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Attn: Docket Number: CDC-2012–0010

Influenza Viruses Containing the Hemagglutinin from the Goose/Guangdong/1/96 Lineage

Dear Dr. Weyant,

The Foundation for Vaccine Research (FVR) is pleased to have this opportunity to respond to the announcement in the Federal Register of February 8, 2013, Docket Number CDC-2012-0010, in which the U.S. Centers for Disease Control and Prevention (CDC) within the U.S. Department of Health and Human Services (HHS) extended their request for comment from the public on questions concerning highly pathogenic avian influenza (HPAI) H5N1 viruses containing a hemagglutinin (HA) from the Goose/Guangdong/1/96 lineage, specifically: 1) whether viruses of this lineage have the potential to pose a severe threat to public health and safety, 2) whether viruses of this lineage should be added to the HHS list of select agents and toxins, and 3) if such viruses should be added to the select agent list, whether they should be considered Tier 1 select agents.

Background
The FVR is an independent advocacy organization dedicated to advancing vaccine research and development against infectious diseases. Our mission is to educate and inform decision makers of the benefits of investing in vaccine research and development and to help mobilize the resources that scientists need to pursue promising lines of research. The Foundation supports prepandemic and pandemic influenza vaccine research and development, as well as basic research that could lead to a universal influenza vaccine. An important part of our mission is to educate and inform the public about vaccines and to build public trust in vaccines, vaccine research, and in biomedical research more broadly. This part of our mission has become increasingly important with falling immunization rates in the United States, a vocal anti-vaccine movement, and doubts among a growing number of people who worry about vaccine safety and have become risk averse to vaccination.

The FVR supports innovation in vaccine research and development in the United States and globally. We believe passionately that breakthroughs emerge when the most talented researchers are given the resources and freedom they need to pursue their goals. In the context of pandemic influenza, we consider it is vital to have a vibrant, dynamic and motivated influenza research community. We consider it is essential to increase surveillance of circulating strains of influenza viruses in the wild, to build diagnostic capacity overseas, and to strengthen virus-sharing networks. We also believe that vaccine manufacturers should be supported in their efforts to develop and introduce improved influenza vaccines, including pre-pandemic and pandemic influenza vaccines.
In March 2012, the FVR took the lead in organizing a 2-day international symposium, “H5N1 Research: Biosafety, Biosecurity and Bioethics,” held on April 3 and 4 at the Royal Society in London. The symposium, organized in partnership with the Royal Society and the UK Academy of Medical Sciences, was made possible by grants from the Bill & Melinda Gates Foundation, the American Society for Microbiology (ASM), the Fondation Méridieux, the German National Academy of Sciences – Leopoldina, Institut Pasteur, and the UK/Eire Society for General Microbiology (SGM). The symposium was the first and remains the largest meeting convened to date on the H5N1 issue. It was also the first international meeting open to the public and the first webcast live:

http://royalsociety.org/events/2012/viruses/

The FVR’s response to the CDC’s request for comment is informed by the scientific information presented at this symposium and by the expert discussions that followed on the risks and benefits of resuming the transmissibility studies at the center of the controversy, with special emphasis on safety concerns. The FVR’s response is also guided by the Foundation’s mission to help advance influenza vaccine research while building public trust in vaccines and vaccine research, and by its commitment to uphold the principles of scientific integrity, transparency and ethical behavior. The FVR does not accept money from industry or government and has no financial ties to any interest group.

**Preliminary remarks**

The Foundation is pleased that the CDC is asking these questions and welcomes the chance to comment. We are of the opinion that highly pathogenic avian influenza H5N1 viruses, whether they contain the hemagglutinin from the Goose/Guangdong/1/96 lineage or not, should be classified as Tier 1 select agents for the purposes of “gain-of-function” experiments to increase transmissibility, pathogenicity, and/or alter the host range of these viruses. There is precedent for the CDC adding constructed forms of pandemic influenza viruses that have been determined to have the potential to pose a severe threat to public health and safety to the HHS list of select agents and toxins.

In October 2005, the CDC added reconstructed replication competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all 8 gene segments to the list of HHS select agents.¹ The CDC took this action for several reasons. First, the pandemic influenza virus of 1918-19 killed up to 50 million people worldwide, including an estimated 675,000 deaths in the United States. Also, the complete coding sequence for the 1918 pandemic influenza A H1N1 virus had been identified, which made it possible for those with knowledge of reverse genetics to reconstruct this virus. In addition, the first published study on a reconstructed 1918 pandemic influenza virus demonstrated high virulence in cell culture, embryonated eggs, and mice relative to other human influenza viruses. The CDC therefore determined that reconstructed replication competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all 8 gene segments have the potential to pose a severe threat to public health and safety. As a result, these forms of the 1918 virus were added to the HHS select agent list.

This action is relevant to the CDC’s request for comment on HPAI H5N1 viruses. In our opinion, the construction of mammalian-transmissible HPAI H5N1 viruses has the potential to pose an equal or even greater threat to public health and safety than a reconstructed replication competent 1918 H1N1 virus. Indeed the threat is inherently greater for H5N1 because there is no pre-existing immunity in the human population whatsoever. For the reconstructed 1918 virus, there is at least some pre-existing immunity.

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¹ The Federal Register, Volume 70, Issue 202, Thursday, October 20, 2005.
The Foundation notes that a reassortant H5 HA/H1N1 virus has already been constructed in the laboratory. An avian-human reassortant H5N1 virus possessing the HA protein from an H5N1 virus and 7 remaining gene segments from a 2009 pandemic H1N1 virus has been generated by investigators at the University of Wisconsin, Madison. In receptor-binding studies and animal experiments, a derivative of this reassortant virus was identified that possessed four mutations in its HA protein (N158D, N224K, Q226L, T318I). These four mutations allowed transmissibility in ferrets – the best animal model for human influenza infection. An additional mutation (E119G) was found outside the region targeted for mutation, demonstrating the possibility of generating novel variants and unanticipated outcomes. The FVR recognizes that the pathogenicity of reassortant viruses is difficult to predict and depends upon the gene constellation. However, the construction of this hybrid virus suggests that any influenza virus strain possessing an HA gene from the Goose/ Guangdong/1/96 lineage could potentially pose a severe threat to public health, even if it were not fully of HPAI H5N1 origin.

Avian-human reassortant influenza viruses are of special concern because they have pandemic potential. Avian-human reassortant viruses caused the 1957 (Asian flu) and the 1968 (Hong Kong flu) influenza pandemics. The 1957 and 1968 human pandemic influenza viruses (H2N2 and H3N2, respectively) arose through reassortment between human and avian viruses. The H1N1 pandemic influenza virus that was responsible for the 2009 swine flu outbreak was also the result of reassortment, combining an unusual mix of swine, avian and human influenza genetic sequences. Given the pandemic potential of avian-human reassortant viruses, it would seem reckless to create an avian-human reassortant H5 HA/H1N1 virus. An avian-human reassortant H5N1 virus possessing the HA protein from an H5N1 virus and 7 remaining gene segments from a 2009 pandemic H1N1 virus would have the potential to pose a unique threat to public health and safety.

Designating HPAI H5N1 viruses as HHS select agents for the purposes of gain-of-function research to increase pathogenicity, transmissibility and/or alter the host range of these viruses that could result in a mammalian-transmissible H5N1 virus of pandemic potential would be consistent with adding reconstructed replication competent forms of the 1918 H1N1 pandemic influenza virus containing any portion of the coding regions of all 8 gene segments 1918 influenza virus to the HHS list of select agents.

Unanswered questions
The Foundation notes that the pathogenicity of reassortant influenza viruses is difficult to predict. Given the unpredictability of avian-human reassortant influenza viruses in particular, the FVR questions the benefits and the fundamental wisdom of conducting such high-risk research if the objective is to increase transmissibility, pathogenicity, and/or alter the host range of these viruses. Many if not most scientists outside the influenza research community, whether engaged in biomedical research or in another branch of the life sciences, would intuitively consider such research to be so dangerous that it is not worth the risk. Indeed, many would deem it unethical to create a pathogen more lethal than exists in nature, regardless of the scientific rationale advanced to justify the research. In this context, we consider that proponents of this research have consistently underestimated the risks and exaggerated the benefits. Even the staunchest proponents of this research acknowledge that the risks are real, while the benefits are hypothetical.

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Lack of an independent risk-benefit assessment
The Foundation notes that no independent formal risk-benefit assessment has been conducted to date in the U.S. or overseas that sets out to identify and quantify the risks and the benefits of this research. To date, the discussion of the risks and benefits has been mostly subjective and qualitative, and dominated by proponents of this research with a profound conflict of interest in seeing it resume. The majority of meetings held to date on this topic have been closed, invitation-only meetings, with the notable exception of the Royal Society symposium on April 3 and 4, 2012, and the NAS H5N1 workshop on May 1, 2012, the only two large meetings open to the public and webcast live.4

In the absence of a comprehensive, fact-driven assessment that would inform the discussion, it is hard to argue that the knowledge that might be gained from this research outweighs the risks. If it is difficult for scientists to assess the risks and benefits, it is even harder for non-scientists. For this reason, the FVR is of the opinion that a rigorous, independent, transparent risk-benefit assessment must be conducted. At this stage, we doubt the competence, the willingness or the good faith of the U.S. National Institutes of Health to conduct an independent, transparent risk-benefit assessment that would quantify the risks and the benefits of this research in an objective and impartial manner. Indeed, the NIH seems to have determined that no such study is required. In this situation, given the profound need to know whether the benefits outweigh the risks, and given the profound global consequences of a potential mishap, the U.S. Congress should step in and commission an independent risk-benefit assessment. Until such an analysis has been conducted, commons sense would suggest that the precautionary principle should be applied and further funding withheld until there is a consensus as to whether the benefits outweigh the risks.

Doubtful benefits of the research
In the last twelve months, exaggerated claims have been made regarding the benefits of H5N1 gain-of-function research without any concerted effort to quantify them. Proponents claim that the H5N1 transmission studies are essential for pandemic preparedness and that identifying mutations that enable H5N1 viruses to adapt to mammals is important for understanding the scientific basis for adaptation to mammals.5 However, we stumble over the assertion that these studies will provide comprehensive data for focused surveillance and help identify appropriate vaccine candidates. There may be some basis for the notion that this research will help inform surveillance. However, there is considerably less support for the notion that this knowledge will help predict an outbreak of pandemic potential, and even less support for the notion that this research will help vaccine manufacturers develop an H5N1 pandemic vaccine in the event of an outbreak.

The argument most frequently advanced by proponents of HPAI H5N1 gain-of-function research is that awareness of HPAI H5N1 viruses containing some or several of the mutations associated with mammalian transmissibility will improve the surveillance of naturally-occurring H5N1 strains in the wild and thereby improve our preparedness for and response to a possible H5N1 pandemic. However, due to the current lag times in obtaining usable surveillance data, this argument is moot. In short, it may be appealing in the abstract but is of questionable value in practice.6

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4 The U.S. Department of Health and Human Services held a meeting on H5N1 gain-of-function research that was billed an international consultative workshop on the NIH campus in Bethesda, MD, December 17-18, 2012.
5 Fouchier RA, García-Sastre A, Kawaoka Y. The pause on avian H5N1 influenza virus transmission research should be ended. MBio. 2012 Nov 1;3(5).
History and recent experience have shown that predicting influenza virus evolution and epidemics is notoriously hazardous. The track record of epidemiologists at the World Health Organization (WHO) and the CDC in predicting what influenza strains will predominate in next year’s flu season has been a hit-and-miss affair. Influenza viruses are RNA viruses with high intrinsic mutation rates and a unique ability to reassort. Predicting phenotypic evolution is probably even harder than prediction of genome sequence evolution. The ways in which selection pressures act on influenza viruses in nature are poorly understood. Virologists should be more modest in their claims to predict what will occur based on a handful of laboratory-generated mutations.

For this reason, most evolutionary biologists, virologists and epidemiologists with experience of influenza and other RNA viruses are of the opinion that the knowledge gained would be of marginal value, at best. Attempting to predict what combination of mutations could evolve naturally in the wild that would confer sustained human-to-human transmissibility based on a small number of mutations observed in the laboratory is not only risky but potentially misleading.7

Regarding the argument that this research will help vaccine manufacturers develop a pandemic vaccine, there is scant support for this notion among vaccine developers. The consensus is that this research will not assist vaccine manufacturers in their efforts to develop an improved H5N1 pandemic vaccine. Vaccine manufacturers do not deal in hypotheticals. They would strive to match the pandemic influenza strain exactly. Indeed, the most effective pandemic vaccine would be a live attenuated influenza virus (LAIV) vaccine that matches the pandemic strain precisely.

There is even less support in industry for the notion that this research will help drug companies develop improved antiviral drugs that could be used in the event of an H5N1 pandemic. The two FDA-approved neuraminidase inhibitors, oseltamivir (Tamiflu) and zanamivir (Relenza), work by blocking the function of the viral neuraminidase enzyme. The primary focus of the H5N1 gain-of-function studies is to create amino acid changes in the highly variable H5 hemagglutinin glycoprotein that could combine to confer efficient aerosol transmissibility between mammals. Drug-resistant compensatory mutations in neuraminidase have been found to occur as a result of mutation in hemagglutinin.8 This finding is of grave concern with regard to containing an exposure to a laboratory-generated variant since it may not be possible to treat a laboratory-acquired infection with existing antivirals. Furthermore, the case has not been made that the H5N1 studies will enable drug companies to develop more efficacious neuraminidase inhibitors. While efforts have been made to develop antiviral compounds that target the highly variable influenza M2 protein (amantadine and rimantadine are no longer recommended by the CDC because of high levels of drug resistance), as far as we are aware there are no efforts under way or planned to develop antiviral compounds that target the even more variable hemagglutinin protein.

In summary, the purported benefits of this research appear to have been overstated to the point of being hyped by proponents of this research. There is widespread skepticism in the broader scientific community for the notion that identifying mutations that could enable HPAI H5N1 viruses to adapt to mammals will provide data for improved surveillance of naturally-circulating H5N1 strains, and even less support for the notion that this research will help vaccine manufacturers identify appropriate vaccine candidates or drug companies develop improved antivirals.

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Evolutionary biology generally has a dim view of prediction. Forecasting how H5N1 viruses might evolve and spread following emergence is more tractable. Moreover, there is a danger that erroneous predictions will result in a misuse of resources and undermine public confidence.

**Biosafety concerns**

The Foundation considers that H5N1 gain-of-function research is inherently dangerous and unsafe. If this research is considered vitally important, internationally agreed guidelines should be put in place and a consensus developed as to the conditions under which the research could be allowed to resume. In the continuing absence of such a consensus, the most prudent action would have been to continue the moratorium on H5N1 gain-of-function research. However, since the unilateral lifting of the moratorium on H5N1 transmission studies on January 23, 2013, by 40 individuals who have a personal and/or an institutional interest in seeing it resume, 9 this may no longer be an option. Therefore it behooves the international community to take a closer look at the safety issues and agree the minimum safety standards under which this research could be conducted.

Despite a flurry of small meetings, which were all invitation-only and closed to the public, there has been no large international meeting of any size or importance convened to discuss and agree the minimum safety standards for this type of research. With the exception of a one-day meeting of the U.S. Recombinant DNA Advisory Committee (RAC) on January 24, 2013, at which there was no consensus on the containment level or special precautions that should be taken for H5N1 gain-of-function research, there has been little expert discussion worthy of the topic. There is an urgent need for frank, open discussion of the safety issues, particularly risk to the public. Risk assessment is recognized as a fundamental cornerstone of biosafety. However, until all the risks associated with this research, including the aggregate risks, have been assessed by independent experts as part of an irrefutable, comprehensive, independent risk-benefit assessment, there can be no basis for confidence.

Oversight plays a critical role in monitoring biosafety and ensuring that high-containment laboratories comply with regulations. However, many aspects of the current U.S. oversight guidelines provided by HHS – and by the U.S. Department of Agriculture USDA) – depend upon entities monitoring themselves and reporting incidents to federal regulators. Oversight of high-containment laboratories in the U.S. has been found to be wanting, according to a recent U.S. Government Accountability Office (GAO) report. 10 A large, more recent international study of scientists’ attitudes and behavior towards laboratory safety found that lab workers have a false sense of security. 11

In this context, current arrangements for the review, regulation and oversight of this type of research are not up to the task. Institutional Biosafety Committees (IBCs) created and mandated under NIH guidelines are not designed or equipped to assess the risk of dual-use research of concern (DURC) and are prone to institutional bias. This problem is compounded by the large variability in the function of IBCs at different institutions, the frequent failure of IBCs to comply with federal rules, the lack of meaningful oversight by the Office of Biotechnology Activities (OBA) at the NIH, the difficulty overseeing foreign institutions conducting research funded by the NIH, and, perhaps most important, the profound conflicts of interest of IBC members on many IBCs.

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In view of the risks involved, it is clear that the oversight system governing this type of research is inadequate and needs to be revamped. Before HPAI H5N1 gain-of-function experiments are allowed to resume, steps must be taken by federal regulators to strengthen the safety, security and oversight of laboratories doing this research. Moreover, rather than encouraging more gain-of-function studies, which would involve more laboratories, we should focus on key efforts in fewer facilities. One step in the right direction would be to limit this research to BSL-4 facilities. This would have the immediate effect of reducing the numbers of laboratories able to conduct this research, and thereby, reduce the chances of an accident. It would also make it easier for regulators to strengthen oversight and ensure that the highest safety standards and procedures are followed.

The FVR notes that HPAI H5N1 viruses are considered so dangerous in the UK and Canada that transmission studies at the center of the current controversy can only be conducted at the highest containment level, BSL-4. It is of concern that there appears to be a “push down” under way in the United States to BSL-3. Federal regulators should resist this push down in the interest of public safety.

Other questions
The H5N1 research controversy poses a unique set of challenges that go beyond assessing the risks and benefits. After more than 12 months of discussion, there is still no international consensus on the conditions under which this research could be allowed to resume. In recent months, it seems that only the United States has any enthusiasm for resuming funding of this kind of research, regardless of what the rest of the world thinks. It is an inconvenient truth that many thorny issues remain. Incomplete answers have been provided to the following five questions:

1. How should gain-of-function research be assessed?
2. By whom should gain-of-function research be assessed?
3. When assessing the risks and benefits of gain-of-function research, where does the burden of proof lie?
4. Under what conditions should gain-of-function research be allowed to resume?
5. Who should have the ultimate responsibility?

In the continuing absence of an international consensus as to whether HPAI H5N1 gain-of-function research should be allowed to resume, and, if so, under what conditions, we are of the opinion that the only prudent course of action for regulators is to apply the precautionary principle. Under this principle, if an action or policy has a suspected risk of causing potential harm to public health or safety, and if there is no consensus that the benefits of the research outweigh the risks, the burden of proof that it is not harmful falls on those conducting the research.

The precautionary approach allows regulators and other policy makers to make discretionary decisions in situations where there is the possibility of harm from taking a particular course of action or making a certain decision when extensive scientific knowledge on the matter is lacking or there is no consensus. The principle implies that there is a social responsibility to protect the public from exposure to harm, when scientific investigation has found a plausible risk. These protections can be relaxed only if further scientific findings emerge that provide sound evidence that no harm will result.
The Foundation considers that the case has not been made by proponents of this research that no harm could result from these gain-of-function experiments. Therefore we urge the CDC to apply the precautionary principle in making their determination as to whether HPAI H5N1 viruses should be added to the HHS list of select agents and toxins for the purposes of gain-of-function research.

Broader considerations
The Foundation sees the H5N1 research controversy as part of a much larger problem: public trust. The H5N1 issue has captured headlines worldwide with sensational stories in the popular press and leading national newspapers about how scientists are making deadly viruses more lethal and capable of causing a pandemic and risking the lives of everybody living on the planet.\(^{12,13}\) As such, the H5N1 controversy undermines the Foundation’s efforts to build public trust in vaccines, vaccine research, and science more broadly, by providing fodder for the anti-vaccine movement, activists who question the good intentions of scientists, and sceptics who have their doubts about synthetic biology. Public trust is fragile. As the CDC knows well, it only takes one incident, mishap or piece of misinformation to undo years of hard work. Falling immunization rates in the U.S. and Europe can be attributed to public doubts about vaccine safety. The advent of the Internet has made it easier to spread misinformation and stoke public doubts. The H5N1 controversy risks reinforcing doubts among the greater population about scientists’ intentions, research priorities, and integrity in a world that is already perceived as dangerous. Despite attempts to better manage the affair, including pushing through new rules, recent developments have not inspired confidence that U.S. federal authorities, and the NIH and HHS in particular, are aware of the extent of the damage to public trust caused by the H5N1 issue.

The NIH’s mission is to protect and promote public health and safety, not to endanger it. The FVR questions the fundamental wisdom and safety of this type of research when the knowledge that could be gained is slim, the attendant risks are unusually high, and there are other lines of research that most experts, including many scientists within the NIH and CDC, consider are more promising and more likely to lead to improvements in public health and safety. From the outside looking in, it seems that the NIH has lost its way. Instead of admitting that this research should probably never have been funded in the first place, the NIH has boxed itself into a corner by insisting this research is safe. Indeed, in recent months the NIH has seemed determined to dig itself into an even deeper hole by twisting arms, cajoling members of advisory boards to change their recommendations regarding the safety of this research, and rallying other federal agencies to its cause with scant regard for public opinion or what others think, whether inside or outside the United States. A recent workshop convened by the NIH to discuss a proposed framework for HHS funding decisions for HPAI H5N1 gain-of-function research was billed as a consultative workshop at which public comment was invited. Few members of the public came because NIH followed its routine practices with no special efforts at engagement to reflect the importance of the controversy. No members of the public were specifically invited, there were no additional initiatives to ensure that the announcement of the meeting reached a wider public audience, and the date chosen (just before Christmas) was at a time when people have other priorities. This leaves the strong impression that there was no genuine desire on the part of the organizers to get public comment.\(^{14}\)

\(^{13}\) The Deadliest Virus: Did a scientist put millions of lives at risk—and was he right to do it? The New Yorker, March 12, 2012.  
\(^{14}\) The U.S. Department of Health and Human Services held a meeting on H5N1 gain-of-function research that was billed an international consultative workshop on the NIH campus in Bethesda, MD, December 17-18, 2012. The only announcements of the workshop were in the Federal Register and on the website of the Office of Biotechnology Activities (OBA) at the NIH. The proceedings of the workshop were not webcast live.
The Office of Biotechnology Activities (OBA) at the NIH has played a central role in helping to manage the NIH response to the H5N1 issue. The OBA is charged with promoting science, safety, and ethics in biotechnology through advancement of knowledge, enhancement of public understanding, and development of sound public policies. The OBA is responsible for overseeing recombinant DNA research and dual-use research funded by the NIH. Of relevance to the H5N1 issue, OBA manages the operations of the NIH Recombinant DNA Advisory Committee (RAC) and the National Science Advisory Board on Biosecurity (NSABB), both designed to provide independent expert advice to the NIH. The OBA also has oversight of Institutional Biosafety Committees (IBCs).

The H5N1 affair has provided a golden opportunity for the OBA, which is not well known outside the NIH, to take the lead and show that it is committed to the principles of openness and transparency. Instead of rising to the H5N1 challenge, the OBA has essentially squandered this opportunity by closing up like a clam. The OBA, which supports the Office of Science Policy, within the Office of the Director of NIH, has been secretive and unresponsive to requests for information on H5N1. A core part of the OBA’s mission is to respond to requests for information on technical matters and matters of public policy related to recombinant DNA research and dual-use research.

In contrast to the CDC and other agencies when they ask for public comment, the OBA has not, at any point in time, posted, made available, or responded to written public comments sent in response to its request for comments of December 20, 2012, on the proposed framework for HHS funding decisions about HPAI H5N1 gain-of-function research. Moreover, the OBA has not, so far, posted, made available, or responded to written public comments sent in response to its request for comments on the RAC meeting on H5N1 gain-of-function research held on January 24, 2013, or its request for comment of February 21, 2013, on the proposed amendments to the NIH guidelines, suggesting that there is no genuine desire to acknowledge, much less engage with, public comments.

Taken together, the overall impression is that the powers that be at the NIH, which includes the leadership of the National Institute of Allergies and Infectious Diseases (NIAID) and the OBA, are not interested in hearing dissenting views, and indeed will not brook dissent, especially from within their own ranks. American scientists with NIH grants who are opposed to this research based on moral or safety grounds have been afraid to speak out for fear of retribution. Scientists who question the wisdom and safety of this research or who consider the benefits are not outweighed by the risks, have been sidelined or excluded by the NIH/NIAID from participating in meetings. Expert panels and committees have been stacked by the NIH/NIAID/OBA with proponents of this research and other scientists who can be counted upon not to oppose it. The NIH had considerable sway over who was invited to attend an invitation-only WHO meeting in Geneva on February 26-28, 2013, and the agenda, because they helped to pay for it. Exerting this kind of control over the international discussion that the NSABB, and subsequently the NIH and HHS, called for in order to ensure that they get the outcome they want is not only unseemly but a disservice to the American people and scientists everywhere who look to the United States for leadership.

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15 The OBA issued a request for public comment on February 21, 2013: Recombinant DNA Research: Actions Under the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines).
16 Letters on file.
Research policy
The H5N1 research controversy diverts attention and resources away from research that the Foundation considers to be more important. In particular, it diverts attention away from research to improve the effectiveness of seasonal influenza vaccines, which are on average only 60% effective. Equally important, it diverts attention – and potentially resources – away from highly promising discovery research that could lead to the development of a universal influenza vaccine.

Seasonal influenza vaccines
The Foundation notes that the estimated overall vaccine effectiveness of the 2012-2013 seasonal influenza vaccine is just 56%, according to the CDC’s interim adjusted estimates as of February 22, 2013.\textsuperscript{17} Vaccine effectiveness is estimated as 47% against influenza A (H3N2) virus infections, this season’s dominant strain accounting for over two-thirds of influenza infections, and 67% against B virus infections. However, when stratified by age group, the estimated vaccine effectiveness against influenza A (H3N2) infections for persons aged $\geq 65$ years is only 9%.

These interim estimates of seasonal influenza vaccine effectiveness highlight the urgent need to improve the effectiveness of seasonal influenza vaccines. Because of the relative severity of this season’s dominant H3N2 influenza strain, it has been said that more than 50,000 people could die from influenza-related illness this year in the United States. According to the CDC, seasonal influenza causes more than 200,000 hospitalizations and up to 49,000 deaths in the U.S. each year, making it the seventh leading cause of death in America. Globally, seasonal influenza epidemics are thought to result in between 3 and 5 million cases of severe illness and between 250,000 and 500,000 deaths each year. The socio-economic impact is also great. The total economic costs caused by seasonal influenza outbreaks in the U.S. have been estimated at over $80 billion each year.

For these reasons, the FVR is of the opinion that research directed towards improving the effectiveness of seasonal influenza vaccines, the breadth of immunity generated by them, and the speed at which they can be produced, should be the first priority for the national influenza research effort.

Other research priorities
In addition to research directed towards improving the effectiveness of seasonal influenza vaccines, which most scientists and public health authorities in the U.S. and overseas consider should be the first priority for influenza research, there are other areas of influenza research that have far greater practical value than risky H5N1 research and the potential to save millions of lives.

Universal influenza vaccine
Foremost among the areas of research that should be prioritized is the search for a “universal” influenza vaccine, so called because such a vaccine could confer decades-long protection from any influenza virus strain. The FVR considers that the impressive and highly promising research being conducted by the Vaccine Research Center (VRC) at the NIH should be prioritized, supported with increased resources, and fast-tracked. The dogged pursuit of research that could lead to a vaccine that would protect populations against multiple strains of seasonal and pandemic influenza without the need for an annual vaccination could save millions of lives and would be of great global economic benefit. In experiments with mice, ferrets and monkeys,
VRC researchers have shown that they can elicit broadly neutralizing antibodies that neutralize a variety of influenza strains by stimulating an immune response to the highly conserved stem of the hemagglutinin protein. Unlike the head of the HA protein, the stem of HA varies relatively little from strain to strain. Investigators have shown that antibodies generated against the HA stem can recognize and neutralize multiple influenza strains. Of relevance to H5N1, antibodies generated by vaccines made from H1 subtypes of influenza A virus successfully neutralized other subtypes, including HPAI H5N1 viruses. This strategy could confer immunity to many or all subtypes of influenza A.

**Reverse genetics** and other technology advances are transforming the way that conventional vaccines have been developed. Plasmid-based reverse genetics systems allow for the generation of viruses of defined genetic composition. Although these processes do not speed up the actual time of manufacture for influenza vaccines, they can provide advantages in the development of seed strains that are sent to manufacturers for bulk vaccine production. Reverse genetics can speed up the generation of the typical reassortant seed strains to seasonal and low pathogenic influenza strains. However, the real value becomes apparent when the circulating virus is one of the highly pathogenic H5 (or H7) strains. In these instances, the molecular features which primarily confer high virulence, and coincidently reside within the HA protein, can be removed to produce a safe matching seed strain. These technologies have been the backbone to the success of the production of inactivated and live attenuated influenza virus (LAIV) vaccines to H5N1 viruses.

**Reverse vaccinology** is another technology that holds promise for the future. The first vaccine developed using this technology was licensed six weeks ago in Europe for meningitis B. Four of the five antigens in the meningitis B vaccine were derived from reverse vaccinology. After the genome of *Neisseria meningitidis* was sequenced, scientists mined the sequence data to discover novel proteins that could serve as potential antigens. While no single antigen alone could protect against the diversity of meningitis B strains, investigators found a combination of antigens were essential for the bacterium’s survival, function, or ability to cause infection, and could be found in most meningitis B strains circulating globally. The successful development of a meningitis B vaccine by reverse vaccinology shows that this approach can be used to develop vaccines against other organisms.

The expansion of **cell-culture technology** for the manufacture of influenza vaccines should be another priority. Cell-culture technology is an alternative production method to traditional egg-based production of influenza vaccines and enables a rapid response to urgent needs, such as a pandemic, within weeks instead of months. Traditional influenza vaccine production depends on a large number of fertilized chicken eggs to grow virus strains and requires many months for the organization of egg supplies, virus incubation and actual production before the vaccine is delivered to physicians or pharmacies. The U.S. Food and Drug Administration (FDA) approved

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19 Novartis’ meningitis B vaccine Bexsero was approved by the European Commission on January 22, 2013, the first time a vaccine has been approved against meningococcus B bacteria. Meningitis B accounts for up to 90% of meningococcal disease cases in Europe and more than 80% of meningococcal cases in Canada.
20 The four antigens in the vaccine are: 1) Neisserial adhesion A ( NadA), a protein that promotes invasion of the bacterium and adhesion to human epithelial cells, 2) Factor H binding protein (fHbp), which binds with the common blood protein Factor H, enabling the bacterium to evade attack by the host immune system, 3) Neisseria heparin binding antigen, which also helps meningitis survive in human blood and is present in nearly all strains of meningococci, and 4) Por A, a protein found in some highly virulent strains of meningitis B.
the first cell-culture-derived vaccine for influenza on November 20, 2012. Flucelvax is the first vaccine of its kind manufactured in the U.S. that utilizes full-scale cell-culture manufacturing technology.

These are just a few of the research areas that we consider have potential for improving public health and safety and should be prioritized, not research that seeks to make deadly pathogens more lethal. At a time when resources are scarce, these are the areas that should be emphasized.

Basic research
Maintaining support for surveillance of circulating influenza strains in the wild and crucial diagnostics work conducted in countries in Southeast Asia and China where most avian-human reassortant influenza viruses have emerged should be prioritized and supported with appropriate resources. Basic influenza research should remain another top priority. The FVR supports basic research to investigate the molecular structure, viral pathogenesis, viral evolution, host immune response to virus infection, adaptation of the virus to the host, and the complex factors that lead to secondary infections. Results from such research will inform the design of improved vaccines and other prevention tools, and are applicable to seasonal epidemic and pandemic strains alike. Basic research on the molecular structure of influenza viruses will lead to advances in the development of improved seasonal influenza vaccines, as well as the development a universal vaccine that could protect people against multiple strains of seasonal and pandemic influenza viruses.

Improved treatments
Two other obvious areas of research that should be emphasized include the need for more effective treatments for influenza infections and its complications, especially improved treatments for acute respiratory distress syndrome (ARDS) that is responsible for most influenza deaths, especially among the elderly, and improved antiviral drugs. It is sad to note that these areas of research with the potential to save millions of lives have been almost completely overlooked in the H5N1 frenzy.

The Foundation considers that all this research – research to improve the effectiveness of seasonal influenza vaccines, research that could lead to a universal influenza vaccine, research into new technologies, such as reverse genetics and improved adjuvants, combined with increased surveillance of naturally occurring influenza strains, improved diagnostics research, and strengthened virus-sharing networks and systems – is more important than the high-risk, low-return H5N1 research at the center of the current controversy. The FVR believes that the research agenda should be shaped and driven by priority areas identified as likely to bear the most fruit and should not be swayed by events if the overarching goals of the national research effort are to develop faster, more cross-reactive, and more effective seasonal and pandemic influenza vaccines, increase the speed of vaccine preparation and delivery, and develop newer generation vaccines that would improve our ability to respond to or prepare for an influenza pandemic.

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21 Novartis’ Flucelvax (Influenza Virus Vaccine) was approved by the FDA for individuals 18 years of age and older on November 20, 2012.
Conclusion
The unprecedented attention generated by the H5N1 controversy has had the unfortunate and undesirable effect of elevating the importance of a relatively obscure area of research that has not been central to the mainstream influenza research effort and is considered by many experts, including vaccine manufacturers, to be non-essential. By dominating the headlines for more than 12 months, the controversy has had the effect of sidelining more promising areas of research. The national research agendas of the United States and other countries should not be shaped or influenced by small, unrepresentative groups of scientists who are enamored of conducting high-risk research, especially experiments that most experts consider to have little or no scientific merit and yet have the potential to cause a pandemic. The NIH strategy of promoting dangerous HPAI H5N1 gain-of-function research risks creating the very threat that it is meant to fight. The Foundation believes that the NIH and proponents of this research need to get their priorities straight.

The Foundation’s responses to the seven specific questions about HPAI H5N1 influenza viruses containing the HA from the Goose/Guangdong/1/96 lineage asked by the CDC are on the next nine pages.
In response to the seven specific questions raised in the *Federal Register*:

1. Do HPAI H5N1 influenza viruses containing the HA from the Goose/Guangdong/1/96 lineage pose a severe threat to public health and safety?

YES and NO.

Depending upon the characteristics of the H5N1 strain, the Foundation considers that HPAI H5N1 viruses of this lineage have the potential to pose a severe threat to public health and safety. The Foundation recognizes that naturally circulating strains of wild-type H5N1 viruses of this lineage do not appear to pose an immediate severe threat to public health and safety because they are currently poorly transmitted between humans. The major threat of HPAI H5N1 viruses is to poultry and poultry workers in countries in Southeast Asia and China, where H5N1 viruses are endemic in birds. As of February 15, 2013, the cumulative number of confirmed human cases for avian influenza A (H5N1) reported to the WHO since 2003 stands at 620 cases with 367 deaths. More than two-thirds of these cases (416) occurred in Southeast Asia and China, with 293 deaths. Despite the continued increase in the number of human cases reported, there is still no evidence of sustained human-to-human transmission. For this reason, the Foundation does not consider that wild-type H5N1 viruses currently pose a severe threat to global public health and safety.

However, HPAI H5N1 viruses would become a severe global health threat to humans if these viruses were to acquire mammalian transmissibility, whether in the wild or in the laboratory. Influenza viruses, like many retroviruses, can undergo extensive genetic changes, resulting in the emergence of novel influenza viruses to which the human population is highly susceptible and may have no preexisting immunity. If HPAI H5N1 viruses of this lineage were to acquire sustained, human-to-human transmissibility, whether in the wild or in the laboratory as a result of human manipulation, and if the virulence and pathogenicity of naturally occurring HPAI H5N1 strains were retained, then the consequences to public health and safety would be extremely severe. We would therefore consider that mammalian transmissible HPAI H5N1 influenza viruses containing the HA from the Goose/Guangdong/1/96 lineage would not only pose a severe threat to public health and safety but, indeed, a unique threat of unprecedented severity.

**Rationale**

Studies conducted by Imai *et al.* and Herfst *et al.* have shown that HPAI H5N1 viruses can acquire mammalian transmissibility in ferrets, suggesting that efficient aerosol transmission by respiratory droplets is possible. If this outcome predicts that H5N1 viruses could acquire human-to-human transmissibility, the Foundation concurs with comments that a potent combination of factors would make mammalian-transmissible H5N1 strains a unique, or nearly unique threat to public health.

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22 Source: WHO/GIP, data in HQ as of 15 February 2013.
This unique combination of factors includes: 1) exceptionally high human virulence and pathogenicity, 2) potentially high human-to-human transmissibility, 3) nonexistence of mammalian-transmissible H5N1 strains in the wild (as far as we are aware), 4) lack of immunity to HPAI H5N1 viruses in the general population, 5) lack of adequate control measures to contain the spread once it is established, 6) incomplete protection of current H5N1 vaccines (if available), and 7) limited effectiveness and limited window to administer antiviral drugs (if available).

Like many other groups, we know of no other virus for which an accidental release followed by several generations of human-to-human transmission, raises the serious possibility of a global pandemic that moves faster than available control measures and could kill (if virulence is even 1% of that estimated for wild H5N1 strains) tens of millions of persons, an estimate that we consider to be conservative. Indeed, we know of no other pathogen, not even Ebola, variola (smallpox) virus, Bacillus anthracis (anthrax), Yersinia pestis (plague), or the SARS coronavirus that has this unique combination of risks. By all measures, an accidental release of a laboratory-engineered, human transmissible H5N1 virus could cause a catastrophic global pandemic that would decimate the world’s population.

Such a pandemic, were it to occur, would overwhelm healthcare systems worldwide. Healthcare workers would be among the first to be infected. No country, rich or poor, would be spared. Even if we had improved H5N1 vaccines, there is no guarantee that they would be fully protective against an escaped mutant. Even if they were, vaccine makers would not have the time, the capacity, or the resources to make 7 billion doses – or even 3.5 billion doses – at short notice. Governments would not have the time to roll out the vaccines quickly enough. It is doubtful that vaccine companies could be persuaded to make even a fraction of the doses required before a pandemic has occurred without large contracts or financial incentives from governments, or if such large quantities of vaccines could be stockpiled in advance. Developing countries would not have the money to purchase vaccines. A global pandemic of unprecedented magnitude would lead to social and economic collapse. The world would be ill-prepared to handle such a pandemic.

2. Are there other influenza strains containing HA from Goose/ Guangdong/1/96 lineage that would also pose a severe threat even if they were not fully of HPAI H5N1 origin?

YES. A reassortant H5 HA/H1N1 virus has been genetically engineered in the laboratory.26

An avian-human reassortant H5N1 virus possessing the HA protein from an H5N1 virus and 7 remaining gene segments from a 2009 pandemic H1N1 virus has been generated by investigators at the University of Wisconsin, Madison. In receptor-binding studies and animal experiments, a derivative of this reassortant virus was identified that possessed 4 mutations in its HA protein. The mutant H5 HA reassortant virus was shown to be capable of respiratory droplet transmission in ferrets. The FVR recognizes that the pathogenicity of reassortant viruses is difficult to predict and depends upon the gene constellation. However, the generation of this hybrid virus suggests that any influenza virus strain possessing an HA gene from the Goose/ Guangdong/1/96 lineage could potentially pose a severe threat to public health, even if it were not fully of HPAI H5N1 origin.

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The creation of an avian-human reassortant H5 HA/H1N1 virus is of special concern since the 1957 and 1968 influenza pandemics were caused by avian-human reassortant viruses, H2N2 and H3N2, respectively, and the H1N1 virus responsible for the 2009 swine flu outbreak had an unusual mix of swine, avian and human influenza genetic sequences. While the 1957 (H2N2) and 1968 (H2N2) pandemic human influenza viruses arose through reassortment between human and avian viruses, the influenza virus that caused the 1918 Spanish flu pandemic appears to be entirely derived from an avian source. Reconstructed replication competent forms of the 1918 H1N1 pandemic influenza virus containing any portion of the coding regions of all 8 gene segments (1918 Influenza virus) are designated HHS select agents. Given the known potential of avian-human reassortant viruses to cause pandemics, the deliberate creation of an avian-human reassortant H5 HA/H1N1 virus is foolhardy and irresponsible. Indeed, the existence of avian-human reassortant H5N1 viruses possessing the HA protein from an H5N1 virus and 7 remaining gene segments from a 2009 pandemic virus has the potential to pose a unique threat to public health and safety.

3. Are there any other HPAI H5N1 influenza strains that have been identified to pose a severe threat to public health and safety?

NO, not as far as we are aware.

The FVR notes that certain other highly pathogenic H5 (and H7) viruses have caused outbreaks in poultry in Japan (2005), Mexico (1994), Italy (1997), and the U.S. (1983). The H5N2 outbreak in Ibaraki prefecture in Japan is the first reported case of H5N2 from chickens to infect humans. Low pathogenic avian influenza H5N2 viruses in poultry gained accentuated virulence in the U.S. and Mexico, leading to a highly pathogenic strain that caused the 1983 outbreak in Pennsylvania. However, none of these H5N2 viruses have become zoonotic or caused lethal infections in humans.

In 2003, The Netherlands reported 83 confirmed cases of human H7N7 avian influenza virus infections among poultry workers and their families. The majority developed minor symptoms only. However, there was one lethal infection. A 57-year-old veterinarian who visited one of the affected farms died of acute respiratory distress syndrome (ARDS) and related complications from H7N7 infection.

4. Should these viruses be regulated as HHS select agents?

YES and NO.

Regulating HPAI H5N1 viruses as HHS select agents for the purposes of gain-of-function research is crucial and would represent an important first step in the right direction. For less risky diagnostics research with naturally occurring HPAI H5N1 strains, these viruses need not be regulated as HHS select agents.

The FVR does not believe that naturally occurring, circulating strains of wild-type H5N1 viruses in Southeast Asia and other endemic regions should be regulated as HHS select agents. This is because naturally occurring wild-type strains are already out there, and because it is crucial to collect and analyze natural isolates of these viruses, as well as other viruses that could contain the HA from the Goose/Guangdong/1/96 lineage.

We support countries in Southeast Asia and around the world in their efforts to increase surveillance of circulating H5N1 strains and we believe that as few barriers as possible should be put in the way of critical diagnostics work conducted to inform public health officials and alert them to pandemic threats.

The FVR considers that live attenuated influenza virus (LAIV) strains should be exempted from regulation as HHS select agents. As few hurdles as possible should be put in the way of vaccine manufacturers’ efforts to conduct research that would allow them to rapidly characterize H5N1 strains with pandemic potential and develop matching vaccines or improve existing vaccines. In addition to being able to rapidly develop LAIV vaccines to respond to public health emergencies, vaccine companies must be able to develop and test investigational LAIV pre-pandemic vaccines for future contingency needs. We note that reverse genetics technology allows vaccine makers to remove the virulence factor of influenza viruses by depleting amino acids from the cleavage site of the HA protein of HPAI H5N1 virus strains, and thereby rapidly produce attenuated vaccine strains, thus accelerating vaccine production. Reverse genetics is particularly useful in the development of H5N1 pandemic vaccines because the process does not require manufacturers to work directly with highly infectious or pathogenic H5N1 strains, rather only with segments of the virus’s genome. Vaccine strains of H5 and other subtypes (H6, H7, H9 and H2) have consistently retained the attenuated phenotype.\(^{29,30,31,32}\)

However, the regulatory landscape for vaccine manufacturers risks becoming more confusing unless the CDC coordinates policy with the USDA. In the meantime, the FVR considers that attenuated strains of HPAI H5N1 viruses used in the manufacture of live attenuated influenza virus (LAIV) vaccines should be exempted from regulation as HHS select agents. Designating all H5N1 strains as select agents could delay or complicate the ability of vaccine manufacturers to rapidly respond to a public health emergency and develop, manufacture and deliver LAIV vaccines to meet public health needs during a pandemic.

**By contrast, the FVR considers that HPAI H5N1 viruses should be regulated as HHS select agents for the purposes of laboratory experiments designed to increase transmissibility, pathogenicity and/or alter the host range of H5N1 viruses.** We consider that this so-called “gain-of-function” research is inherently unsafe and not worth the risk. This type of research should be tightly regulated if is allowed to resume and additional safety precautions taken to minimize the risk of an accident.

**Rationale**

Designating HPAI H5N1 viruses as HHS select agents for the purposes of gain-of-function research to increase pathogenicity, transmissibility and/or alter the host range of these viruses that could result in mammalian transmissible H5N1 viruses of pandemic potential would be consistent with adding reconstructed replication competent forms of the 1918 H1N1 pandemic influenza virus containing any portion of the coding regions of all 8 gene segments of the 1918 influenza virus to the list of HHS select agents.

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In October 2005, the CDC added reconstructed replication competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all 8 gene segments to the list of HHS select agents and toxins.\textsuperscript{33} The CDC took this action for several reasons. First, the pandemic influenza virus of 1918-19 killed up to 50 million people worldwide, including an estimated 675,000 deaths in the United States. Also, the complete coding sequence for the 1918 pandemic influenza A H1N1 virus had been identified, which would make it possible for those with knowledge of reverse genetics to reconstruct this virus. In addition, the first published study on a reconstructed 1918 pandemic influenza virus demonstrated the high virulence of this virus in cell culture, embryonated eggs, and in mice relative to other human influenza viruses. The CDC correctly determined that reconstructed replication competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all eight gene segments have the potential to pose a severe threat to public health and safety.

\textbf{The creation of human transmissible HPAI H5N1 strains has the potential to pose an equal or even greater threat to public health and safety than a reconstructed 1918 H1N1 pandemic influenza virus.} Designating HPAI H5N1 viruses as HHS select agents for the purposes of gain-of-function research would send a powerful message that special precautions (safety and containment measures) must be taken.

Designating HPAI H5N1 viruses as HHS select agents for the purposes of gain-of-function research would increase the regulation and oversight of laboratories engaged in conducting these experiments. It would also serve to remind investigators of the dangers and reinforce the need for special training of laboratory workers, and the need to take special precautions. Laboratory workers routinely underestimate the risks associated with laboratory research. Indeed, laboratory workers have a false sense of security, according to a new international laboratory safety survey conducted by the University of California, Los Angeles.\textsuperscript{34} In the UCLA study, the first and largest survey of scientists' attitudes and behavior towards laboratory safety, some 86% of the approximately 2,400 scientists who responded said that they believed their laboratories were safe places to work. Yet just under half of these laboratory workers reported experiencing a wide range of accidents in the laboratory, and large fractions noted frequent lone working, unreported injuries and insufficient safety training on specific hazards.

5. **If these viruses should be regulated as HHS select agents, should these viruses be designated as Tier 1 select agents?**

YES and NO.

Naturally occurring strains of wild-type H5N1 viruses in Southeast Asia and other endemic regions need not be regulated as Tier 1 select agents, for the reasons stated in answer to the previous question. In the same way, live attenuated influenza virus (LAIV) strains developed by vaccine manufacturers need not be regulated as Tier 1 agents for the reasons stated in answer to the same question.

However, HPAI H5N1 viruses should definitely be regulated as Tier 1 select agents for the purposes of gain-of-function research to increase transmissibility, pathogenicity and/or alter the host range of H5N1 viruses. The FVR considers that this type of research is inherently dangerous and should be tightly regulated if it is allowed to resume. Moreover, given the extremely high risks and the global consequences of an accidental release of a mutated H5N1 virus, the FVR considers that it is imperative that additional safety precautions are taken in order to mitigate such risks.

Rationale
In the absence of internationally agreed guidelines for minimum laboratory safety standards under which HPAI H5N1 gain-of-function research could be allowed to resume, the lack of a consensus on other conditions under which this research could be allowed to resume, and the lack of an independent formal risk-benefit assessment, the FVR is of the opinion that HPAI H5N1 viruses should be designated as HHS Tier 1 select agents for the purposes of gain-of-function research.

The regulation of HPAI H5N1 viruses as Tier 1 select agents for this type of research would have the effect of reducing the number of laboratories able to embark upon this type of research. Limiting the number of laboratories doing this dangerous work is in the public interest. If HPAI H5N1 gain-of-function experiments are allowed to resume and it becomes “legitimate” to mutate a deadly virus we will see an explosion in this type of research. There are many more avian than human influenza viruses. If this controversial work is allowed to continue, more laboratories will become involved and the risk of an accidental release of a mutated H5N1 virus increases exponentially.

Proponents of this research overlook the inconvenient truth that laboratory accidents do happen. These accidents include laboratory-acquired infections and the accidental releases of pathogens into the community. One needs look no further than the re-emergence of the H1N1 virus in 1977, after a 20-year hiatus. A group of US scientists investigating the 1977 outbreak concluded that it leaked out of a Russian lab that was working on a live-attenuated H1N1 virus vaccine. We are of the opinion that an accident is less likely to happen if HPAI H5N1 viruses are regulated as HHS Tier 1 select agents for the purposes of the gain-of-function experiments that lie at the heart of the controversy.

Designating HPAI H5N1 viruses as HHS Tier 1 select agents for gain-of-function research would also align CDC regulations more closely with U.S. Department of Agriculture (USDA) regulations. The USDA already regulates HPAI viruses as select agents.35 The USDA requires BSL-3 containment plus enhancements for work with HPAI viruses in the laboratory, ABSL-3 with enhancement when working with animals in negative pressure animal isolators, and BSL-3 Ag containment when working with loose-housed animals. BSL-3 and ABSL-3 containment plus enhancements and BSL-3 Ag provide appropriate protection of workers and the environment for work with HPAI H5N1 strains in the laboratory. We consider that even BSL-3 Ag containment provides insufficient protection of workers and the public for HPAI H5N1 gain-of-function experiments to produce modified HPAI H5N1 viruses capable of being transmitted from human to human.

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35 Low pathogenic strains of avian influenza virus are excluded from the USDA select agent list. Reconstructed replication competent forms of the 1918 H1N1 pandemic influenza virus containing any portion of the coding regions of all eight gene segments (Reconstructed 1918 Influenza virus) are already included on the HHS select agent list.
Designating HPAI H5N1 viruses as HHS Tier 1 select agents for gain-of-function research would also align CDC regulations more closely with Canadian and UK requirements for this type of research. In the UK and Canada, HPAI H5N1 gain-of-function research must be conducted in BSL-4 facilities.

6. Should special precautions (i.e., safety and containment measures) be considered when working with diagnostic specimens suspected of containing HPAI H5N1 influenza viruses containing the HA from the Goose/Guangdong/1/96 lineage (i.e., any precautions versus none at all, precautions beyond those usual for clinical samples and/or laboratory microbes, etc.)?

YES and NO.

The FVR considers that special precautions (safety and containment measures) should always be taken when working with a deadly pathogen that has a potential mortality rate among humans of nearly 60%. This applies to diagnostic work with specimens collected in the wild and clinical samples suspected of containing HPAI H5N1 influenza viruses containing the HA from the Goose/Guangdong/1/96 lineage, as well as basic research to investigate the molecular structure of such viruses, pathogenesis, viral evolution, host immune responses, and adaptation to the host, etc.

Regarding diagnostics work, diagnostic laboratories play a critical role in the early detection of an outbreak. Such laboratories are typically equipped to operate at biosafety level-2 (BSL-2) and are staffed by technicians who are properly trained to work at this containment level. The FVR shares the view of the American Biological Safety Association (ABSAA) that clinical samples suspected of containing HPAI H5N1 viruses of this lineage can be safely handled at an enhanced BSL-2 level, which includes performing all open container work and aerosol-producing procedures in a Class II biological safety cabinet. The FVR notes that very few diagnostic laboratories in developing countries operate at an enhanced BSL-2 level, and that a special effort should be made to help upgrade diagnostic laboratories in H5N1 endemic countries to enhanced BSL-2.

For the purposes of basic research with HPAI H5N1 influenza viruses, the FVR would defer to biosafety experts who are more qualified to assess the risks associated with the proposed line of research.

Regarding gain-of-function experiments to increase transmissibility, pathogenicity and/or alter the host range of H5N1 viruses, the FVR considers that this work should only be performed in highest biocontainment level laboratories. The FVR is of the opinion that experiments to increase the transmissibility of HPAI H5N1 viruses should only be performed in BSL-4 laboratories and, crucially, should not be performed in BSL-3 or even BSL-3 Enhanced facilities.

7. Should special precautions (i.e., safety and containment measures) be considered when working with strains of HPAI containing the HA from the Goose/Guangdong/1/96 lineage that have been shown to be transmissible between mammals beyond those recommended for non-mammalian transmissible HPAI (Ref 13 and Ref 14)?

YES.

We consider that research with strains of HPAI H5N1 viruses that have been shown to be transmissible between mammals, as well as gain-of-function experiments designed to modify HPAI H5N1 viruses by genetic manipulation and/or by forced evolution to produce strains that could become transmissible between mammals, should only be performed, if at all, under the highest biocontainment level, BSL-4.

Moreover, the number of labs authorized to do this research, if it is to be authorized at all, should be restricted to 1 or 2 labs where special precautions beyond BSL-4 should be taken. The argument advanced by proponents of this research that BSL-4 is no safer than BSL-3 or BSL-3 Enhanced ignores the crucial fact that there are few BSL-4 facilities but thousands of BSL-3 facilities. If it becomes "legitimate" to mutate a deadly virus we will see an explosion in this type of research. There are many more avian than human influenza viruses. Moreover, there are reports that groups are poised to conduct similar gain-of-function experiments with the SARS coronavirus. Indeed such experiments may already be underway. If more labs are going to be involved, the risk of an accidental release increases exponentially. Restriction to BSL-4 would de facto reduce the number of labs able to conduct this research and thereby reduce the risk of an accident, even if BSL-4 and BSL-3 facilities have comparable rates of lab-acquired infections or releases per lab.

For these reasons, we believe that the "push down" to BSL-3 by proponents of this research should be resisted. We note again that HPAI H5N1 gain-of-function experiments can only be conducted in BSL-4 facilities in the UK and Canada. We also note that there is no appetite for conducting HPAI H5N1 gain-of-function studies in Japan at this time, whether in BSL-3 or BSL-4, because of public aversion to high-risk research. We further note that there was no consensus during a recent RAC committee meeting on HPAI H5N1 gain-of-function research regarding the biocontainment level for this type of research, nor on the special precautions that should be taken.

Conclusion
1. HPAI H5N1 viruses pose a unique threat to public health and safety if they were to become as easily transmitted from human to human as seasonal influenza due to a unique combination of factors: 1) exceptionally high human virulence and pathogenicity, 2) potentially high human-to-human transmissibility, 3) nonexistence of mammalian-transmissible H5N1 strains in the wild, 4) lack of immunity to HPAI H5N1 viruses in the general population, 5) lack of adequate control measures to contain the spread once it is established, 6) incomplete protection of current H5N1 vaccines (if available), and 7) limited effectiveness and limited window to administer antiviral drugs (if available).

37 According to R. Fouchier, as reported in Science, March 1, 2013, a lab in China that has stayed under the radar has likely resumed its work on H5N1 transmissibility. Chen Hualan and colleagues at the Harbin Veterinary Research Institute published a paper in 2009, co-authored by Y. Kawaoka, that homed in on mutations that made the H5N1 virus more transmissible in guinea pigs. Fouchier said a new paper by the same group had recently been submitted to a journal. Fouchier added that he planned to expand his H5N1 transmission studies and would be conducting experiments to see whether other avian influenza subtypes, such as H7N7, could become airborne as well. Fouchier said he had also applied for an E.U. grant to do similar studies in the coronavirus family, including the SARS virus, which caused a fast-moving global outbreak in 2003.

38 The Recombinant DNA Advisory Committee (RAC) held a meeting on January 24, 2013, at which there was no consensus on the containment level or special precautions that should be taken for H5N1 gain-of-function research.
2. No other pathogen has this unique combination of risks, not Ebola, variola major virus, *Bacillus anthracis*, *Yersinia pestis*, or SARS coronavirus, all of which are already classified as HHS Tier 1 select agents. An engineered HPAI H5N1 virus capable of sustained human-to-human transmission has greater pandemic potential than any other HHS select agent, including reconstructed replication competent forms of the 1918 H1N1 pandemic influenza virus. An avian-human reassortant H5N1 virus possessing the HA protein from an H5N1 virus and 7 remaining gene segments from a 2009 pandemic H1N1 virus has the potential to pose an immediate threat to public health and safety.

3. The CDC and other regulatory authorities must consider the global consequences of a laboratory-acquired infection or accidental release of a human-transmissible HPAI H5N1 virus and do everything possible to mitigate that risk. Designating HPAI H5N1 viruses as HHS Tier 1 select agents for the purposes of gain-of-function research would be a first step in the right direction.

4. Designating HPAI H5N1 viruses as HHS Tier 1 select agents for the purposes of gain-of-function research would align CDC regulations more closely with USDA regulations, as well as with Canadian and UK regulations.

5. There are other areas of influenza research that are more promising; have greater practical value and the potential to yield greater knowledge than HPAI H5N1 gain-of-function research to increase the transmissibility, pathogenicity and/or alter the host range of these viruses. The search for a universal influenza vaccine that has the potential to protect against multiple influenza strains, including H5N1 and other strains with pandemic potential, should be prioritized.

6. We question the ethics, the morality, and the fundamental wisdom of creating a pathogen more lethal than exists in nature.

7. Internationally agreed guidelines for the regulation and oversight of such research should be put in place and a consensus developed as to the conditions under which the research could be allowed to resume.

8. There needs to be a broader, truly international discussion on the wisdom, safety and the consequences of this type of research. This discussion, which has so far not taken place, should involve experts from all fields of the life sciences and other stakeholders, including civil society, and should focus on the scientific, social and ethical advisability of pursuing biomedical research that aims to create pathogens more lethal than exist in nature – and on the consequences of succeeding.

These remarks have been framed in a U.S.-based context. The recent report that HPAI H5N1 gain-of-function research is being funded and performed in other countries\(^\text{39}\) that are beyond the reach and unaffected by U.S. government review, regulation and oversight is a development that emphasizes the urgency of working openly with other nations to address the pros and cons of the gain-of-function approach in microbial research. In this context, the Foundation considers that the international discussion that has been called for by U.S. government and other groups has just begun. In the absence of an imminent threat, it would be wise to consult more fully with other countries and reach an international consensus before resuming funding of H5N1 gain-of-function research.

The Foundation would like to thank the CDC for soliciting information and public comment on this issue and extending the deadline for comment. We appreciate the opportunity to provide comment.

Sincerely,

[Signature]

Professor Simon Wain-Hobson, D.Phil.
Board Chair
The Foundation for Vaccine Research

[Signature]

Peter Hale
Executive Director
The Foundation for Vaccine Research

[Signature]

Professor Robert May
Former Chief Scientific Officer to the Prime Minister and UK Government (1995-2000); Former President of the Royal Society (2000-2005)
SELECT AGENTS AND TOXINS
Updated January 7, 2013

The following biological agents and toxins have been determined to have the potential to pose a severe threat to both human and animal health, to plant health, or to animal and plant products. An attenuated strain of a select agent or an inactive form of a select toxin may be excluded from the requirements of the Select Agent Regulations.

HHS SELECT AGENTS AND TOXINS
Abrin
Botulinum neurotoxins*
Botulinum neurotoxin producing species of Clostridium*
Conotoxins (Short, paralytic alpha conotoxins containing the following amino acid sequence X(CX$_2$PACGX)$_3$X$_3$X$_3$X$_3$(CX$_7$))
Coxiella burnetii
Crimean-Congo haemorrhagic fever virus
Diacetoxyscirpenol
Eastern Equine Encephalitis virus¹
Ebola virus*
Francisella tularensis*
Lassa fever virus
Lujo virus
Marburg virus*
Monkeypox virus¹
Reconstructed replication competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all eight gene segments (Reconstructed 1918 Influenza virus)
Ricin
Rickettsia prowazekii
SARS-associated coronavirus (SARS-CoV)
Saxitoxin
South American Haemorrhagic Fever viruses:
Chapare
Guanarito
Junin
Machupo
Sabia
Staphylococcal enterotoxins A,B,C,D,E subtypes
T-2 toxin
Tetrodotoxin
Tick-borne encephalitis complex (flavi) viruses:
Far Eastern subtype
Siberian subtype
Kyasanur Forest disease virus
Omsk hemorrhagic fever virus
Variola major virus (Smallpox virus)*
Variola minor virus (Alastrim)*
Yersinia pestis*

*Denotes Tier 1 agent

¹ National Select Agents Registry, Updated January 7, 2013.
OVERLAP SELECT AGENTS AND TOXINS

*Bacillus anthracis*  
*Brucella abortus*  
*Brucella melitensis*  
*Brucella suis*  
*Burkholderia mallei*  
*Burkholderia pseudomallei*  
Hendra virus  
Nipah virus  
Rift Valley fever virus  
Venezuelan equine encephalitis virus

USDA SELECT AGENTS AND TOXINS

African horse sickness virus  
African swine fever virus  
Avian influenza virus  
Classical swine fever virus  
Foot-and-mouth disease virus*  
Goat pox virus  
Lumpy skin disease virus  
*Mycoplasma capricolum*  
*Mycoplasma mycoides*  
Newcastle disease virus*  
Peste des petits ruminants virus  
Rinderpest virus*  
Sheep pox virus  
Swine vesicular disease virus