* dual use life science research issues affect the entire life science enterprise. Therefore, in addition to addressing dual use concerns in its own activities, as described above, DHS is an active participant in a "whole-of-government" approach to address dual use concerns more broadly. The Department addresses aspects of this problem that are beyond its direct control through a number of mechanisms. This is an area in which policy is still developing, and to which DHS is strongly contributing.

This approach is predicated on the recognition that life science research and technology development is essential to meet national objectives in public health, economic development, environmental protection, and quality of life, as well as national and homeland security. The source of the dual use dilemma is that legitimate and illicit applications of the life sciences both draw on the same science and technology, making it inherently difficult to counter one without interfering with the other. Although the United States is a leader in world life science research,

we do not monopolize it. Furthermore, we will be effective at addressing dual use research risks worldwide only to the extent that we can help develop a shared understanding of the risks. After the publication of the National Academy's 2004 study, the U.S. government created the National Science Advisory Board for Biosecurity to "provide advice on and recommend specific strategies for the efficient and effective oversight of federally conducted or supported dual use biological research." The NSABB reports to the Secretary of Health and Human Services, whose department funds the vast majority of U.S. life science research, but its purview is life science research government-wide.

NSABB is strictly an advisory board, with no policymaking or regulatory authority, and its voting members are all nongovernmental. However, it also has *ex officio* members from across the U.S. government, including DHS. The DHS *ex officio* member of the NSABB contributes a departmental perspective to these discussions, one that emphasizes the importance of scientific research to meeting DHS's mission, and the consideration of dual use concerns.

DHS is also an active participant in the formulation of U.S. government policy on dual use research, such as was issued on March 29. We pay attention not only to those aspects that directly affect DHS operations, but also to the effect such policies have on mitigating dual use risks more widely as the government seeks to provide security from malicious dual use of research while at the same time allowing for the open and unfettered innovation by our nation's scientists and laboratories.

Dual use research is one of the tenets of the *National Strategy for Countering Biological Threats*, published by the White House in late 2009, which recognized the importance of encouraging alignment of "global attitudes against the intentional misuse of the life sciences or derivative materials, techniques, or expertise to harm people, agriculture, or other critical resources." The strategy is targeted to reduce biological threats by: (1) improving global access to the life sciences to combat infectious disease regardless of its cause; (2) establishing and reinforcing norms against the misuse of the life sciences; and (3) instituting a suite of coordinated activities that collectively will help influence, identify, inhibit, and/or interdict those who seek to misuse the life sciences. The strategy requires the annual submission of interagency contributions towards meeting this goal.

As part of supporting the broader DURC process, DHS has also engaged in external efforts to improve the management of dual use issues. Recognizing the importance of responsible life sciences both here in the United States and globally, DHS has supported visits – foreign and domestic – to our laboratory facilities as well as to discuss our compliance program. At the recent Biological and Toxin Weapons Convention (BWC) – the international treaty banning the development of biological weapons – review conference held in Geneva in December 2011, DHS briefed international delegations, scientific community representatives, members of nongovernmental organizations, and representatives of other international organizations about United States biodefense activities with an emphasis on development of national laws and controls, the importance of conducting sound scientific research, and doing so in a responsible manner.

Even with the kind of internal oversight policies described previously and the U.S. government-wide policy on oversight of U.S. funded life sciences research, DHS believes that responsibility

for addressing security concerns related to DURC must be shared. The international nature of life sciences coupled with the explosion in life science research and biotechnology development that is funded by private sources means that much of the DURC being conducted is not under direct U.S. government control. Advances in the life sciences are going to inexorably create powerful technological capabilities which will be of tremendous benefit to humankind, but will also require careful stewardship including development of appropriate national laws, regulations and policies as well as continued emphasis on strong biorisk management programs that emphasize standards for biosafety, biosecurity and bioethics. Ultimately, we strongly recommend the international life science community appreciate the DURC problem and internalize these concerns while developing and conducting research.

Conclusion

Mr. Chairman and members of the Committee, I am pleased to have been able to review with you the Department of Homeland Security's interest and involvement in the review and oversight of dual use life science research of concern.

We greatly depend on the U.S. life science enterprise – one that is open to the world's best students and researchers – to help develop solutions to homeland security needs. We appreciate the importance to our own mission – and to other national objectives – that scientific research be conducted in the way science works best – with the widest possible engagement of researchers and open publication of research results.

We support, and are implementing, the U.S. government's March 29 policy to consider the dual use implications of federally funded research before it is conducted, and we will be part of the process of developing additional policy that will help research institutions address these concerns.

Ultimately, we recognize that these are issues that affect the global scientific community as a whole, much of which the U.S. government has no direct control over. We are pleased to be able to offer our own procedures as one set of best practices for dealing with this issue, recognizing that our model will not necessarily be applicable in other situations. We will continue working as a Department and as a government on how to address and mitigate the risks of dual use research while ensuring that the Department, the United States, and the world continue to harness or leverage its benefits.

Testimony of Dr. Paul S. Keim

Acting Chair, National Science Advisory Board for Biosecurity

Before the U.S. Senate Committee on Homeland Security and Government Affairs

Oversight Hearing on Biological Security: The Risk of Dual-Use Research

April 26, 2012

Chairman Lieberman, Ranking Member Collins, and distinguished members of the Committee, thank you for holding this hearing on "Biological Security: The Risk of Dual-Use Research." I am Dr. Paul Keim, Acting Chair of the National Science Advisory Board on Biosecurity (NSABB). I appreciate the opportunity to speak to you about Dual Use Research, and in particular, the Board's activities and of our recent evaluation of two scientific papers concerning the avian H5N1 influenza virus

It has been recognized for many years that science and technology can be used for both good and bad purposes. It is this "two-sided coin" that we refer to as dual use research. The problem is that that all biological research can be construed as having potential bad applications as well as their good ones. NSABB created a new term – dual use research of concern or DURC – to distinguish normal research from that with an exceptionally high potential to be misused. Parameters defining DURC would include the magnitude of any danger and the immediacy of any threat, as balanced against the overall benefits of the work. Over the last 8 years, the Board has advised the U. S. government on best practices and policy approaches for research communication, personnel reliability standards, codes of

conduct and international engagement for the issues associated with DURC. The Board has recognized that good policy needs to protect us from scientific misuse and protect the scientific enterprise from being overburdened with unnecessary regulation. Both are essential for our country to be safe, productive and to remain a global leader.

The National Science Advisory Board for Biosecurity is comprised of well-respected scientists, lawyers, infectious disease experts, scientific editors and public health experts. We have an 8-year track record of protecting academic freedom while seeking policy recommendations that will minimize the misuse of biological sciences research. With that in mind, recognize the significance for the Board to unanimously recommend against the full publication of two scientific papers in November 2011 due to their potential to be misused. The U. S. government asked the Board to review two NIH funded studies reporting mutations that allowed a highly dangerous bird flu virus to transmit from one ferret to another. By a split vote, the Board instead recommended to the government that key elements of the studies not be published and that only redacted papers were acceptable for general distribution.

These recommendations were based upon the Board's findings that if this avian influenza virus acquires the capacity for human-to-human spread and retained its current virulence, the world could face a pandemic of significant proportions. We found the potential risk of public harm to be of unusually high magnitude.

The Board published its recommendations to the U. S. government along with its rationale. Importantly, we pointed out that an international discussion was needed amongst multiple societal components to develop policy in this arena of high consequence DURC. I would further note that in the few months since our

recommendations were released, there has been a flurry of U.S. and international meetings to discuss the risks and benefits of these experiments. The research, issues and policy consequences are now commonly known and being debated. This continuing global conversation is good for the scientific endeavor and for our biosecurity.

In late March 2012, the U. S. government tasked NSABB with reviewing revised versions of the two original manuscripts. This was coupled with a face-to-face meeting such that the Board could hear directly from the investigators about their research.

In this meeting, the Board received nonpublic information about the risks and benefits of the research from the international public health and research community, as well as from the United States intelligence community. In a classified briefing from National Intelligence Council and National Counterterrorism Center representatives, the Board heard an assessment of the risk for misuse and of the global political ramifications associated with these papers. The details of this briefing are classified, but I can tell you that many of the Board were left with the impression that the risk of misuse did not appreciably increase with full publication and there is a high likelihood of undesirable political consequences to not publishing.

In addition, the U. S. government issued new policy guidelines targeting high consequence DURC. This is based upon NSABB's definition of DURC and seven categories of experiments that warrant special consideration, and targeting particular high-consequence pathogens.

It was in this context that the Board arrived at different recommendations for the revised manuscripts. One paper was unanimously recommended for full

publication, while the other was recommended by a split 12 to 6 vote. In balancing the risks against the benefits of the revised manuscripts in the context of additional information and new U. S. government policy, the Board shifted its position.

In my opinion, the split vote is highly significant and signals that the Board still believes there is great potential for misuse of information generated by these types of experiments. The majority of Board members voted for publication, but they were clearly still troubled by this research and its potential to be misused. It is fair to say that the Board believes that these types of experiments will arise again and that these issues are not fully settled. As one Board member noted, "We have only kicked this can down the road and we'll be dealing with it again in the future."

It is critical that we establish policy that intensely monitors high potential DURC research from "cradle to grave" in order to protect us from misuse, but also to free low-potential DURC research from onerous regulations. We must be careful that we don't destroy the scientific enterprise as we try to protect against the misuse of some research.

Thank you for your attention.

United States Senate
Committee on Homeland Security and Governmental Affairs

Biological Security: The Risk of Dual-Use Research.

Testimony of Tom Inglesby, MD
Director, Center for Biosecurity of UPMC
April 26, 2012

Mr. Chairman, Senator Collins, and members of the Committee, thank you for the opportunity to speak to you today on the issues related to Biological Security and the Risk of Dual Use Research.

My name is Tom Inglesby. I am the Director and CEO of the Center for Biosecurity of UPMC and Associate Professor of Medicine at the University of Pittsburgh. The Center for Biosecurity is an independent nonprofit organization of UPMC. Our mission is to strengthen U.S. national security and resilience by reducing dangers posed by epidemics, biothreats, nuclear disasters, and other destabilizing events. Our staff comprises experts in medicine, public health, national security, law, economics, the biological and social sciences, and global health. Our Center is the biggest and longest serving academic think tank dedicated to biosecurity.

As requested by the Committee, I will first offer my views on the issues surrounding research with mammalian-transmissible strains of H5N1 influenza virus. I will then provide the Committee my views on the new U.S. Government Policy for Oversight of Life Sciences Dual Use Research of Concern.

H5N1 Mammalian Transmissibility Research

Let me start with my professional background to give you sense of my perspectives on the H5N1 issue. I'm an infectious disease physician by training. I've seen many patients with influenza infection in the last 2 decades. I've seen flu spread through families and communities quickly. I've seen many people die from influenza despite medical care from excellent hospitals.

My colleagues at the Center for Biosecurity and I have committed a substantial part of our professional lives to analyzing biological threats and pandemic flu as well as the public health policies and actions that would help us prepare for and respond to those threats. We have published academic papers on many aspects of flu preparedness, including hospital preparedness and medical surge, antiviral and vaccine development, countermeasure distribution and dispensing, legal issues, and non-pharmaceutical public health interventions. We have served on advisory committees to the U.S. CDC, the National Academy of Sciences, and other entities on flu preparedness. We've worked to enlist business sectors in greater flu preparedness efforts, and we've argued for increased funding for flu vaccine and antiviral development.

I am certainly convinced that the H5N1 influenza virus poses a serious threat. I also believe that wherever one stands in this dialogue about H5N1 research and dual use research more generally, we are all seeking to protect the public from life-threatening pandemics.

In my testimony today, I will address 3 topics:

1. The reasons why I am concerned with research on H5N1 avian influenza virus engineered for mammalian transmissibility.
2. The steps I believe we should take now to address these issues.
3. My recommendations for ensuring the success of the new U.S. Government Policy for Oversight of Life Sciences Dual Use Research of Concern

I have been opposed to the publication of the revised Fouchier manuscript now under consideration at *Science*. The reason I am opposed is because this new modified virus, if released through accident or intention, could have an extraordinarily high case fatality rate in humans and a capacity to spread by aerosol transmission which would be very difficult to stop with isolation, quarantine, antivirals, or a vaccine, particularly in countries with limited resources and limited access to medical care. The breakthrough in Dr. Fouchier's experiment was rendering the H5N1 virus transmissible through the air between ferrets – the best mammalian surrogate for transmissibility between humans. The experiment is reported to not have made the virus more virulent, or deadly. However there is no clear evidence yet presented publicly that the engineered virus has a lower virulence than wildtype H5N1 virus which has an approximately 60% case fatality rate in the series of cases in the WHO database.

Some proponents of full publication have stated that the experiment was not as dangerous as the community first thought, since ferrets infected via the respiratory route did not die of the disease until they were directly injected with the virus. I think we can take very little comfort from this, however, since transmission via respiratory route is not a reliable procedure for assessment of actual virulence in ferrets. Furthermore, once these viruses enter new mammalian host populations and transmit via respiratory routes, they will evolve and acquire new virulence properties that we have no way to predict. We will then have lost any control over these viruses.

I agree with experts on both sides of this issue that we need a disciplined evaluation of the risks and benefits of research that attempts to increase the human transmissibility of avian influenza. As for the potential benefits of the H5N1 mammalian transmissibility research, I do not judge that the published results would be immediately helpful for pandemic preparedness, as I will explain below.

That said, I do appreciate the deliberative process that has taken place in the scientific community over the last 6 months. I acknowledge that the majority of NSABB members, the involved U.S. government agencies, and the journal *Science* have decided that the benefits of this work outweigh the risks, and so it appears that the paper will be published with all details. I am concerned about this outcome, but I do recognize that decisions have been made regarding the publication of the paper. Now it is time to look forward and anticipate the future related research by these and other scientists and the attending issues that will come next. Unless there is a change in direction, scientists will continue work on virulent H5N1 strains engineered for mammalian transmissibility.

Therefore, it does not make sense to wait for the next paper that explains how to create yet another novel virulent H5N1 mammalian-transmissible strain to be submitted for publication before we reach agreement on how to consider this line of research. I will offer my thinking about the future of this work by summarizing what I see as the possible concrete benefits of the work, its risks and consequences, and what I recommend.

Questions and Risks

Will engineering novel H5N1 mammalian-transmissible viruses help us improve surveillance for avian flu?

Everyone in the flu community can agree that we need better tools for surveillance and early detection. In defense of this H5N1 research, it has been argued that if we know the mutations that (experimentally) confer mammalian transmissibility, we could use that knowledge to improve surveillance for H5N1.

This could be a valid argument if the data from the H5N1 studies in question would lead to on-the-ground, practical improvements within our existing avian flu surveillance systems. This is highly unlikely at the present time and for the near future because: (1) genetic mutation data is not now routinely used in our surveillance systems; (2) it would be a mistake to narrow surveillance efforts to only look for mutation data coming from these particular experiments, since a vast number of potential mutations in nature are possible; and (3) even if we did discover that this particular genetic mutation was present in birds, the prescribed response would still be the same— that is, culling of the whole bird flock, regardless of the specific mutation of the virus infecting them.

Specimens from only a tiny fraction of avian influenza (AI) infections are sequenced now. In fact, very few specimens are submitted from countries that experience H5N1 infections. A recent study indicates that half of the Asian and African countries that submitted any specimens for the relevant genetic sequencing, submitted 10 or fewer specimens over the last 8 years. Cambodia submitted 37 specimens over that time.

Out of the millions of H5N1 infections that have occurred in birds, people, and other animals since this strain started circulating, only 2,934 HA sequences have been submitted in the last 8 years to the Influenza Resource databank which compiles data from Genbank, NIAID, and the J Craig Venter Institute. Last year, only 160 partial sequences were submitted to Genbank. Even when countries do submit specimens, the resulting sequence data may not be analyzed or published for months or years.

We should think clearly and concretely about what we would do with the data generated from future transmissibility studies. What surveillance-related actions might be prompted? Right now the standard recommended action is to cull all flocks of poultry known to be infected with H5N1. What would we do differently if we knew these strains had mutations that matched mutations engineered in the lab? If there are other actions (beyond culling) that might be taken on the basis

of finding a match to engineered strains, let's make sure those actions are actually feasible before additional studies of engineered transmissibility are pursued.

Finally, we can't and shouldn't narrow the genetic search to only the mutations we find in a particular set of experiments, because in nature an H5N1 virus that is configured very differently might emerge as the strain that starts a future pandemic.

We all hope that in the future there'll be a much more robust system for collecting and sequencing H5N1 viruses. We do need better surveillance to monitor how viruses are evolving in nature, to ensure that diagnostics can identify emerging strains, and to make sure that medicines and vaccines are effective against new strains as they evolve naturally. Improved surveillance systems will require substantial investments in animal and human health infrastructure in the countries now coping with H5N1. Everyone would like to see that vision realized. But we also have to acknowledge that this vision doesn't reflect current reality. . Until we do have in place systems that collect far more sequence information, that do so in timeframes that are meaningful, and that have widely accepted predictive value sufficient to lead to additional actions in the field, the results of this research seem unlikely to have practical surveillance applications.

For these reasons, I suspect, more than a dozen flu scientists contacted by *Nature News* in January said that virus surveillance systems are now ill-equipped to detect such mutations arising in flu viruses, and so this work is unlikely to offer significant, immediate public health benefits.

If we are able to improve surveillance systems, the benefits of identifying mutations through studies of virulent mammalian-transmissible H5N1 strains might increase, but the benefits of this research would still have to be weighed against the risks.

Will research on novel mammalian-transmissible H5N1 virus help us improve vaccine development?

In Europe, the U.S., Japan, China, and elsewhere, big pharmaceutical companies, with funding support from the NIH and BARDA and other sources, have done crucial work on H5N1 vaccine development. In the EU, there are 4 approved pandemic vaccines in a "mock-up" format, with the intent to grant final EMEA approval for a vaccine during a pandemic, after the strain-causing disease is identified.

If a pandemic occurs, the vaccine would be designed to include a close match to the actual pandemic strain and then put on a fast track for approval. H5N1 vaccine development does not depend on knowledge of engineered mutations, and it does not depend on animal testing of an engineered mammalian-transmissible strain of H5N1. In short, vaccine can be created without testing it against the mammalian-transmissible H5N1 strain. An editorial about the H5N1 research published by *Nature* in February 2012 concurs: [Creating vaccine] *faster and in much larger quantities is the most urgent public health priority when it comes to planning for the next pandemic. These studies offer no serious immediate application in vaccine research.*

Although I do not see near-term, concrete benefits of this work for surveillance or vaccine development, I do recognize that there is scientific value to these recent basic research experiments on H5N1, in that they may help us to better understand the potential mechanisms of

transmissibility of H5N1. Given that value, I would be in favor of open publication of this research were it not for the grave consequences if something went wrong.

What could go wrong in future work with novel virulent mammalian-transmissible strains of H5N1?

One of the reasons why scientists publish is so their work can be readily replicated by other scientists and their results validated. After this H5N1 research is published as expected in *Science,* it would be prudent to expect that other scientists will seek to replicate these studies and build on the results. As new H5N1 transmissibility experiments are conducted by additional scientists, in the same lab or in other labs, it would also be prudent to expect that the risk of accidents will increase, along with the risk of misuse.

Could an accident occur?

Biosafety at modern biocontainment labs is generally excellent. Even in the uncommon event of accidental infection of a laboratorian, most pathogens would lead to no further consequence. Most pathogens have little capacity for ongoing spread in society. However, the accidental escape of an engineered mammalian-transmissible H5N1 strain into a population with little or no immunity could result in a catastrophe.

Although it's uncommon, accidents do happen. We saw the results when a mini-pandemic was started in 1977 by H1N1 influenza virus that is believed to have resulted from a lab release. We saw this again 9 years ago, in the year after the SARS outbreak. At a time when this lethal disease was at the very forefront of international public health concern, there were at least 3 incidents in which researchers working in BSL-3 and -4 laboratories in Singapore, Taiwan, and China accidently infected themselves with SARS. In at least one case, an infected researcher transmitted SARS to a person who then transmitted it to another, who in turn transmitted it to another. In all of these SARS accidents, subsequent investigations identified breaches in laboratory protocol and improper procedures. Clearly, mistakes are made and accidents happen—even at high containment labs during times of extraordinarily heightened awareness and caution.

I am not singling out laboratorians for criticism. Mistakes are made by all types of professionals—doctors, pilots, rocket scientists, anyone—because we are human. That means we have to factor human error, surprise, and accidents into our calculations of the risk of this research, just as we factor those elements into calculations of risk in other fields.

Could an individual, or a group, or a state replicate or steal an engineered flu strain with the intention of deliberately releasing it?

Some people involved in this debate have asserted that it is ridiculous to be afraid of terrorists living in caves doing this work. That is an overly simplistic and dismissive way of viewing the potential for terrorism as we consider the issues at hand.

We can't accurately predict the chances of this work being replicated by a malevolent or deeply disaffected scientist somewhere in the world; a terrorist group; or, a nation-state. We can't accurately judge the capabilities and actions of all those who may seek to cause harm. We can hope that nations, groups, or individual terrorists will not be knowledgeable enough or adequately equipped to re-create mammalian-transmissible H5N1, although it is clear that publishing this work will lower the technical barriers to doing so. We can imagine that all terrorists live in dirty caves, with little or no lab equipment, and insignificant science education. But history is full of examples of our misjudgments of the intentions and/or capabilities of others; it provides many examples of science and technology used in ways for which they were not intended. We would be fooling ourselves if we think we know the full range of competencies and intentions of countries, groups, individual terrorists, or individual researchers at the present, let alone going into the future.

What could happen if an engineered strain of mammalian-transmissible H5N1 started to spread widely in the world?

If a new engineered H5N1 strain has no or minimal capacity for mammalian aerosol transmission, then it is a risk only to those working with it directly. But one of the explicit purposes of this line of work is to engineer strains of avian influenza that are transmissible between mammals, which means we should consider the potential impact of deliberately increasing transmissibility.

If a new engineered H5N1 strain that is as transmissible in humans as seasonal flu were to be released into the population, either intentionally or by accident, it could lead to a new flu pandemic. Seasonal flu infects 10% to 20%, or a billion or more, of the world's population every year. The case fatality rate of wild H5N1 in the WHO database of confirmed cases is nearly 60%. If the case fatality rate of a novel engineered strain of H5N1 approached that level, and if that strain spread as effectively as seasonal flu, then **hundreds** of millions of people could be killed.

With a case fatality rate 10 times lower than that of wild H5N1, but the ability to spread as effectively as seasonal flu, that engineered virus could kill **tens** of millions of people. Even with a case fatality rate 100 times lower than that of wild H5N1, a novel engineered strain able to spread as effectively as seasonal flu could threaten the lives of millions of people.

Some have argued that if an engineered mammalian-transmissible H5N1 strain did start spreading in the human population, it would be possible to contain and stop it. I don't agree. If an engineered H5N1 strain as contagious as seasonal flu started spreading in the world, I think it's highly unlikely we could contain and stop it.

Flu is like a wildfire—it ignites and spreads very quickly and widely. The incubation period and generation time of flu is very short. Viral shedding can occur before people have fever. In other words, by the time you know you have flu, you may have already spread it. As we saw with the 2009 H1N1 influenza virus, by the time we recognized it, we were in the middle of a new pandemic. The virus had already been spread around the world, and there was nothing to stop it.

Every year a number of influenza strains circulate in the world despite large supplies of vaccine, large numbers of vaccinated people, and ready availability of antiviral medication. The strains circulate despite advance forecasting, preparation, and prevention measures. Although vaccines and antivirals prevent many people from getting ill, they are not able to stop flu from circulating around the world.

To cope with an H5N1 pandemic, we have enough vaccine only for a small portion of the world's population. We should not push ahead with this research based on the assumption that we would be able to stop an engineered H5N1 pandemic strain from spreading if it were deliberately or accidentally released in the world.

What Should We Do Now?

It already has been decided that the papers in discussion will be published. I don't agree with that decision, but I do agree that we should now focus on how to handle future experiments in this area. The question of how to do that has not yet been sufficiently resolved. I now offer my recommendations for how we should manage studies of novel H5N1 mammalian-transmissible strains going forward.

Extend the moratorium on research involving engineered virulent mammalian-transmissible H5N1.

Research on influenza is extraordinarily important. Understanding transmissibility is valuable. But before proceeding, we have to work through substantial issues of public health, biosafety, and biosecurity in an open and transparent way. We should have confidence in the useful application of this research and in our ability to reap the proposed benefits. We also should strive to reduce the risks of this research to the greatest degree possible by, for instance, examining other possible ways to study transmissibility without engineering live virulent strains that are mammalian-transmissible. In short, we should not rush forward when the stakes are so high—a sentiment echoed in *Nature's* February editorial: *The fact that the risks seem to far outweigh the public-health benefits of the research, at least in the short term, means that there is no need to rush headlong into an expansion of the work.* If this work must and is allowed to continue, then it should be limited to the smallest number of labs possible.

Define redlines now.

If this work with engineered mammalian-transmissible H5N1 virus is allowed to continue, then we should now engage in a focused discussion to identify whether there are any redlines for that research; we should know going into this where the uncrossable lines are. That means asking and answering some important questions well in advance. For instance: Should H5N1 strains be engineered to increase the efficiency of airborne transmission while maintaining full virulence? Should virulence and lethality be enhanced in H5N1 strains that have been engineered for transmissibility so we can understand what would make them even more virulent? Should other highly pathogenic influenza virus strains be engineered for mammalian transmissibility so that we can understand the mechanisms of transmissibility? Should those novel mammalian-

transmissible influenza virus strains be engineered for increased lethality and virulence as well? Should transmissible avian flu strains be engineered further to make them resistant to vaccines or antivirals so we can discern the genetics of vaccine or antiviral resistance? Will we already have stepped over them before we know we need them?

Even as the new U.S. Government Policy on Life Sciences Dual Use Research of Concern (DURC) policy is implemented, it is important that the scientific and policy communities consider these H5N1 redline questions now to avoid trying to reconcile them after new grants have been awarded, research conducted, and papers submitted for publication. I encourage the U.S. government to consider an appropriate process to have this dialogue. The time to wrestle with these issues is now, before the next controversial paper comes to the fore and while we are already thinking about these questions.

Increase U.S. efforts to prepare for influenza pandemics so we can diminish their consequences should they occur.

The U.S. should continue its important pandemic planning efforts and continue to place priority on developing the capacity to manufacture large quantities of flu vaccine during crises. Developing a universal flu vaccine should be a top priority of pharmaceutical companies, funding entities, and regulators. The U.S. and its partners also should continue work to develop new antivirals and continue research on the role of statins and other anti-inflammatory agents. The U.S. and its partners should prioritize efforts to improve surveillance and culling of avian flu infected flocks by committing greater and stable funding.

U.S. Government Policy for Oversight of Dual Use Research of Concern

The new DURC policy is an important step toward addressing the types of issues raised by the H5N1 controversy. This policy begins the process of systematizing a number of review processes that were proposed in the 2003 National Academy of Sciences Report "Biotechnology Research in the Age of Terrorism" and in several subsequent reports of the National Science Advisory Board on Biosecurity.

The policy puts forth a set of principles as guidance. I believe these principles (or judgments) are correct and critical for the policy's success. In summary, they state the following:

- Life sciences research is essential to scientific advances in public health and safety, agriculture, environment, and national security.
- Despite this, some research could be misused for harmful purpose.
- Some degree of federal and institutional oversight of dual use research of concern is necessary.
- Mitigating risks associated with this research should be done in a way that minimizes the impact on research and is commensurate with the risks.
- The U.S. government will continue to be committed to the principle of broad sharing of research while taking into account U.S. national security interests.

This new policy is a pragmatic step forward toward reducing the risks of DURC, but its effectiveness will depend on how well it is implemented. I believe there are 5 ingredients for success, which I detail below.

1. Implement Effectively at the Local Level

The policy espouses the right principles. It defines the 7 research questions that should trigger review. The policy offers a number of possible mitigation plans if one is called for in a review process. It directs federal agencies to review their portfolios for DURC. The policy stipulates a logical process that serves the goal of reducing the risk of DURC. To be effective, though, local implementation will have to be successful.

By "local implementation" I mean this: scientists, the institutions they work for, and their Institutional Biosafety Committees (IBCs) will be very important to the success of this policy. Earlier research from some of my Center for Biosecurity colleagues found that scientists often respect the decisions made by their own institutions and peers more than they respect the decisions of federal agencies, regardless of the esteem with which they regard an agency. To engage scientists and to garner their respect for the new policy, it must be implemented effectively at the local, institutional level.

For local implementation to succeed, institutions will have to have training and educational materials, such as those now available through the NIH Office of Biotechnology Assessment. The responsibility for managing these issues at the institutional level will presumably be assigned to institutional IBCs, which are not currently constituted or educated to consider biosecurity issues. IBCs will, therefore, require need new training and possibly additional members or resources.

IBCs will also have to develop clear decision making processes to address DURC issues when they arise. The process for resolving disagreements will have to be practical and accessible. Anecdotally, we have learned that some IBCs have lost members who felt ill-equipped to review select agent research. Training and education have to be provided to prevent loss of IBC members who do not feel prepared to review DURC.

2. Learn from Experience

We need to learn from experiences with this policy as it is implemented, and be able to evolve the policy as we go. My understanding is that the NIH review of its portfolio found only 10 experiments warranting further risk management. It would be valuable for the scientific community to understand more about the 10 cases that were noted in the initial review of the NIH portfolio. Specifically, what caused the concern, and how were risks mitigated? If made available to the scientific community, those 10 cases would be a valuable learning tool. They could be de-identified to avoid public intrusion into the work of the scientists.

Determining the applicability of the DURC policy to particular experiments and deciding what, if any, measures will mitigate the attendant risks will be a challenging and subjective task. Therefore it would be helpful for the federal government to provide hypothetical scenarios that

demonstrate both the types of research that would raise concern under the DURC policy and the possible measures that would effectively mitigate the risks. It would be instructive to know the types of mitigation measures that would be insufficient for addressing various types of DURC risks. While the government could not address every possible situation, the community would benefit greatly from a range of instructive examples that make clear how the DURC policy is meant to work in practice. This would be a key part of the education of the life sciences community that has been called for by the NSABB, and which will be critical to the success of this effort. My sense is that few in this community now would know how to successfully implement the new DURC policy should they identify experiments that pose dual use concerns.

It also would be useful to understand the effect of the DURC policy on the H5N1 research under discussion for the past 6 months. I suspect the review process would have triggered additional risk mitigation. It would be helpful to understand how that process would have played out had this new DURC policy been in place

This new U.S. policy importantly commits to domestic dialogue, international engagement, and input from scientists, national security officials, and global health specialists. While informal exchanges with these communities will be valuable, to the government should consider whether to engage other countries more formally, as well as other national and international scientific bodies, to ascertain their views. For instance, perhaps it is time to solicit input from the inter-academy council of national science academies.

In the 1970s, when the NIH released guidelines for safety oversight of recombinant DNA research, there was concern initially that the guidelines would affect only U.S.-funded research. Over time, the guidelines have been widely adopted internationally. In the same vein, it would be in the best interest of all if the U.S. DURC policy prompted broad international discussion of these issues.

3. Attend to Regulatory Burden

While I do think that the new DURC policy is a step in the right direction, it will add another administrative process to be navigated by a scientific community that is already heavily regulated. As we add the DURC policy into the mix, we should understand the burden imposed on U.S. scientists by existing policies and regulations.

At a recent presentation, Carrie Wolinetz, Associate VP for Federal Relations of the Association of American Universities, provided a useful hypothetical example that illustrates this point: Dr. XX, working in a lab funded by both NIH and Amgen, is searching for a therapy for a serious viral infection. She plans to take a cell from a patient and use it to create pluripotent embryonic stem cells. Then, she plans to introduce those cells into an animal model and use radioisotopes to study physiological changes. Before she can do any of this, her work must be reviewed and approved by her IRB and IBC; it must be in compliance with the select agent regulations and radiation safety regulations; she must comply with the guidelines of the Association for the Accreditation of Human Research Protection Programs; comply with the USDA Animal Welfare Act (AWA); have an assurance on file with the NIH Office of Laboratory Animal Welfare (OLAW); comply with rules of the Association for Assessment and Accreditation of Laboratory

Animal Care (AAALAC); work under the oversight of the Embryonic Stem Cell Research Oversight (ESCRO) Committees and NIH Stem cell guidelines; and comply with Conflict of Interest policy. She must also ensure that all laboratorians have training in animal care and use, biosafety, chemical safety, research ethics, and management of human subjects.

In an effort to increase U.S. lab security in recent years, some new regulations have been imposed that in my view have not improved security appreciably. For example: my colleagues and I initially supported creation of tiers of select agents because we believed doing so would sharpen focus on the select agents of greatest concern, while reducing the regulatory burdens related to lower tiered agents. Implementation, though, has not produced this result. Instead, top tier agents are now more heavily regulated while the rest of the restrictions still apply to agents on lower tires. This is an unfortunate outcome.

Current select agent regulation also requires periodic inventory of specimens stored in every lab. Counting the number of vials containing select agents provides a false sense of security and raises false alarms of no significance. Word has it that vials of pathogens are being removed from freezers so frequently to be counted that specimen viability is being compromised.

We have to make sure that we don't impose such a heavy regulatory burden on U.S. scientists that they cannot continue their work, or that they come to consider it more trouble than it's worth to conduct research that is of importance to the country. The greater the regulatory burden, the more likely it is that our best scientists will stop working on the pathogens that cause the most dangerous diseases, or that they will leave the U.S. to conduct their research elsewhere. Beyond this, the regulatory burden overall threatens to diminish the U.S. competitive edge in the life sciences.

I recommend engaging the National Academy of Sciences to examine the extent and effects of existing policy and regulatory burdens on U.S. scientists. The NAS could consider as well the benefits and consequences of both the overall regulatory regime and individual policies and regulations, and could make recommendations for change when a burden is greater than any benefit it confers, whether related to security, safety, or other concerns.

4. Reaffirm the Role of NSABB

The NSABB deserves great deal of credit for its efforts. Over the last few years the group has released a series of valuable documents and guidelines that appear to have informed the new U.S. DURC policy. Under time pressure and with the international community watching, NSABB members expended a great deal of thought, effort, and personal and professional time in addressing the issues surrounding the H5N1 research. Perhaps most importantly, the NSABB members have no personal or professional stake in the outcomes of their deliberations.

The NSABB has expertly assisted the government, including in the preparation of the very useful June 2007 document titled *Proposed Framework for the Oversight of Dual Use Life Sciences Research: Strategies for Minimizing the Potential Misuse of Research Information*. The NSABB has served the government with great professionalism, though often under the radar screen. It is a good moment to reaffirm and recognize the role of this committee going forward.

The charter for the NSABB outlines what I think should continue to be important roles going forward: recommend strategies and guidance for personnel reliability; provide recommendations on the development of programs for outreach, education, and training in dual use research; advise on policies governing publication, communication, and dissemination of dual use research; recommend strategies for international engagement on these issues; advise on codes of conduct; and, advise on the conduct of dual use research and the Select Agent Program.

In some ways, the NSABB is like other safety/security programs and entities that are criticized for adding cost and time to an effort and assigned blame when something goes wrong. The FDA is perhaps the best example of this: the agency is urged to speed up the drug approval process, criticized roundly for slowing the advance of progress, and then castigated if a patient is harmed or, worse, killed by an adverse drug effect. Going forward, if the NSABB has the responsibility of advising the government whether to proceed with or publish high risk research, we should recognize these pressures in the event that it issues recommendations to alter a research proposal or recommend against publication. When the NSABB does support a project or publication, it will, predictably, shoulder blame if something goes wrong.

It is my hope that with effective implementation of the DURC policy, NSABB would rarely be in the position again of entering into the review of research at the tail end, and considering DURC experiments for the first time only after the research has concluded and manuscripts have been submitted for publication.

5. Focus Attention Where Risk is Greatest

Most U.S. labs have good safety records. Even when accidents have occurred, the consequences for the surrounding communities almost always have been insignificant. Nonetheless, an accident or misuse of a very small set of experiments could pose risks—perhaps of great consequence—to surrounding communities and perhaps to the public at large. Research with agents that pose the greatest risk to the public in the event of an accident is, in my view, the kind of research that should prompt the greatest dual use concerns.

Experimental work that, through accident or deliberate misuse, poses the greatest potential direct adverse consequences to society should be the highest priority of the DURC (and biosafety related) policies. As I have explained above, my view is that future experimentation with novel strains of H5N1 influenza engineered for mammalian-transmissibility is research that falls into this category.

One clear potential benefit of the new DURC policy, if properly implemented, is that it will help us to address dual use issues of risk much earlier in the process, so that we avoid a situation when the debate is happening only after the research is funded, concluded, and submitted for publication to scientific journals. I believe that the policy takes us an important step in the right direction.

Conclusion

It is worth underscoring that the scientists who undertake research on influenza and other agents of infectious diseases are doing so to improve our fundamental understanding of biology and to improve the world. The U.S. needs to continue funding the entrepreneurial and talented scientists with the best ideas. The support and publication of their work will help drive serious improvements in our preparedness and response to these diseases.

At the same time, we do need to acknowledge that there are rare situations in which the consequences of an accident or misuse regarding a certain line of research are so serious that special processes are needed to assess and mitigate the risks to the public. This new DURC policy provides a practical framework for moving forward in this process. The details of its implementation will determine its effectiveness going forward.

SUBMITTED BY SEN. LIEBERMAN

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Dear Amy,

We all realize that the National Science Advisory Board for Biosecurity (NSABB) is currently in "uncharted scientific and public policy waters" with the request by the United States Government (USG) to review and make recommendations regarding publication of manuscripts from Dr. Ron Fouchier and colleagues and Dr. Yoshihiro Kawaoka and colleagues reporting their respective research methods and results related to the transmissibility of H5N1 in mammals. As a member of the NSABB, I appreciate the extensive efforts by the Board over the past six months to provide this comprehensive review and to make recommendations based on the previous extensive work of the Board to define dual-use research of concern (DURC.) It has been a gratifying professional and personal experience for me to work with such a dedicated group of scientific and policy leaders with a common purpose of both enabling the ongoing critical life science research that provides answers to some our most challenging health and environmental issues and at the same time protecting the world from potential catastrophic outcomes resulting from similar research.

It has been two weeks since the NSABB meeting of March 29-30 where the Board was requested by the USG to reconsider our previous decision recommending the redaction of both the above referenced manuscripts before publication. During this time I have given considerable thought to the way the meeting was conducted and the subsequent decision by the NSABB to change its recommendation to full publication of both manuscripts without redaction. While we all realize any effort by the NSABB members and staff to arrive at a "Solomon-like" decision regarding the dissemination of the methods and results included in these manuscripts will be questioned by those who do not agree with the outcome, there is also a critical consideration for establishing precedence for how the NSABB will move forward with similar complex issues in the future. It is for this reason I share this letter with the NSABB members and the National Institutes of Health (NIH) Office of Biotechnology Activities (OBA) staff that support the Board's work. The views in this letter are mine and mine alone; I have not communicated with members of the NSABB or staff since the meeting. I write this letter in the spirit of moving forward and with an understanding of how the recent events related to the H5N1 influenza manuscript review informs us on why the USG-NSABB process for evaluating DURC issues must fundamentally change to

both protect life science research and the risk to the public of such research. For the record, I voted at the meeting to approve the full publication of the Kawaoka manuscript and the continued requirement of redaction of the Fouchier manuscript.

First, I believe that 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. While I don't suggest that there was a sinister motive by the USG with regard to either the agenda or invited speakers, I believe there was a bias toward finding a solution that was a lot less about a robust science- and policy-based risk-benefit analysis and more about how to get us out of this difficult situation. 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. Merely providing a "minority report" in the final findings and recommendations of the meeting does nothing to address the fundamental issues of how the risk and benefits were determined, described, and considered at the meeting. For example we heard from Dr. Fouchier that he has already identified an additional mutation (not included in his current manuscript) that results in ferret-to-ferret transmission (mammalian transmission) without the need for repeated passage of the virus in ferrets. This work, which may have been supported by NIH funds, surely must be considered as a candidate for the next manuscript to be before the NSABB for review. What scientific and policy issues will differ with this "incrementally changed manuscript" compared with the issues we just considered? If such work represents only incremental changes in results from previously approved work, will the Board ever find a bright line for redacting publication and all the issues that go with that decision?

For you to better understand my concerns, I will detail specific examples of how I believe the agenda and selected speakers resulted in the one-sided risk-benefit analysis that I described above. I will use in part the general considerations and conclusions in the April 11th draft NSABB findings and recommendations document as the framework for these points.

The data in the newly revised manuscripts are immediately and directly enabling.

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. The implications of doing such work, even by well-meaning scientists who do not have adequate biosafety measures in place, should have been reviewed. The subject matter experts that addressed this issue at the meeting have a real conflict of interest in that their laboratories are involved in this same type of work and the results of our deliberations directly affect them, too. The same can be said about the attendees and outcome of the February World Health Organization consultation. In short, it was the "involved influenza research community" telling us what they should and shouldn't be allowed to do based on their interested perspective. Such a

perspective is very important and should be included in this discussion, but it shouldn't be the only voice.

As director of one of the five NIH-supported centers of excellence in influenza research and surveillance, I can speak with firsthand knowledge and experience that 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. One of them wrote me a very clear and compelling comment on the potential for the information in one of the manuscripts to be immediately and directly enabling. He stated;

> "I am an influenza virologist myself, and we routinely create viral mutants in my lab using reverse genetics, so I have a good sense of the technical issues involved. As such, I can recognize that some outspoken researchers in our field have been under-representing the increased risk that would be entailed by full publication of the specific mutations versus the current situation where only the general outline of the ferret-passage scheme is known. A ferret-passage experiment is expensive and technically demanding, and could only be done by a handful of labs in the world. Once the mutations are public, individuals in my lab (or many other labs) could generate the mutants in a few weeks given several thousand dollars for gene synthesis.
>
> I remain agnostic about what is the best policy going forward. I recognize that there also important potential benefits from this research, and think that research along these lines does have valid scientific and public-health justifications. But these benefits need to be carefully weighed against the real risks, and I am definitely concerned that there has been a rush to judgment for full publication within our own research community."

I have talked with many similarly minded influenza researchers from around the world who agree with the above statement. Yet these voices were notably absent in the NSABB deliberations.

The data may benefit public health and surveillance efforts.

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 have discussed with officials from both organizations the implications of sharing the mutation data; the general response indicated that such information without major new resources and government commitment to active animal surveillance and control would not fundamentally change current surveillance and control practices in most of the endemic H5N1 countries. Yet, there was a series of very general and unsubstantiated statements made by others invited to the meeting who are not involved in the day-to-day animal surveillance activities in the H5N1 endemic countries (including the authors) as to the benefits of making the mutational data available for this purpose.

Our NIH-supported center of excellence is supporting surveillance for H5N1 virus in domestic animals in one of the H5N1 endemic countries; our surveillance researchers have told us that the finding of an H5N1 virus with specific mutational changes in poultry would not result in widespread culling activities unless the birds are sick. Immediate culling is supposed to be the standard protocol now for the control of H5N1 virus, but resources for a number of the H5N1 endemic countries are often lacking to detect the virus or support programs. The voice of these and similar on-the-ground experts was missing from our discussion regarding the benefit of making these mutation data general available.

Setting aside the fact that surveillance experts noted above were not invited as subject matter experts, it is notable that current news sections in both *Science* and *Nature* have published a series of articles on the controversy of using the H5N1 virus mutation information for surveillance and control purposes. Several of these stories were well researched, with numerous interviews with some of the experts I noted above. Their conclusions were consistent with my comments above regarding the utility of making the mutation data from these studies generally available and the impact on the control of H5N1 infection in poultry. None of these news stories were referenced in the meeting (except by me) or provided as important background information leading to a more complete risk-benefit analysis. There was no discussion as to the limited number (and time from sampling to testing) of H5N1 viruses sequenced from endemic countries or how to improve that situation in the endemic countries before the release of the mutation data could yield even remote benefit.

The most important aspect of the results in these two studies on surveillance and control has already been accomplished; namely alerting the world to the possibility that H5N1 influenza virus surely can become a mammalian-transmitted virus and poses real pandemic potential. We must be much better prepared to respond to a possible H5N1 influenza pandemic than we are today. Publication of the full study methods and result of either manuscript will not enhance this conclusion.

Finally, I believe it was unfortunate 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. Was the manuscript that Dr. Smith presented peer-reviewed? While I appreciate that he is a leading influenza researcher, for the sake of balance others without a primary interest in these manuscripts should have led this discussion.

Security considerations and the risk of malevolent applications of the mutation data.

One of the most disturbing aspects of the meeting was the security briefing on the evening of March 29th. It was one of them most incomplete and, dare I say, useless classified security briefings I've ever attended. For the past 20 years, I have held security clearances in my work with international and national bioterrorism, including a top secret clearance in my role as a special assistant to HHS Secretary Tommy Thompson from 2001 to 2004. I have served as a briefer for some of our leading government officials during that time. I do understand threat assessment and the limitations and strengths of intelligence.

I realize I'm limited in to what I can share here because of the classified nature of the briefing, but in short the briefing we received can be summed up by saying "We don't know much about anyone wanting to use this information for malevolent reasons, so it's probably not a risk." I would agree that few persons in the terrorism and intelligence worlds see this as a primary or even secondary weapon of choice for international terrorism for all the obvious reasons. But the absence of any discussions regarding international or national rogue scientists or irresponsible researchers not using adequate biosafety to conduct "now enabled work" was a major flaw in the briefing. These types of scientists are exactly the ones who would benefit immensely in conducting work of serious concern with the recipe and methods defined in fully published manuscripts. There was no discussion of eco-terrorists whose single purpose is to disrupt animal production activities. A release of a mammalian-transmitted H5N1 virus in swine would devastate that industry even if limited illness occurred because of the public relations issue of "killer bird flu virus in pigs." I can't think of a worse scenario than having H5N1 virus circulating widely in swine with a critical reassortment likely to occur and human transmission not far off.

The briefing (or the meeting as a whole) did not cover the historical perspective of why influenza virus is truly different than any Class A pathogen we worry about because of it the consequences of its accidental release and our inability to stop transmission once it occurs in the community. As bad as an accidental release of variola virus, *Bacillus anthracis*, *Yersinia pestis*, or SARS virus might be, we could—based on agent transmissibility, incubation period, clinical recognition and countermeasures—effectively stop a global pandemic from occurring. We can't do that with influenza virus. There is no margin for error. 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.

I am particularly concerned about this aspect of the two days of deliberations, because I heard several members remark how the security briefing had a substantial impact on their decision of how to vote.

The use of the mutation data to enhance countermeasure preparedness.

Although this issue came up several times in terms of the importance for sharing the mutation data for the development of countermeasures (vaccines and antiviral drugs), there were no data-related presentations addressing this issue. Again the *Science* and *Nature* news stories of the previous three months did an outstanding job of researching the claim that the mutation data were critical in developing and deploying H5N1 countermeasures. The authors of the articles 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.

A previous decision.

Throughout the discussion of the current review of the two manuscripts, the issue surrounding the NSABB's approval of publication of the 1918 H1N1 virus paper in 2005 has been raised as precedence for how we might proceed in this situation. I want for the record to be clear that I firmly believe we made a mistake in approving the publication of the 1918 virus paper. At the time I was one of the supporters of publication. We reasoned that the 1918 H1N1 virus, if it were to accidently escape or be intentionally released, would cause little public health consequence because of the previous circulation of H1N1 influenza virus prior to 1958 and again since 1977. We believed that the vast majority of the world's population would have sufficient cross-protective immunity to prevent any kind of H1N1 influenza pandemic as experienced in 1918. Well, with the appearance of A(H1N1)pdm09, we now realize there was virtually no population-based immunity to either the new H1N1 virus or the closely related virus, the 1918 H1N1 strain. The exception was for those who had experienced H1N1 infection prior to the early 1950's when those circulating strains in humans did provide cross protection.

Had someone taken the published data on the 1918 virus mutations, they could have created a virus that, had it been even accidently released, could have caused a pandemic much as the A(H1N1)pdm09 virus did. I share this observation not to be critical of the 2005 NSABB decision, as I was part of that decision. Rather, it's to remind us that you can't unring a bell. 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.

Summary

In short, the NSABB March meeting should be a very important learning experience for the USG, the journal editors, and life scientists in general as to the need for a much more effective system to address DURC issues. One primary lesson that I believe is critical: The Board must involve disinterested subject matter experts to provide technical advice. I believe that the relative lack of subject matter expert input from those without a direct interest in the Board's decision be viewed critically by the larger policy and life science communities as the decision is debated over the upcoming days.

As I stated before, I believe our recent experience is just the beginning, not the end of this type of scientific and policy conflict. As a said to Dr. Collins toward the conclusion of the March meeting, I wouldn't want to be in his shoes sitting before a Congressional hearing trying to explain why the NSABB and likely the USG supported the full Fouchier publication when we heard at the meeting that he has done more work and found one additional mutation that now confers H5N1 transmissibility between mammals without ferret passage. How will we justify one more "incremental finding paper" that now is a pretty complete cookbook when we didn't recommend redaction for the vast body of his work? If we believe redaction of the current manuscript is problematic in terms of international agreements, I think the next mutation paper will prove to be the straw that breaks the camel's back. It is unfortunate that the current NSABB action just kicked the can down the road to the next manuscript.

I hope these comments are helpful as the NSABB moves forward. As someone who will soon be rotating off the Board after 7 years of service, I believe now, more than ever, of its importance.

Thank you for the honor and opportunity to participate.

Sincerely,

Michael T. Osterholm, PhD, MPH
Director, Center for Infectious Disease Research and Policy
Director, Minnesota Center of Excellence for Influenza Research and Surveillance
Professor, Division of Environmental Health Sciences, School of Public Health
Adjunct Professor, Medical School

Cc: NSABB Members
NSABB Staff

Questions from Sen. Joseph Lieberman in Follow-up to the April 26, 2012 Hearing of the Senate Committee on Homeland Security and Governmental Affairs on "Biological Security: The Risk of Dual-Use Research"

Responses from NIH/HHS and DHS

1. Initially it appeared that one of the options for publication of the H5N1 studies was a public version in which certain elements were redacted, and then a system would be developed to allow legitimate scientific and public health entities to have access to the full study. This option was taken off the table for the NSABB's second look at the studies.

   We have been told that one of the reasons for this was that limited distribution would not fall within the basic research exemption under export control laws, and this is an issue also currently being debated by the Dutch government with respect to the Erasmus Medical Center study. The apparent limitation of options under export control laws to either full or no publication, what effect, if any does that have on the NSABB's options when reviewing this kind of work?

ANSWER

In general, when the United States Government (USG) asks the National Science Advisory Board for Biosecurity (NSABB or the Board) to make recommendations regarding the dual use potential of research, the Board advises on whether and how to communicate information about such research. To inform the NSABB's deliberations and development of their recommendations, the USG briefs the NSABB on any legal and policy constraints that might be pertinent to possible communication options.

Export control laws do not limit communication options to full or no publication. However, fundamental research is generally exempt from licensing requirements under the export control laws, and the portion of the information that is restricted and not made publicly available may not fall under that exemption. Distribution of that information outside the United States may therefore require export licenses, the majority of which are generally approved.

In the case of the H5N1 influenza manuscripts, the NSABB initially recommended that the general conclusions highlighting the novel findings in the papers be published, but that the published papers not include the methodological and other specific details that could enable replication of the experiments. When this recommendation was conveyed to the journals to which the manuscripts were submitted for publication (*Science* and *Nature*), the editors requested that the USG explore developing a system by which the specific details could be accessed in a secure, controlled fashion by those with legitimate scientific and public health aims. As the USG worked on conceptualizing such a "controlled access" mechanism, it became clear that there were a number of legal and practical challenges, including export control requirements and provisions of the Freedom of Information Act (FOIA).

When the NSABB met to consider the revised H5N1 manuscripts, the Board requested an update on the development of a controlled access mechanism and was, thus, briefed on the pertinent legal and practical challenges. The Board was advised that even if such a mechanism could be developed, it could not be implemented in the timeframe necessary to address the issues related to communicating information in these two specific manuscripts.

This briefing was not intended to limit the NSABB's recommendations in any way, but rather to ensure that its recommendations were supported by all pertinent facts. The USG will continue its analysis of the practical and legal considerations associated with disseminating sensitive life sciences research information while minimizing the safety and security risks associated with sharing the information. In any future NSABB deliberation on similar matters, the USG will brief the Board on the latest legal analysis of these issues. The USG will encourage the Board to explore all options in developing recommendations and to weigh those options in light of any pertinent legal, policy, and practical considerations.

2. What is the federal government doing today or planning to do to promote US policies and standards for dual-use research of concern (DURC) among all nations that carry out this type of research? Is there a plan in place for promoting these policies? Who is in charge of leading this outreach within the federal government?

ANSWER

In all of its engagement efforts, the United States Government (USG) takes a collaborative approach by fostering dialogue with other nations, seeking input and feedback from our international partners, and through promoting responsible conduct by the individual life scientist. The experience over the past 35 years with the National Institutes of Health (NIH) Guidelines for Research Involving Recombinant DNA Molecules shows that this can be a very positive, effective, and sustainable way to reinforce the culture of responsibility globally. In a similar vein, the USG has undertaken international engagement efforts on the dual use issue, including those related to policy development. The Department of State leads USG efforts to promote appropriate policies and standards internationally, in close cooperation with the NIH Office of Science Policy, the Department of Health and Human Services (HHS) Office of Global Affairs, and other relevant Federal agencies and offices.

With the growing recognition of the pertinence of dual use concerns to the life sciences, the USG has been conducting outreach on dual use issues, both domestically and internationally. International outreach and engagement efforts have covered every major region of the globe and have included multiple modalities, such as conferences, roundtables, webinars, videoconferences, and presentations. Most recently, the governments of the United States and the Netherlands provided a joint briefing on the recent H5N1 controversy and moderated an open discussion on dual-use oversight issues at the July 2012 Meeting of Experts under the Biological Weapons Convention. In June 2012, the USG organized a panel on dual use research at the African Biosafety Association Meeting in Johannesburg, which was well attended and served to

raise awareness among research organizations across the African continent. Earlier events have targeted other regions of the globe, including Southeast Asia, China, the Middle East, Eastern Europe, and the Americas. In November 2008, the USG and the World Health Organization hosted a conference attended by over 130 scientists, government officials, ethicists, journal editors, and representatives from non-governmental organizations, intergovernmental organizations, philanthropic organizations, funding organizations, and industry to discuss their specific activities regarding dual use research issues and related topics. Participants came from 37 countries and had leadership roles in over 72 organizations. These events were follow-on to the first International Roundtable that was held February 2007 in Bethesda, Maryland, and was cosponsored by the USG and the World Health Organization. This first-of-its kind meeting involved participants from over 14 nations representing all regions of the globe and a number of international research organizations. The meeting promoted dialogue and raised awareness of the issue of dual use life sciences research, and catalyzed policy development among participating nations and societies. The impact of that original meeting has been seen subsequently, as a number of other countries have reported addressing the issue of dual use research and developing policies locally. More about these efforts can be found at: http://oba.od.nih.gov/biosecurity/internationalwebcast.html

The Department of Homeland Security (DHS) Science and Technology Directorate (S&T) actively promotes standards for dual use research of concern (DURC) by sharing best practices and standards with international partners through multilateral fora.

The USG continues to work closely with the World Health Organization on efforts to crystallize international consensus on approaches to dual-use oversight.

3. The new US government policy on Dual Use Research of Concern (DURC), in its discussion of options for risk mitigation, mentions the option of security classification if risks cannot be adequately mitigated by other means as described in the policy.

The use of classification authority has a long history with respect to research related to nuclear and biological weapons, but has not been generally used with respect to the broader domain of biotechnology research. These two H5N1 studies raise questions as to whether we need to think about the potential circumstances under which such research should be considered for security classification if other risk mitigation steps are insufficient.

a. Do you believe are the circumstances under which such Dual Use Research of Concern should be considered for security classification? If so, what are they?

b. Is the overall system for the classification of information within your agencies and other key agencies adequate to consider this as an option? If not, what needs to be done to allow for such risk mitigation steps? (For example: classification guides, secure workspaces, classified network connectivity, issuance of security clearances.)

ANSWER

The March 29, 2012, USG policy on the oversight of DURC requires that Federal funding departments and agencies (including DHS and HHS) assess the potential risks and benefits of any DURC projects identified under the policy. Based on this assessment, the Federal agency, in collaboration with the institution or researcher conducting the research, develops an appropriate risk mitigation plan to ensure that the risk can be adequately mitigated.

A risk mitigation strategy might include security classification of DURC information only if the following criteria apply: (1) the unauthorized disclosure of this information would cause damage to national security; (2) the information is owned by, produced by or for, or under the control of the USG; and, (3) the information is not a prohibited category in accordance with Executive Order (EO) 13526, "Classified National Security Information." The second of these criteria will preclude the use of classification in many circumstances involving DURC.

For information that is eligible for classification, both DHS and HHS have appropriate authorities and systems to consider national security classification in accordance with EO 13526 and can thereby protect information of importance to national security. The DHS Under Secretary for Science and Technology makes original classification decisions and issues classification guides based on the recommendation of the S&T Classification Review Panel. Classification guides, secure work spaces, and secure communication are the appropriate procedures and tools to ensure that classified information is properly controlled.

Even where national security classification is legally available, its use for DURC presents challenges to both the sharing and safeguarding of the information, both of which are pertinent considerations since DURC, while sensitive, may yield information vital to public health and scientific aims. In some cases, DURC, even where it might pose risks to national security, may fail to meet one or both of the other criteria for classification outlined above. Moreover, classifying DURC may present the following challenges:

- It may limit the ability to share this information with foreign governments, academic institutions, and non-governmental scientists who have the need to know the information to protect public health.

- The ability to safeguard DURC information appropriately using security classification is complicated by the fact that the dual-use nature of the research may not be identified until the research is in progress or after the research has been completed.

- Federally-funded or sponsored life sciences research, particularly that supported by HHS, is frequently conducted at non-government facilities, some of which may employ non-U.S. citizens, who are normally not cleared to receive classified information.

- By restricting the free and rapid flow of information, as well as the number of scientists and laboratories with appropriate clearance to access the information, classification of DURC could slow down important public health research and innovation. This could have the dual effect of endangering both domestic and international public health, as well as hindering U.S. competitiveness in the life sciences.

It is for these reasons that the March 29, 2012, policy suggests that classification be considered only if other possible risk mitigations approaches are deemed to be unworkable.

Post-Hearing Questions for the Record
Submitted to Daniel M. Gerstein, Ph.D.
From Senator Joseph I. Lieberman

"Biological Security: The Risk of Dual-Use Research"
April 26, 2012

Question#:	1
Topic:	DURC 1
Hearing:	Biological Security: The Risk of Dual-Use Research
Primary:	The Honorable Joseph I. Lieberman
Committee:	HOMELAND SECURITY (SENATE)

Question: What is the federal government doing today or planning to do to promote US policies and standards for dual-use research of concern (DURC) among all nations that carry out this type of research? Is there a plan in place for promoting these policies? Who is in charge of leading this outreach within the federal government?

Response: In all of its engagement efforts, the U.S. Government (USG) takes a collaborative approach by fostering dialogue with other nations, seeking input and feedback from our international partners, and through promoting responsible conduct by the individual life scientist. The experience over the past 35 years with the National Institutes of Health (NIH) Guidelines for Research Involving Recombinant DNA Molecules shows that this can be a very positive, effective, and sustainable way to reinforce a culture of responsibility globally. In a similar vein, the USG has undertaken international engagement efforts on the dual use issue, including those related to policy development. The Department of State leads USG efforts to promote appropriate policies and standards internationally, in close cooperation with the NIH Office of Science Policy, the Department of Health and Human Services (HHS) Office of Global Affairs, and other relevant Federal agencies and offices.

With the growing recognition of the pertinence of dual use concerns to the life sciences, the USG has been conducting outreach on dual use issues, both domestically and internationally. International outreach and engagement efforts have covered every major region of the globe and have included multiple modalities, such as conferences, roundtables, webinars, videoconferences, and presentations. Most recently, the governments of the United States and the Netherlands provided a joint briefing on the recent H5N1 controversy and moderated an open discussion on dual-use oversight issues at the July 2012 Meeting of Experts under the Biological Weapons Convention. In June 2012, the USG organized a panel on dual use research at the African Biosafety Association Meeting in Johannesburg, which was well attended and served to raise awareness among research organizations across the African continent. Earlier events

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Topic:	DURC 1
Hearing:	Biological Security: The Risk of Dual-Use Research
Primary:	The Honorable Joseph I. Lieberman
Committee:	HOMELAND SECURITY (SENATE)

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The Department of Homeland Security (DHS) Science and Technology Directorate (S&T) actively promotes standards for dual use research of concern (DURC) by sharing best practices and standards with international partners through multilateral fora.

The USG continues to work closely with the World Health Organization on efforts to crystallize international consensus on approaches to dual-use oversight.

Question#:	2
Topic:	DURC 2
Hearing:	Biological Security: The Risk of Dual-Use Research
Primary:	The Honorable Joseph I. Lieberman
Committee:	HOMELAND SECURITY (SENATE)

Question: The new US government policy on Dual Use Research of Concern (DURC), in its discussion of options for risk mitigation, mentions the option of security classification if risks cannot be adequately mitigated by other means as described in the policy.

The use of classification authority has a long history with respect to research related to nuclear and biological weapons, but has not been generally used with respect to the broader domain of biotechnology research. These two H5N1 studies raise questions as to whether we need to think about the potential circumstances under which such research should be considered for security classification if other risk mitigation steps are insufficient.

Do you believe are the circumstances under which such Dual Use Research of Concern should be considered for security classification? If so, what are they?

Is the overall system for the classification of information within your agencies and other key agencies adequate to consider this as an option? If not, what needs to be done to allow for such risk mitigation steps? (For example: classification guides, secure workspaces, classified network connectivity, issuance of security clearances.)

Response: The March 29, 2012, USG policy on the oversight of Dual Use Reasearch of Concern (DURC) requires that Federal departments and agencies (including DHS and HHS) assess the potential risks and benefits of any DURC projects identified under the policy. Based on this assessment, the Federal agency, in collaboration with the institution or researcher conducting the research, develops an appropriate risk mitigation plan to ensure that the risk cannot be adequately mitigated.

A risk mitigation strategy might include security classification of DURC information if the following criteria apply: (1) the unauthorized disclosure of this information would cause damage to national security; (2) the information is owned by, produced by or for, or under the control of the USG; and, (3) the information is not a prohibited category in accordance with Executive Order (EO) 13526, "Classified National Security Information." The second of these criteria will preclude the use of classification in many circumstances involving DURC.

For information that is eligible for classification, both DHS and HHS have appropriate authorities and systems to consider national security classification in accordance with EO

Question#:	2
Topic:	DURC 2
Hearing:	Biological Security: The Risk of Dual-Use Research
Primary:	The Honorable Joseph I. Lieberman
Committee:	HOMELAND SECURITY (SENATE)

13526 and thereby protect information of importance to national security concerns. The DHS Under Secretary for Science and Technology makes original classification decisions and issues classification guides based on the recommendation of the S&T Classification Review Panel. Classification guides, secure work spaces, and secure communication are the appropriate procedures and tools to ensure that classified information is properly controlled.

The use of the existing national security classification system for DURC presents challenges to both the sharing and safeguarding of the information, both of which are pertinent considerations since DURC, while sensitive, may yield information vital to public health and scientific aims. In some cases, DURC, even where it might pose risks to national security, may fail to meet one or both of the other criteria for classification outlined above. Moreover, classifying DURC may present the following challenges:

- It may limit the ability to share this information with other foreign governments, academic institutions, and non-governmental scientists who have the need to know the information to protect public health.

- The ability to safeguard DURC information appropriately using security classification is complicated by the fact that the dual-use nature of the research may not be identified until the research is in progress or after the research has been completed.

- Federally-funded or sponsored life sciences research, particularly that supported by HHS, is frequently conducted at non-government facilities, some of which may employ non-U.S. citizens, who are normally not cleared to received classified information.

- By restricting the free and rapid flow of information, as well as the number of scientists and laboratories with appropriate clearance to access the information, classification of DURC could slow down important public health research and innovation. This could have the dual effect of endangering both domestic and international public health, as well as hindering U.S. competitiveness in the life sciences.

It is for these reasons that the March 29, 2012, policy suggests that classification be considered only if other possible risk mitigations approaches are deemed to be unworkable.

Post-Hearing Questions for the Record
Submitted to Daniel M. Gerstein, Ph.D.
From Senator Claire McCaskill

"Biological Security: The Risk of Dual-Use Research"
April 26, 2012

Question#:	3
Topic:	NBAF 1
Hearing:	Biological Security: The Risk of Dual-Use Research
Primary:	The Honorable Claire McCaskill
Committee:	HOMELAND SECURITY (SENATE)

Question: In your testimony, you described the critical work at the aging Plum Island Animal Disease Center and the importance of developing a vaccine for foot and mouth disease. Over three years ago, Manhattan, Kansas was selected as the site of the new National Bio and Agro-Defense Facility (NBAF), which is scheduled to be a Biosafety Level 4 (BSL-4) facility, meaning the highest possible containment measures will be in place. Do you believe the United States needs a BSL-4 facility, and that the construction of this facility is vital to our nation's food and agriculture security?

Response: The lack of Biosafety Level 4 agricultural (BSL-4Ag) research space in the United States endangers the lives of those exposed to zoonotic diseases and emperils the $1 trillion agriculture and food industry which represents one-sixth of U.S. gross national product. For more than 50 years, the Plum Island Animal Disease Center (PIADC) has served as the primary U.S. laboratory facility for conducting vital livestock disease research. Despite its many successes, the age of PIADC facilities and its limited capacity restricts research and impedes the development of needed medical countermeasures, in the case of a serious foreign disease outbreak. PIADC has no capacity to do research at BSL-4, the highest biosafety level, which is essential to combating the most dangerous animal disease threats. Moreover, political opposition at the local, state, and federal levels preclude the construction of a BSL-4 facility at PIADC.

Over the last three decades, approximately 75% of new and emerging infectious diseases have originated in animals; moreover, approximately 60% of all human pathogens are zoonotic. Currently, the U.S. must rely on partnerships with BSL-4Ag labs in Australia and Canada to conduct in vivo studies in livestock – essential to fully understanding these diseases and quickly developing countermeasures. In addition to the lack of BSL-4Ag, PIADC has no surge capacity for response to wide-scale events. In the event of an outbreak or an attack employing a foreign animal or zoonotic disease, the U.S. would be unable to do the critical research needed for response.

Question#:	3
Topic:	NBAF 1
Hearing:	Biological Security: The Risk of Dual-Use Research
Primary:	The Honorable Claire McCaskill
Committee:	HOMELAND SECURITY (SENATE)

The National Bio and Agro-Defense Facility (NBAF) will provide a fundamental and needed capability for U.S. national security – the ability to diagnose and create countermeasures against large animal diseases requiring the highest level of biosafety, such as Nipah and Hendra. NBAF will be an integrated facility for studying foreign animal and zoonotic diseases both in vivo and in vitro as well as capacity for advanced test and evaluation (T&E) for threat detection, vulnerability, and countermeasure development. NBAF continues to receive strong support from Kansas, including gift funds.

Two recent National Academy of Sciences reports, along with other government reports including the 2004 Office of Science and Technology Policy (OSTP) Blue Ribbon Panel, stated unequivocally the imperative need for a large livestock BSL-4 facility in the United States and concluded that reliance on foreign countries for this capability is not in the best interests of the United States. Failure to build the NBAF will not only place the security of U.S. food and agriculture in jeopardy, but would seriously impair U.S. scientific eminence in this important field.

Question#:	4
Topic:	NBAF 2
Hearing:	Biological Security: The Risk of Dual-Use Research
Primary:	The Honorable Claire McCaskill
Committee:	HOMELAND SECURITY (SENATE)

Question: Would conducting dual-use research of concern at a new BSL-4 facility like NBAF be safer, or allow for more research opportunities, than continuing research at Plum Island?

Response: The USG cannot conduct any research studies in livestock species that require Biosafety Level 4 (BSL-4) containment of groups of animals in the U.S. because there are no BSL-4 livestock facilities. BSL-4 livestock facilities are required to allow any research to be conducted safely with these species and agents, including potential dual use research of concern. NBAF will provide more research opportunities compared to Plum Island because of the expanded mission that adds Biosafety Level (BSL3) and BSL-4 zoonotic diseases (e.g., Nipah and Hendra viruses). These studies will be reviewed by the Department of Homeland Security's Science and Technology Directorate (S&T) Compliance Assurance Program Office for Dual Use Research of Concern.

Currently, the United States does not have the ability to conduct BSL-4 testing on large livestock. A state-of-the-art biocontainment that meets modern standards and supports conducting emerging and zoonotic disease research at the required containment level (BSL-4) is needed. Department of Homeland Security places a priority on ensuring these facilities are safe, and therefore has ensured the NBAF design incorporates lessons learned from current high containment operating facilities around the world to ensure it will be a safe and secure facility.

Question: What are some of the limitations S&T faces at the existing Plum Island facility that will be addressed when NBAF is constructed?

Response: Since 1954, PIADC has been the key research and development facility in the United States for countering high consequence and agricultural biological threats. However, PIADC has the following limitations:

1) PIADC cannot handle outbreaks of emerging and zoonotic diseases and related research that require a BSL-4 level capability. To offset these capability shortfalls, S&T is developing cooperative agreements with Australia and Canada to utilize their agro-defense BSL-4 capabilities until NBAF is operational. These agreements are only a short term solution, since using outside facilities will significantly limit the U.S. response capability and timely ability to develop countermeasures.

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2) PIADC has limited capacity BSL-3 Agro space. The lack of capacity limits timely Foot and Mouth Disease (FMD) trials and vaccine development. The facility lacks the overall capacity to work with multiple pathogens simultaneously. Currently, PIADC is the only U.S. facility able to work with FMD, Classical Swine Fever, and African Swine Fever. Subject experts have determined that the foreign animal disease research program should include seven different classes of pathogens to adequately prepare for the next emerging foreign animal disease (FAD).

3) Due to its age, PIADC faces serious facility challenges that include: a) not meeting modern biocontainment standards, b) requiring significant recapitalization, and c) posing recruiting challenges by not being near robust research capabilities.

NBAF will address these limitations by building a modern biocontainment facility including BSL-4 capability. The new facility will provide enhanced research capabilities to diagnose and control FAD and emerging zoonotic diseases of large livestock, expanded vaccine development capabilities for large livestock, and increased links with the research community and industry to further accelerate vaccine development, training, and diagnostic capabilities.

Post-Hearing Questions for the Record
Submitted to Paul S. Keim, Ph.D.
From Senator Joseph I. Lieberman

"Biological Security: The Risk of Dual-Use Research"
April 26, 2012

1. Initially it appeared that one of the options for publication of the H5N1 studies was a public version in which certain elements were redacted, and then a system would be developed to allow legitimate scientific and public health entities to have access to the full study. This option was taken off the table for the NSABB's second look at the studies.

   We have been told that one of the reasons for this was that limited distribution would not fall within the basic research exemption under export control laws, and this is an issue also currently being debated by the Dutch government with respect to the Erasmus Medical Center study. The apparent limitation of options under export control laws to either full or no publication, what effect, if any does that have on the NSABB's options when reviewing this kind of work?

Response:
In my opinion, the lack of a redacted publication mechanism was central to the Board's recommendation to publish. Dr. Francis Collins, director of NIH, presented to the Board on March 30th the U.S. government's efforts to develop a limited distribution procedure and he was quite convincing that this could not be done in a short time frame. There is still great uncertainty amongst board members about how capable the respiratory-transmissible H5N1 virus would be at causing a global pandemic and at what mortality rate. It was this uncertainty that moved the board to the recommendation to withhold some information to minimize risk, while communicating other information to maximize the benefits from this work. The redacted publication and limited distribution of sensitive data was seen as an important tool for maximizing benefits and minimizing risks. Without that option, individual board members were forced to vote for full publication or full redaction. In the case of the Erasmus University work, the vote was 12 to 6 in favor of publication.

Post-Hearing Questions for the Record
Submitted to Paul S. Keim, Ph.D.
From Senator Mark L. Pryor

"Biological Security: The Risk of Dual-Use Research"
April 26, 2012

1. Your written testimony says that the U.S. needs to establish policy that "intensely monitors high potential dual use research of concern…in order to protect us from misuse." What do you anticipate will be the biggest challenges in the development and implementation of adequate policy? Can you discuss the role of Congress in the development of this policy and describe how it can be most useful?

Response:

Implementing the new policy faces two challenges:

The first challenge will be to identify high potential dual research of concern (DURC) and then effectively manage its risk. As currently stated, the policy will target a very small part of federally funded research based upon the NSABB seven experiments of concern and short list of tier I select agents (plus the avian H5N1). Lists of threats and agents makes regulatory monitoring and compliance easier, but unfortunately lists are "mindless" and can make us myopic to very real risks that are not on the lists. In recent bioterror incidences, diseases causing agents not targeted (Salmonella) have been successfully used to harm the American public. While research within the proposed framework must be closely examined for DURC potential, other research should not be ignored or given carte blanche. This will mean broad education of federal program managers and research review panels to be vigilante for "off target" DURC. Management of high potential DURC needs to be foresighted to avoid dangerous experiments before they are performed and to carefully consider how to communicate the research to maximize its benefits to human kind while minimizing its risks. This will take a coordinated effort between the research groups and their federal program managers.

Secondly, it is important that research with low potential as DURC be kept as free as possible from onerous oversight. Over regulation kills innovation, which is a critical to the scientific enterprise. Our welfare depends upon continuing innovation in biological science. We have to avoid damping our progress in this arena.

Congress can help in several ways. The first is simply though monitoring the federal DURC regulatory efforts. Congressional hearings, even without legislation, will insure that this new policy is being implemented in a rigorous fashion. Secondly, some high potential DURC research is critical to public health and welfare. Additional regulatory burden on such research will slow or even eliminate progress unless it is adequately funded to compensate. Some research must be regulated as high potential DURC, but if it is important and is critical to our country, then Congress must insure that it is economically feasible to perform. Finally, if a legislative regulatory path is taken, it should be very carefully considered. It will take intense study to fully understand the both intended and unintended consequences of Congressional action. Don't legislate lightly.