Subject: NSABB Public Comment

Dear NSABB:
I am writing to express my deep concerns about the gain-of-function research that has been conducted by Ron Fouchier, Yoshihiro Kawaoka, and other senior influenza researchers.

I have a longstanding interest in influenza research and vaccine design, and I am one of the co-founders of the Influenza Genome Sequencing Project, an NIAID-funded effort that has sequenced over 10,000 isolates since 2004. I have published scientific papers on the flu virus (Ghedin et al., Nature (2005), 1162) as well as commentaries (see my 2008 Nature commentary).

Gain-of-function research on the flu has created new, dangerous strains that would never occur in nature. There is no evidence that these provide any benefit in predicting the natural evolution of the flu, help to design vaccines, or aid surveillance in any way. Fouchier and colleagues have made arguments that amount to little more than hand waving, such as "this will aid our understanding of the flu." Bluntly speaking, that is nonsense.

I write a widely-read column at Forbes magazine and have just recently posted an article expressing my opposition to gain of function research (Forbes 10/20/2014). I wrote about it a year ago as well (Forbes 8/8/2013), in a piece that now has over 50,000 views.

As I wrote in my Forbes column, we have enough problems simply keeping up with the current flu outbreaks - and now with Ebola - without scientists creating incredibly deadly new viruses that might accidentally escape their labs. Fouchier and Kawaoka's research hasn't changed our ability to respond to a pandemic, not even slightly. Nor has it changed our strategy for vaccine design - and I can't see that it ever will.

Gain-of-function research on viruses is both dangerous and irresponsible. The benefits are minimal if not zero. (And note that I am strongly in favor of investing in research on better treatments for influenza and other viruses, as well as better surveillance.) I strongly support a permanent ban on this research. Please shut it down and keep it shut down.
Sincerely,
Steven Salzberg

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Subject**:** NSABB Public Comment

Dear Madame or Sir:

I am writing to express my personal and professional concerns about ongoing "Gain of Function" (GOF) experimentation performed by some academic researchers in the USA and internationally.

As a practicing epidemiologist with 30 years of experience in disease management and infection control, I understand the powerful forces that nature brings to bear on all of us. The public health community must constantly be on guard for novel, emerging infectious agents, or mutated agents capable of causing pandemics. Recent examples of these include the H1N1 swine influenza pandemic, emergence of MERS, and ongoing outbreak from the Ebola virus.

The rationale for performing GOF experiments on dangerous pathogens including avian influenza types H5N1 and H7N9 is weak at best. Researchers say that this will inform the scientific community about specific genetic mutations to be vigilant against; however, nature itself is the world's largest laboratory, and the odds of creating a mutation in the lab that will be identical to a natural mutation are vanishingly small.

Other reasons given for GOF research (scientific curiosity etc.) are hollow, since the risk of accidental release of a mutated pathogen into society far outweighs any insights we might obtain from this experimental work. The funding would be better spent on field surveillance for emergence of dangerous pathogens in animal and human hosts, research for a "universal" influenza vaccine, and improved vaccination of vulnerable populations. Humanity cannot afford to have a lab-originated pandemic occur when we have enough problems with naturally occurring emergent pathogens.

Therefore, I support ongoing efforts of the NIH to suspend funding for GOF experimentation until all of the scientific, ethical, and safety issues can be thoroughly discussed in an open forum. As a Charter Member of the Cambridge Working Group, I support Dr. Marc Lipsitch and my colleagues in their work to inform the public about the true risks of GOF research and evaluate the safety of these procedures.

Thank you for your consideration of my statement, and I wish you well in your upcoming deliberations.

Sincerely,

Charles Stack, MPH

DrPH Candidate

Estelle Goldstein Memorial Scholar

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Healthcare/Public Health Deputy Sector Chief for Chicago Infragard (nominee) http://chicagoinfragard.org/

Charter Member, Cambridge Working Group http://www.cambridgeworkinggroup.org/

Certified Leader

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President, Board of Directors

AIM Center for Independent Living

NSABB Meeting

November 25, 2014 --- 11:00am to 1:00pm

Written public comment submitted by

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Our written comment for the meeting of the NSABB is submitted in the form of an article that has been accepted for publication in *mBio*, the flagship journal of the American Society for Microbiology. It consists of 15 pages including this cover.

Moratorium on Research Intended to Create Novel Potential Pandemic Pathogens

ACCEPTED MANUSCRIPT TO APPEAR in mBio

Marc Lipsitch 1 and Thomas V. Inglesby 2

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ABSTRACT: We applaud the US government's funding pause on gain---of---function experiments that create potential pandemic pathogens while deliberation about risks and benefits of such experiments occurs. The risks of some such experiments, which create transmissible strains of highly virulent influenza strains, are so large that a quantitative risk assessment will almost certainly find them unacceptably high. Other types of experiments covered by the moratorium may have different risk profiles. We discuss benefit assessment and emphasize the need for weighing concrete benefits of portfolios of approaches excluding and including PPP experiments against the unique risk of PPP experiments. Other risks, including biosecurity risks in general, and biosafety risks of experiments on coronaviruses and experiments to enhance pathogenicity, should also be quantified. The US plays a leadership role as funder of much of the PPP research at the moment and must seek significant international input to arrive at appropriate policy decisions.

MAIN TEXT

Research on highly pathogenic organisms is crucial for medicine and public health, and we strongly support it. This work creates a foundation of new knowledge that provides critical insights around the world's most deadly infectious diseases, and it can lay groundwork for the future development of new

Almost all such research can be performed in ways that pose negligible or no risk of epidemic or global spread of a novel pathogen. However, research that aims to create new potential pandemic pathogens (PPP)[1] – novel microbes that combine likely human virulence with likely efficient transmission in humans ------ is an exception to that rule.

While this research represents a tiny portion of the experimental work done in infectious disease research, it poses extraordinary potential risks to the public.

Experiments that create the possibility of initiating a pandemic should be subject to a rigorous quantitative risk assessment and a search for safer alternatives *before* they are approved or performed. Yet a rigorous and transparent risk assessment process for this work has not yet been established. This is why we support the recently---announced moratorium on funding new "gain---of---function" experiments that enhance mammalian transmissibility or virulence in SARS, MERS and influenza viruses. This realm of work roughly corresponds with the work we have termed PPP above. Because the term "gain of function" in other contexts can be used to describe techniques of scientific research that have nothing to do with the creation of novel potential pandemic pathogens, we think the term can be too broad and can mislead. Throughout this commentary we focus on research designed to create PPP strains of influenza, the type of research that initially attracted attention leading to the moratorium and for which the most discussion has already occurred. Other types of gain---of---function research on influenza, and studies intended to enhance pathogenicity or transmissibility of MERS and SARS coronaviruses, may or may not fit the definition of PPP research that we established, and further clarification is needed and ongoing. As we discuss near the end of this article, it will be essential to clarify the different risks and benefits entailed by different types of experiments covered by the funding pause.[2]

The purpose of this research funding pause is to complete "a robust and broad deliberative process…that results in the adoption of a new US government gain---of--- function research policy"[3]. The moratorium would stop new funding for:

"research projects that may be reasonably anticipated to confer attributes to influenza, MERS, or SARS viruses such that the virus would have enhanced pathogenicity and/or transmissibility in mammals via the respiratory route. The research funding pause would not apply to characterization or testing of naturally occurring influenza, MERS, and SARS viruses, unless the tests are reasonably anticipated to increase transmissibility and/or pathogenicity."[3]

The new US government policy also encourages the currently---funded US government and non---government research community to join in adopting a voluntary pause on research that meets this gain of function definition. Some 18 NIH research projects have been identified that possibly meet that definition[2].

The moratorium does not apply to the larger infectious disease research portfolio supported by the US government. The announced moratorium does not affect disease surveillance or vaccine development programs. During the moratorium, a deliberative process will occur that will be led by the National Science Advisory Board for Biosecurity and the National Academy of Sciences. This process is intended to produce "recommendations for risk mitigation, potential courses of action in light of this assessment, and propose methodologies for the objective and rigorous assessment of risks and potential benefits that might be applied to the approval and conduct of individual experiments or classes of experiments." [3]

In this commentary, we discuss key elements of risk analysis and offer an example of an approach that could be taken. We describe benefit analysis, offering an account of the kinds of benefits that are relevant and our own view of those at this point. We note other factors that are important to consider. And we argue that a moratorium is the right approach until a rigorous, objective and credible risk assessment process can be established.

RISK ANALYSIS

Risk assessment for GOF work should be quantitative, objective, and credible. Extensive qualitative arguments have been made on both sides of this issue, and these arguments have not provided sufficient clarity or evidence to resolve concerns or identify a consensus path forward. Quantitative assessments should now be performed so as to provide specific calculations and information to inform decisions. It is also important for these risk assessments to be objective. Given the stakes in this process, the risk assessment process should be directed by those without a clear personal stake in the outcome. Just as peer review of science is performed by those without a direct stake in the outcome, so too should these risk assessments be performed in the same way. The credibility of the risk assessment will depend both on the rigor of the quantitative process and the perceived objectivity of the process.

The record of laboratory incidents and accidental infections in biosafety level 3 (BSL3) laboratories provides a starting point for quantifying risk. Concentrating on the generation of transmissible variants of avian influenza, we provide an illustrative calculation of the sort that would be performed in greater detail in a fuller risk analysis. Previous publications have suggested similar approaches to this problem.[1, 4]

Insurers and risk analysts define risk as the product of probability times

consequence. Data on the probability of a laboratory---associated infection in US BSL3 labs using Select Agents show that 4 infections have been observed over < 2,044 laboratory---years of observation, indicating at least a 0.2% chance of a laboratory---acquired infection[5] per BSL3 laboratory---year. An alternative data source is from the intramural BSL3 labs at the National Institutes of Allergy and Infectious Diseases (NIAID), which report in a slightly different way – 3 accidental infections in 634,500 person---hours of work between 1982 and 2003, or about 1 accidental infection for every 100 full time person---years (2000 hours) of work.[6]

Risk Analysis continued

A simulation model of an accidental infection of a laboratory worker with a transmissible influenza strain estimated about a 10---20% risk that such an infection would escape control and spread widely.[7] Alternative estimates from simple models range from about 5% to 60%. Multiplying Probability of an accidental laboratory---acquired infection per lab---year (0.2%) or full---time worker---year (1%)

X

Probability the infection leads to global spread (5%---60%)

provides an estimate that work with a novel, transmissible form of influenza carries a risk of between 0.01% and 0.1% per laboratory---year of creating a pandemic, using the Select Agent data, or between 0.05% and 0.6% per full---time worker---year using the NIAID data.

Readily transmissible influenza, once widespread, has never before been controlled before it spreads globally, and influenza pandemics historically have infected about 24--- 38% of the world's population[8, 9]. The case---fatality ratio of a novel strain is of course unpredictable. The worst case might be a case---fatality ratio similar to that of avian H5N1 influenza in people, which approaches 60%.[10] A greatly attenuated version of the same virus might have a case---fatality ratio of "only" 1%.

Again, multiplying

Pandemic attack rate (24%---38%) X

Global population (~7 billion) X

Case---fatality ratio (1%---60%)

would produce an estimate of between 2 million and 1.4 billion fatalities from a pandemic of a highly virulent influenza strain.

Putting all these numbers together, the Select Agent data suggest that a laboratory---year of experimentation on virulent, transmissible influenza might have an 0.01%---0.1% chance of killing 2 million---1.4 billion, or an expected death toll of 2000---1.4 million fatalities per BSL3---laboratory---year. From the NIAID data, for each full---time person---year of BSL---3 work we might expect a toll of between 10,000 and over 10 million.

Risk Analysis continued

These numbers should be discussed, challenged, and modified to fit the particularities of specific types of PPP experiments. For creation of novel, transmissible, virulent influenza strains, they may overstate the risk for the following reasons: 1) most work is done in BSL3+, which may be safer than BSL3; 2) control measures, including vaccination and antiviral prophylaxis of laboratory workers, might reduce the risk of infection and of spread, although none of these is perfect; 3) the human case---fatality ratio of an avian influenza strain that gains transmissibility could be below 1%; 4) transmissibility in laboratory animals does not necessarily indicate transmissibility in humans[11, 12]; 5) novel strategies of molecular biocontainment[13], if employed, might reduce the risk of human transmission of a strain used in transmission experiments in other mammals.

On the other hand, these numbers may understate the risk because 1) the Select Agents calculation includes in its numerator only BSL3 labs, but in the denominator BSL3 as well as BSL2 and BSL4 "registered entities" as separate figures for BSL3 are not publicly available[5]; 2) the rate of accidents is calculated for US labs, while GOF experiments are performed in many countries; if this work expands to some of the many countries with less stringent standards than the US[14], risks could be higher; 3) the costs of an accidental pandemic considered here are deaths only, but additional losses would include scientific credibility, nonfatal health outcomes, economic and educational losses, etc.

The illustrative calculations above show that approximate risk estimates are possible for creation of PPP strains of influenza. During the deliberative process initiated with this moratorium, the risk assessment approach that is established should be able to provide calculations that reflect these and other available probability and consequence estimates and take into account the range of modifying factors including those just described. The risk assessment process should also be able to provide calculations related to PPP experiments where the risks are harder to calculate given more limited data, such as enhancement

of coronavirus pathogenicity in small mammals.

BENEFIT ANALYSIS

On the surface, analyzing the benefits of PPP experimentation would seem more difficult. In the cumulative process of knowledge acquisition that is science, it is hard to see far ahead where a particular type of research may lead. On the other hand, scientists make judgments about the relative merits of experimental approaches on a daily basis in their roles as investigators and grant reviewers. Doing and funding science is a process of severe winnowing (especially severe in today's tight funding climate) in which we choose to pursue one approach and not to pursue others based on judgments of which approaches are expected to have lowest cost, highest probability of success, and greatest yield of valuable findings, among other considerations. Implicit in this process is the idea of opportunity cost. In prioritizing the week's or the year's research work, we do not judge in isolation whether a particular experiment should be done or not done. We decide how to allocate our time and funding among possible approaches, devoting resources to the portfolio of efforts that seems most promising. Similar prioritizations are made by funders when they decide which kinds of research will be funded, and which research will not.

The analysis of benefits of PPP experiments should follow this familiar approach. The choice is not: do PPP experiments or do nothing. Rather, the appropriate question is: within a portfolio of scientific and public health activities designed to understand and combat influenza or a coronavirus (or, perhaps, a broader subset of infectious diseases),
what are the benefits of including PPP approaches compared to the benefits of expanding other parts of the portfolio to use the resources in another way? From the perspective of public health and the practical goal of preventing and treating flu, alternative approaches include those which, like PPP experiments, seek to enhance our scientific understanding of biology, pathogenesis and transmission. Alternatives also include efforts to develop treatments and prevention measures, including surveillance, through means other than improving our basic biological understanding of influenza.[4] This approach is shown graphically in Figure 1, which also depicts the risks of PPP research. Such risks should be weighed against the risks of alternatives, which are typically much smaller or even negligible. Figure 1 embodies the idea PPP research should be a component of our research portfolio only if devoting resources to PPP studies at the expense of alternatives has net benefits that outweigh the unique risks of PPP studies.

This comparative approach to benefits should be informed by a hardnosed look at the benefits that are readily achievable by PPP experiments, not to hypothetical outcomes that could someday lead to unspecified benefits. We acknowledge the possibility that PPP experiments may lead to benefits we cannot today envision. But so could the experiments that are done in their place if support for PPP is reallocated to other scientific approaches. The possibility of unanticipated benefits is surely a reason to do science, but it is not a reason to favor PPP approaches over others, unless some specific case can be made for the unique yet unanticipated benefits of PPP work. Such a case seems hard to imagine for benefits that are by assumption unanticipated.

Benefit Analysis continued

For example, it has been suggested that mutations or phenotypes identified through PPP experiments could be used to sort through the massive diversity of nonhuman influenza strains to prioritize those that should trigger countermeasures, including pre--- pandemic vaccine manufacturing. While this might be is possible in principle, there are many practical barriers to achieving public health benefits of this sort from PPP studies.[15] Lists of mutations, and even phenotypes, associated with PPP studies, can be compiled and compared against isolates of influenza from birds and other nonhuman sources[16]. We know that these lists are unreliable and can even be misleading: the mutations in hemagglutinin identified by two prominent PPP experiments on H5N1 do not reliably confer human receptor specificity even on other H5N1 viruses[17]. The E627K mutation in the PB2 gene, known as a virulence and transmissibility determinant before GoF experiments[16, 18, 19], found repeatedly in GoF experiments in H5N1[20, 21], and used for pandemic risk assessment in H7 viruses[16], was found in some isolates of the H1N1pdm strain in 2009, leading to concern about possible increased virulence and transmissibility. Yet it conferred neither trait in this genetic background.[22]

At the present time, the high levels of epistasis – dependence of phenotype on the genetic background on which a mutation is found – make prediction of pandemic risk for any given strain more of an art than a science. Indeed, the very presumption that we will see human cases of an incipient pandemic before that pandemic occurs has never been met in practice[23]: we have never observed zoonotic cases of any flu virus before it caused a pandemic. This is not to deny that PPP experiments provide any useful data for surveillance and prioritization. Rather, it is to say that other approaches can also identify such predictors (as in the case of the PB2 mutation[11, 13, 14]) and that the ability to use markers of putative transmissibility or virulence to make reliable predictions remains far in the future.[23] The fact that some analysts consider mutations identified in PPP

experiments when assessing threats of viruses found in surveillance does not mean that the use of such mutations improves the predictions, a claim for which we have no evidence because no pandemic strain has ever been identified in advance. The analysis of benefits of PPP creation should reflect this state of science.

According to some proponents, the most valuable scientific finding of experiments to make ferret---transmissible mutants of influenza A/H5N1 is the definitive proof that such variants could be produced with a small number of mutations. This could not be definitively proven without doing the PPP experiment to manufacture a potentially pandemic variant of H5N1[24]. While it is now undeniable that a ferret---transmissible mutants of influenza A/H5N1 can be created experimentally, the impact on scientific opinion about the risk of a pandemic from H5N1 has been hard to gauge. Prior to the gain---of---function experiments there was a wide range of expert opinion on the likelihood of an H5N1 pandemic [25]. Some influenza experts questioned whether H5N1 was a major pandemic threat. After the publication of the experiments producing potentially pandemic H5N1, one prominent member of this group, Peter Palese, noted the shortcomings of the ferret model for humans and correctly concluded that the question of whether H5N1 can transmit efficiently in people remains unsettled[26], as it must until the phenomenon is directly observed in nature. From a practical perspective, responsible policy makers and public health leaders should have been planning for the possibility of H5N1 pandemic before PPP experiments on H5N1 were undertaken. In some countries of the world they were making stockpiling vaccines against H5N1[27, 28] and making plans for nonpharmaceutical [8] interventions in the event of a pandemic. The same remains true after the experiments. We have observed no discernible influence of the H5N1 PPP experiments on H5N1 policy preparations.

CALCULATING OTHER FACTORS

During the moratorium, progress should also be made in calculating the risks associated with potential deliberate misuse of PPP strains and with potential deliberate misuse of the information that is created and published following PPP experimental work. This calculation should take into account the possibility of deliberate theft and dissemination by either persons working within a lab or theft by those outside the lab. While the probability of this is likely to be very low for most scientists and most laboratories, it is not zero. There is precedent of scientists using pathogens from their own labs to cause harm. And as with potential accidents, while the probability may be very low, the consequences could be very high.

This assessment should also take into account the possibility that scientists may deliberately misuse the knowledge gained and published following the

experiments by recreating the novel PPP strains in another laboratory using methods from published papers and then purposefully disseminating it. This possibility is typically dismissed out of hand by many scientists. But before dismissing that possibility, an analysis by an assembly of experts in the best position to make that judgment should be conducted. What is the possibility that individuals or groups who would seek to carry out such an act would develop the capacity and skill to carry it out? Given that once knowledge is published, it will be available forever, these questions are not just about the possibility of this happening in today's world, but also anytime in the future. Despite the inherent uncertainties in trying to answer these questions, they should be answered with the best possible expertise.

Similarly, the moratorium should be used as a time to answer, or at least be addressing, another major issue as well: the international approach to funding, authorizing and overseeing PPP. An accident or deliberate act involving PPP anywhere in the world could conceivably impact the public around the world. Therefore, the community of nations has an abiding interest to set common rules for how this work will be pursued. However at this point, few countries have begun any kind of deliberative process on an approach to research with these unique dangers. Country X should have the right to know if this work is going on in Country Y, and if yes, what is being done to ensure it is done with the greatest safety and security. But currently, the way Country X finds out about PPP work being done elsewhere in the world is when it is published in a science journal. Given the prestige that some scientists have received for pursuing PPP research, it would be surprising if scientists from countries around the world did not increasingly pursue it. As comparatively less experienced labs decided to pursue this work, this will increase potential dangers.

A MORATORIUM IS THE RIGHT STEP

There are prominent scientists who agree that there are potential serious dangers to this work and agree that a risk assessment process is needed, but who are opposed to a moratorium being imposed while such a the risk assessment process is undertaken.

They believe that a moratorium should be avoided for reasons that include the potential damage it can do to the funding and work of that lab, as well as to the careers of those involved in the work.

We have a different view. A substantial number of scientists agree there are extraordinary potential consequences of the work.[15] There is no rigorous, objective, credible risk assessment process to judge the risks and benefits of proceeding with it. We believe that the responsible course is to take a research

pause until such a risk assessment process is established which creates a stronger basis for decisions and actions. This is not solely a scientific issue. It is a scientific, public health and safety issue, and it is an issue where the public itself has an abiding interest.

We have no interest in stopping scientists from doing their work or preventing laboratories from receiving funding. The narrow and defined area of GOF research intended to create novel potential pandemic strains should be put on pause until the risk assessment process is completed. The same laboratories and scientists whose work has been stopped by the moratorium are free and able to pursue all other avenues of infectious disease research except for that narrowly defined by the GOF definition in the new policy; to the extent that other activities not meeting the narrow definition in the pause have been included in letters to principal investigators ordering or requesting work stoppage, the boundaries of the funding pause should be quickly clarified to allow important alternative work on flu to continue. We note that there are over 250 NIH---funded projects listed as active with titles containing MERS, SARS, coronavirus, or influenza[29] of which 18 have been affected by the funding pause. The number that remain on pause may be further reduced by negotiations between investigators and the NIH that are now underway that will define which projects truly are within the scope of

the moratorium vs. those that do not meet its terms and can resume.

The character and scope of the risk assessments that are applied is important. To establish methodologies and approaches for risk assessment and risk mitigation for this context, it would be valuable to start with a global assessment of the risks and benefits of this realm of research, identifying the common aspects of risk and benefit within PPP experiments and other approaches covered in the funding pause. For example, any risk assessment should include estimates of the probabilities of accidental infection and extensive spread, as well as estimates of the impacts of these events should they occur. The specific values of these estimated parameters will differ for different types of experiments. It will then be necessary to set standards and expectations for the quality and characteristics of risk---benefit assessments for individual experiments, for example to distinguish coronavirus research from influenza research, enhancements of pathogenicity from enhancements of transmissibility, and other important distinctions. Given that the term “risk assessment” is used to mean different things by different people, an agreement on an approach to individual risk assessments would be needed to ensure rigor and credibility. Once this kind of analytic structure is established, individual risk assessments on GOF experiments that meet the definition in the new USG policy[3] should become the norm before such experiments are funded. Crucially, this process should be quantitative, rather than relying on unquantified and unverifiable assurances that particular laboratories are safe.

CONCLUSIONS

The results of this risk assessment process are not only important to the US Government

------ which had been a major funder of PPP experiments ------ but also to other funders, regulators, and investigators worldwide who consider such experiments. Our support for the funding pause and associated deliberative process does not indicate that we would support a permanent end to all experiments subject to the pause. There may be research endeavors that are subject to the moratorium that have a risk---benefit profile sufficiently favorable to justify their resumption, once risks and benefits have been explicitly set forth. After two years of debate, we think the balance is evidently unfavorable for experiments to enhance avian influenza transmissibility, but other classes of experiments may be different. In the meantime, the moratorium is an appropriate and responsible step while dedicated and rigorous efforts are made to understand the risks and benefits of this work.

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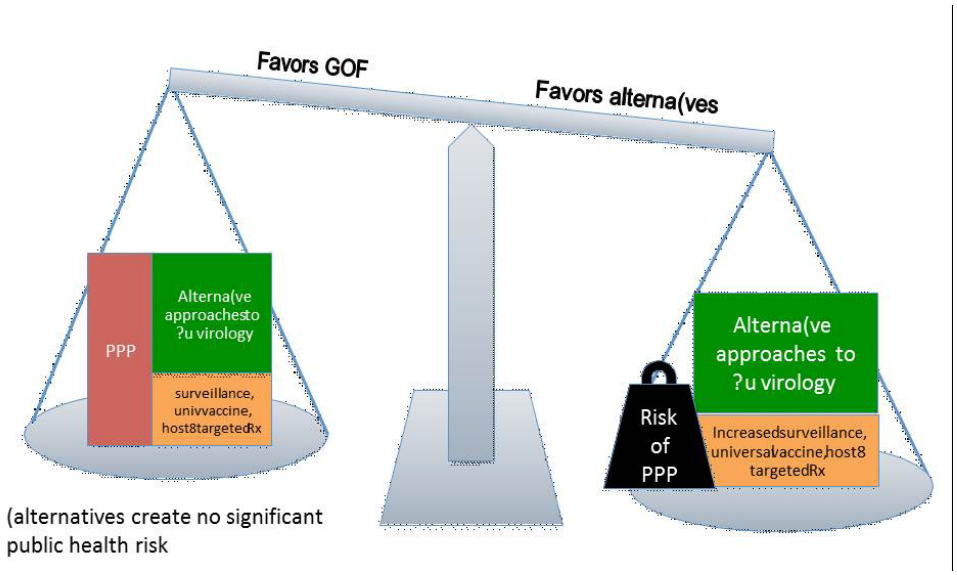

FIGURE: Weighing risks and benefits. The benefits (squares) of spending a fixed quantity of resources on a portfolio of activities including PPP research (red), other approaches to influenza virology (green), and other public health activities to defeat influenza (yellow), should be weighed against the benefits a portfolio in which the other activities are expanded to use the resources freed by not supporting PPP activities, reflecting the opportunity cost of the PPP research. If there are net benefits to including PPP activities in the portfolio, then they should be weighed against the net risks created by PPP experiments, which in the case of influenza transmissibility enhancement we have argued (see main text, RISK ANALYSIS) are exceptionally high. The balance may differ for other activities, but this comparison of benefits of portfolios with and without gain--of-- function experiments is the appropriate comparison, with any net benefits weighed against net risks.

The Vagueness and Costs of the Pause on Gain-of-Function (GOF) Experiments on Pathogens with pandemic potential including influenza virus

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Since the spring of 2012 there has been a raging controversy in scientific circles on the wisdom of carrying out so called 'gain-of-function' (GOF) experiments with pathogens of pandemic potential (PPP) such as influenza virus [1]. Although the phrase 'GOF' has been much criticized because of its inexactness, the terminology has been adopted by many including the media to mean experiments where the result is a change in virulence or host tropism for a PPP. The nugget of the debate is a disagreement over the practical value of such experiments relative to the information that they produce with opponents arguing that risk, whether from intentional release or, more likely, laboratory accidents, outweighs any knowledge gained [1]. Some anti- and pro-GOF experiment proponents have organized themselves into two camps known as the Cambridge Working Group (CWG, (http://www.cambridgeworkinggroup.org/)and Scientists for Science (SFS, http://www.scientistsforscience.org/), respectively, that have issued statements. However, these groups are heterogeneous and their members have varied views on the problem. Both authors have signed the CWG statement and one author (MJI) has also co- signed the SFS statement because both authors see important benefits for GOF work involving PPP, are nonetheless concerned about safety issues, and most importantly strongly support the common call for discussion. However, neither author has supported the idea of a moratorium on this type of research [1, 2].

In October 2014, the White House announced that the US Government (USG) was implementing a "pause" of new funding for research involving GOF experiments with three respiratory viruses, influenza virus, MERS coronavirus, and SARS coronavirus, if that research could be "reasonably anticipated" to result in enhanced pathogenicity or increased transmissibility (http://www.whitehouse.gov/blog/2014/10/17/doing-diligence-assess-risks-and-benefits-life-sciences-gain-function-research). They also asked that ongoing experiments which fall into this category be voluntarily stopped. During the pause, the USG has asked both the National Science Advisory Board for Biosecurity (NSABB) and the National Academies to engage in discussions aimed at how to assess the risks and benefits of GOF research. We ourselves have been calling for such deliberations and welcome that aspect of the White House announcement [1]. The events at the CDC this summer, in which a highly pathogenic avian influenza strain was accidentally shipped to a USDA lab, and in which *B. anthracis* spores were taken out of a lab without proper disinfection, heightened concern both in the scientific community and in the public about whether research with dangerous pathogens is being carried out with appropriate safety measure in place. These accidents, together with a growing chorus of scientists who are worried about GOF experiments [3], seem to have precipitated the government action.

Pauses and moratoriums are blunt instruments in science and carry the potential for

unintended consequences. We recognize that the pause is a response from well-meaning government officials who are tasked with trying to find ways to minimize potential dangers from GOF experiments. We note, however, that depending on what interruption of work is counted, this is at least the third pause/moratorium in this field with the first being voluntary, the second requested by the USG [4, 5], and the third being the current 'pause'. We have numerous concerns with this third stoppage that include the timing of the announcement relative to the ongoing debate, the vagueness in the wording of the statement, and the potential effects on the fields of influenza virus and coronavirus research. Each concern will be discussed separately.

The timing of this 'pause' is perplexing given that one might have expected this action to follow a concerted effort to explore the issues rather than to precede detailed discussions. Many have drawn the analogy between the current situation and that surrounding the advent of recombinant DNA technologies. However, there are significant differences: the discussions at Asilomar preceded a self-imposed moratorium by molecular biologists working on recombinant DNA technology [6]. It seems that this should have been the case now: the NSABB could have been deliberating on this topic in the two years that have passed since the GOF debate began with the publication of the two manuscripts describing mammalian transmission of H5N1 influenza virus [7, 8]. Instead, it did not even meet and this created a vacuum of discussion that may have contributed to the current crisis. In contrast, the government has responded to the heightened controversy by reactivating the NSABB while simultaneously calling for a pause of GOF work before a meaningful discussion. Although this course of action seems to emphasize safety and caution, it carries significant risks that we will discuss below. It is also unclear to us why the pause is necessary given that the government is already presumably providing an extra layer of review of GOF experiments that followed the prior moratoriums (http://www.phe.gov/s3/dualuse/Documents/us-policy-durc-032812.pdf) and has asked institutions to do the same (http://www.phe.gov/s3/dualuse/Documents/durc-policy.pdf).

We are concerned that the wording of the pause is vague and could have unintended consequences. First, the pause has no end date. Will the NSABB and the Academies be nimble enough to make concrete recommendations that are broadly acceptable within months? Given the pace at which these committees generally function we worry that this will not be the case.

Having the pause drag on for too long will not only affect research progress, but also the careers of the scientists engaged in that research. Second, we worry about the meaning of "reasonably anticipated." Obviously this phrase is very subjective, and similar wording in the definition of dual use research of concern (DURC) has already made assessments of what constitutes DURC very problematic for journals and

authors [9]. At one extreme cautious researchers could over interpret the vague wording and stop experiments that were not intended for inclusion in the pause order. For example, albeit somewhat extreme, any time one grows an RNA virus in the laboratory, even in cell culture, the error prone nature of the viral RNA polymerase results in each progeny genome containing more or less one mutation. Any scientist versed in RNA virus biology could 'reasonably anticipate' some of these mutations would impose a gain of function on the virus. However, if one does not select for that function, it is extremely unlikely that that mutant will overtake the population. We therefore suggest that the intent of the experiment must be considered before making a determination of whether it should be paused.

The pause will almost certainly have a disruptive effect on several laboratories at a time when information derived from GOF experiments is beginning to bear fruit in pandemic preparedness. In this issue of *mBio*, Stacey Schultz-Cherry and colleagues describe how mutational information from GOF is producing actionable information on surveillance studies and selection of strains for vaccines (insert ref). The pause means that some information from GOF experiments will cease to become available, with potential negative consequences on preparedness. Ongoing experiments will stop and the vagueness of the wording raises the possibility that other work will not be done due to an abundance of caution. For example, there is tremendous need for rodent models of coronaviruses with pandemic potential including the agents responsible for MERS and SARS. Such models could greatly facilitate the discovery of new drugs and vaccines. However, developing such models requires changing the host tropism of the virus and as such they fall under experiments of concern despite the fact that human viruses often lose virulence as they adapt to other species. The current pause affects two dozen studies that include experiments to develop rodent models of coronavirus research [10]. In this regard, the reader may want to listen to a story on National Public Radio in which researchers discuss how the pause is affecting coronavirus research (http://www.npr.org/blogs/health/2014/11/07/361219361/how-a-tilt-toward-safety-stopped-a- scientists-virus-research).The inclusion of this work is an example of how pauses and moratoriums can be blunt instruments with major unintended consequences.

Finally, we worry that work being carried out by graduate students and postdoctoral fellows will be put on hiatus, causing disruption to their plans for completing their training. Although some will argue that this is a small price to pay for ensuring safety, we worry that this could have a tremendous effect downstream as investigators may be discouraged from resuming such studies in the future. Furthermore, bright young scientists who have a choice of what research to pursue may avoid this area of investigation because of its controversy, unpredictability, and increased restrictions. Research output is not like a factory line that can be shut down and re- started depending on supply and demand. Instead research output is dependent on the presence of ongoing projects by dedicated scientists who carried them out in good faith, hoping to generate useful information. When students and postdoctoral fellows stop such projects they inevitably move to other problems and it may be difficult to jump start GOF experiments once laboratories cease doing that type of work. As such, we are more concerned about pausing ongoing projects than delaying the start of new lines of investigation. Given that a healthy research enterprise is humanity's best defense against future threats from these respiratory pathogens, the pause could hurt future progress by discouraging the best and the brightest from joining this field. Hence, this pause, which is presumably intended to safeguard society from laboratory accidents and unintentional releases, could have the paradoxical effect of leaving humanity more vulnerable to future pandemics by virtue of the information that was not obtained.

As we have written previously, understanding the pathogenicity of these viruses is necessary if we want to develop new therapies and vaccines, and ensure useful surveillance [1, 2]. Clearly, the research must be performed under biocontainment conditions that minimize the risk of accidental release. The discussion that the White House is asking for must occur because the status quo is not acceptable. We call on the government to provide clarity regarding what truly should be paused and for how long. We call on the NSABB and the NAS to move rapidly on this issue, to consider whether the current biosafety practices put in place after the prior moratoriums are sufficient, and if found to be so, to state so without a need for new layers of mandates for what is already a highly supervised field. To repeat ourselves [1], we must get this right.

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RE: Gain of Function Pause and Implications for Coronavirus Animal Model Development

To NSABB members,

As virologists engaged in genetic studies of coronavirus replication, pathogenesis, evolution, receptor recognition, adaptation, and vaccine and therapeutic interventions, we express our profound concerns regarding the recent US Government directive to "*temporarily halt all new funding for experiments that seek to study MERS-CoV and SARS-CoV using gain of function strategies that might increase pathogenesis and transmissibility in mammals"*. The term, "gain of function" (GOF)" has become so broadly over-used and encompassing that it now poses a serious risk to block development of new public health intervention strategies to combat the ongoing MERS-CoV outbreak. Additionally, this decision will significantly inhibit our capacity to respond quickly and effectively to future outbreaks of SARS-like or MERS-like coronaviruses, which continue to circulate in bat populations and camels. To our disappointment, the recent NSAAB meeting (Oct 22) which was called to initiate a deliberative process toward a standardized policy on GOF studies did not include a single nationally or internationally recognized coronavirologist, especially one who regularly performs genetic studies on SARS-CoV and MERS-CoV. Rather, the initial meeting focused almost exclusively on the risks – and much less so on the benefits - of "gain of function" (GOF) transmission studies of influenza viruses. The inclusion of SARS-CoV and MERS-CoV, as best we can glean, is based on the pandemic potential and respiratory transmission of the natural isolates and fails to recognize the substantial biological differences that exist between myxoviruses and coronaviruses***.*** We would note that studies to enhance transmissibility have never been conducted using a coronavirus. ***In fact, model systems to perform such studies in coronaviruses <u>do not exist</u>.***

We would like to present several experimentally-validated positions that document: 1) the ongoing emergence and high mortality of the MERS-CoV without a vaccine or therapeutic; 2) no transmission models for SARS-CoV or MERS-CoV; 3) critical need for animal models and lack of safe alternatives to animal testing for emerging coronavirus therapeutic and vaccine design; and 4) the benefits of the few GOF related studies that have been performed using MERS-CoV and SARS-CoV. All of these will be highly negatively impacted if not aborted by a pause on MERS-CoV and SARS-CoV research, to the great detriment of global health preparedness.

1. **Emerging coronaviruses in nature do not observe a mandated pause.** Phylogenetic studies supports the hypothesis that all currently known Human CoVs have emerged in the past ~800 years. Since 2003, three new emerging coronaviruses have circulated the globe – 2 human and one mammalian: Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV; 2003), Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV; 2012) and Porcine Epidemic Diarrhea Virus (PEDV; 2012). Since 2012, PEDV has caused millions of deaths in young piglets to the detriment to the US porcine industry. SARS-CoV had every characteristic of a pandemic virus. Fortunately it was controlled by aggressive public health interventions. However, that success was highly likely predicated on the fortuitous presence of biological vulnerabilities of SARS-CoV: a low R0 and a requirement for symptomatic disease for transmission (Fraser PNAS 2004). Any confidence in the elimination of risk for future SARS-like CoV outbreaks is not well supported. In fact, recent studies demonstrate the existence of heterologous bat strains of a SARS-like CoV that are capable of using human receptors for docking and entry (Ge et al., Nature 2013). Thus the threat of a SARS-CoV or SARS-like virus still exists and is it unknown if existing public health or medical countermeasures would control disease outcomes or the pandemic potential of these heterologous isolates.

MERS-CoV, in contrast to SARS-CoV, poses an ongoing serious risk to US and global public health. MERS-CoV was initially identified in April 2012, and approximately 929 documented infections and 372 deaths have been reported in 23 countries, including the United States (proMed Mail.org). Of great concern, the pace of new cases once again is increasing and mortality remains ~40%. Dromedary camels and bats are thought to represent intermediate and primary hosts, respectively. It is possible that human infections have occurred for years, since camel sera from the early 1990's neutralize human MERS-CoV strains. Millions of dromedary camels are distributed widely from equatorial Western and Northern Africa through the Middle East. These camels are also traded across the globe. Camel-to-human and human-human transmission has been repeatedly documented during the outbreak. Thus it is likely that sporadic disease has occurred for years in Africa and the Middle East. In severe cases, MERS-CoV infection results in acute respiratory distress syndrome (ARDS), a clinically challenging severe end stage lung disease resulting in mortality rates of 30-50%. Importantly, milder illness and subclinical infections have also been identified and asymptomatic spread also appears to occur in human populations. Thus the MERS CoV outbreak has all of the features that made SARS-CoV so formidable in 2003, important additional features that complicate control and termination of the epidemic, specifically ongoing camel-human transmission and lower level infections with human-human transmission. *These features demonstrate the significant pandemic potential of MERS-CoV and argue that investment in diagnostics, basic research, vaccine design, and therapeutic testing is critical to prevent significant economic losses, and importantly, continued human morbidity and mortality worldwide.*

2. Transmission models have never been developed for SARS-CoV and MERS-CoV. In fact, MERS-CoV does not replicate in mice, guinea pigs and ferrets. The block in MERS-CoV replication is robust, driven by sequence differences that impede spike-receptor interactions and the presence of a glycosylation site which presents a large bulky carbohydrate moiety at the virus receptor binding interface, preventing binding and entry (Cockrell A, 2013, JV). Attempts to adapt by passage or engineer by structure-guided redesign have failed to isolate MERS-CoV host range mutants in multiple laboratories. If developed, the significant differences in primary sequence and carbohydrate presentation seen in the mouse, ferret, guinea pig DPP4 virus-receptor binding interface, which are substantially different in the human DPP4 receptor, will select for mutants that gain animal DPP4 usage while losing significant affinity for the human DPP4 receptor, attenuating pathogenesis. ***Thus, the classic flu transmission model systems which use identical receptor moieties across mammalian species simply don't exist for MERS-CoV.*** SARS-CoV does not replicate in the guinea pig, and replication in the ferret is limited, resulting in minimal disease phenotypes. SARS- CoV binding to the ferret angiotensin 1 converting enzyme 2 receptor (ACE2) is weak, requiring adaptive changes to enhance replication efficiency in this species. While it is possible to select for virus mutants that could use the ferret receptor more efficiently, human receptor usage will likely suffer substantially in these ferret adapted viruses. Moreover, passage experiments have not been reported, because research laboratories have focused their studies in the mouse model, which more accurately and faithfully reproduces the human disease condition (see below). In addition, no one has reported or attempted to develop a SARS-CoV transmission model.

3. A critical need for MERS-CoV animal model development. *Mouse adaptation of human viruses is a common practice, viewed safe as these viruses oftentimes replicate less efficiently in human cells.* For instance, we note that the mouse adapted influenza PR8 strain is fully attenuated, and won't revert even after repeated passage in humans (Beare and Hall, 1971; Beare A et al., 1975). The US government directive halts all animal virus passage studies with influenza, MERS-CoV, and SARS-CoV, including in mice. Unlike influenza, the science behind emerging CoV inclusion has never

been openly discussed or debated in an open forum. Therefore, this decision is potentially dangerous and likely based on misinformation, especially troubling in light of the ongoing epidemic and complete lack of therapeutics and vaccines for MERS-CoV. The development of drugs and vaccines require robust small and large animal models of human disease. Further, the FDA will likely apply a three animal rule for the emergency use of drugs and vaccines in an outbreak setting for any newly emerging coronavirus. Please note the following facts:

i) Lack of robust animal models for MERS-CoV disease. In the current MERS-CoV models, which include various primate species and camels, infection severity is limited and the

disease outcomes do not reflect clinical disease seen in severe human infections, e.g., those at most risk for fatal disease outcomes. Mortality in these animals is very low and some models like the marmoset do not appear reproducible across laboratories, and acquiring these rare animals is difficult. MERS-CoV does not replicate in mice, hamsters, ferrets or guinea pigs or any other readily affordable and malleable small animal model species. High-throughput drug and vaccine testing is seriously constrained in primates or camels, because of ethical concerns, lack of facilities for large animal testing, and cost, so most candidate therapies are sitting on a shelf and not being evaluated. ***Thus, mouse models represent the only viable alternative.*** Mouse models under development include mice transduced with Adenovirus vectors encoding the DPP4 receptor, or transgenic mouse lines; (Perlman, 2014) however these models appear to support virus replication without serious clinical disease and do not replicate the end stage lung disease ARDS phenotypes reported in human populations. Vector and transgene induced inflammation further complicate immune readouts as well.

ii) In vivo passage is essential to the development of robust, safe, small animal models of MERS-CoV human disease. Many human and animal respiratory viruses have been adapted to mice. This requires iterative passage to select for multiple mutations that afford alternative species receptor usage, increased virus replication, increased yields/cell and enhance severe clinical disease outcomes. In SARS-CoV, 6-9 mutations are selected in 4-5 genes; the spike glycoprotein receptor binding domain mutations in combination with 2 or more other mutations regulate lethal outcomes (Roberts et al., 2006). Critically, ***no evidence link coronavirus in vivo mouse passage with increased human ris***k. These outcomes also reflect well-described results in many virus systems that serial passage in one species usually attenuates virus pathogenesis in the original species. Mice infected with wildtype or mouse-adapted SARS-CoV do not transmit these viruses to co-housed naive animals. In fact, serial passage in alternative hosts is an accepted strategy that has been widely used to attenuate many human viruses, resulting in live-attenuated viruses that have saved hundreds of millions of lives since the late 1950's.

ii) Mouse adaptation of SARS-CoV. Based on the new criteria for GOF outlined in the US Government directive, three gain of function experiments have been performed with SARS-CoV since 2003 and none have been performed with MERS-CoV***.*** Wildtype SARS-CoV replicates poorly and does not produce clinical disease or pathology in mice. Doubly-inactivated, vectored and recombinant protein vaccines provide robust protection in this model ( ). However, two groups have shown that serial *in vivo* passage rapidly selects for mouse-adapted strains that produce more severe clinical disease and death in young mice, and ARDS and death in aged mice. In aged mice, the LD_{50} drops significantly and disease vulnerabilities and outcomes phenocopy those seen in aged human populations.

Correlates of protection are key metrics used in vaccine development and therapeutics must effectively reduce peak virus titers seen in human patients. Importantly, these correlates can vary depending on virus replication efficacy and the severity of

disease pathology noted in humans and in animals. For example, correlates needed to reduce virus titers from 10^5 to 10^3 or 10^8 to 10^6 (two logs) might be substantially different. Vaccines can also elicit protective or pathogenic responses, which can only be identified using animal models. Thus, robust animal models are key to human health.

4. SARS-CoV and MERS-CoV Gain of Function Experiments. Based on influenza virus transmission studies, the underlying assumption appears to be that all GOF studies pose grave public health risk. This represents a very negative over-simplification of a classical, critical and essential genetic approach to defining pathogenesis, virulence, and mechanisms of therapeutic and vaccine efficacy. This is particularly the case for coronaviruses.

Implications in model development. Importantly, vectored and doubly inactivated vaccines work well in virus replication mouse models, but fail to protect against the lethal challenges, especially in aged immunosenescent animals that recapitulate severe lung pathologies. More seriously, doubly inactivated vaccines induced a Th2 immune pathology associated with massive influxes in the numbers of eosinophils and neutrophils; effectively causing a gain in virus pathogenic potential in an unpredictable manner (Bolles et al., 2012). The resulting increased immune pathology can sometimes progress to fatal disease and similar findings have been reported in primates. Thus under the most literal interpretation, experiments to unravel mechanism must cease immediately and be subject to review. If in vitro correlates of protection (e.g., neutralization titers, T cell responses, etc.) and minimal animal models are used to justify human vaccine use, the surprising outcome would have been that the existing data would have supported the use of doubly inactivated vaccines in human populations, potentially enhancing serious disease outcomes and death in a SARS outbreak setting. This revelation was absolutely dependent on the availability of a robust animal model of human disease. In a second example, Deng X, et al 2013 used GOF approaches to re-engineer an alphavirus, sindbis virus, to express the SARS-CoV papain like protease, designing a safer BSL2 virus surrogate pathogenesis model for rapid drug screening. Insertion of the SARS gene into sindbis attenuated pathogenesis in wildtype but not especially designed mutant mice. Sindbis causes systemic disease, viremia, and replicates in multiple organs but is most tropic for the brain and CNS. SARS-CoV is a pneumoenteric pathogen. Under identical conditions, drugs that were highly efficacious in the surrogate model, failed to protect animals from lethal SARS-CoV challenge (PMC4178736). Thus, results in surrogate models should be evaluated cautiously.

ii) Zoonotic SARS-CoV. Emerging viruses exist in swarms of highly heterologous but related viruses, thus, future outbreaks could be derived from other precursor strains which are antigenically and genetically distinct. Antigenic variation could obviate the potency and efficacy of SARS-CoV vaccines and immunotherapeutics or erode the therapeutic potency of antiviral drugs. To address this issue, the spike glycoproteins of several zoonotic SARS like viruses (e.g., civet, raccoon dog and bat) have been incorporated into the wildtype SARS

molecular clone, producing chimeric viruses that encode natural variation in the S glycoprotein (PMC1933338, PMC2588415, PMC3977350, PMID:24172901). These recombinants can use the human, bat and civet receptor, some produce lethal disease with ARDS in aged mice, and demonstrate a 5-100+ fold reduction in neutralization by sera targeting the epidemic SARS-CoV S glycoprotein. Vaccines using the SARS S glycoprotein do not protect against lethal heterologous spike challenge, especially in aged animals; thus, current SARS vaccines will fail to protect against these precursor strains should they seed future outbreaks. In fact, the doubly inactivated vaccines don't protect but do stimulate the Th2 immune pathology noted above (PMC3209347). Similarily, one strain appears resistant to the existing panel of broadly neutralizing human monoclonal antibodies. It should be noted that none of these strains are transmissible in the mouse and most replicate poorly in primary human airway epithelial cells. For surveillance and the development of public health intervention platforms, these data have huge implications, demonstrating that existing vaccines require reformulation. These outcomes could not have been predicted from in silico sequence information, biochemical assays, neutralization assays with surrogate viruses or surrogate in vivo models of human disease. Animal models can lie, however, their reliability is oftentimes directly proportional to their capacity to replicate human disease.

Lack of Safe Alternatives to Animal Testing. Concerns around influenza virus transmissibility studies have now encompassed any gain of function study performed with certain high path viruses in mammals. Various groups have suggested that "ethical" and safer alternative approaches exist that provide equivalent information in the absence of risk. These include the use of pseudotyped defective viruses, recombinant protein biochemical assays, and dynamic modeling of biological processes. These approaches are not robust surrogates of disease models. For example, we note that virus particles breathe, thus some immune epitopes are quaternary in design and are only formed in intact virus particles (PMC4178732). Essentially their existence is entirely dependent on the conformational ensemble that exists in a mature virus preparation, not necessarily in pseudotypes or in recombinant proteins (PMC3358852; PMC4136251). Thus, neutralization and biochemical assays using pseudotype particles or recombinant proteins can provide misinformation. While vaccine and therapeutic potential can be predicted using biochemical assays, dynamic modeling simulations and in vitro neutralization assays and T cell killing assays, these studies are subject to error and protective efficacy can only be evaluated in the context of an animal model of human disease. If these animal models are not robust, correlates of protection may change or be over-interpreted as manufacturers move their products into human populations.

Expert Recommendations. ***First*** and foremost, we argue that it is premature to include the emerging coronaviruses under these restrictions, as scientific dialogue that seriously argues the biology, pros, cons, likely risks to the public, and ethics of GOF have not been discussed in a serious forum. ***Second,*** we recognize the potential dangers of transmission models and encourage open diaglog and discussion. ***Third,*** we propose that the development of a graduated system be considered that captures perceived risk as a function of the significant biological

differences that exist between viruses. As such, we note the: a) significant barriers and difficulties in developing emerging CoV transmission models (which don't yet exist); and b) differences in virus-receptor engagement and host range restrictions that would likely occur should someone actually decide to develop transmissibility models for these particular emerging coronaviruses. ***Forth,*** we note that reverse genetic approaches that employ loss of function strategies (gene inactivation/deletion) almost universally result in severe attenuation and that mouse-adapted models are key to reduced public health risk. These scientific approaches should be encouraged, not discouraged. ***Fifth,*** developing a regulatory framework that over-reaches and hampers these traditional genetic strategies are not in the public interest, as these basic studies in pathogenesis provide gateway discoveries for future treatment strategies. In the case of the emerging coronaviruses, the lack of targeted scientific discourse detracts from the credibility of the process.

We live in unprecedented times, as four highly pathogenic emerging viruses (e.g., H5N1, H7N9, MERS-CoV, Ebola) are currently circulating and causing severe disease in human and animal (PEDV) populations. Decades of research on emerging pathogens have revealed a common pattern; specifically, recurrent introductions of zoonotic strains into human populations, the emergence of mutations that promote adaptation and then transmissibility in the new host, and virus spread throughout the target populations. Influenza viruses and coronaviruses are examples of viruses that crossed and rapidly adapted to new species, resulting in high mortality and disruption of global economy. The pandemic potential of these viruses is clear, but they also are vulnerable in the early stages of an outbreak to public health intervention methods. For public health preparedness, a well- defined and rapidly implemented program of research is needed including the availability of robust small and large animal models of human disease. GOF experiments are a documented, powerful tool to understand viral pathogenic mechanisms, to attenuate virus pathogenesis, to identify new paradigms of disease causation. We are willing to participate at any level in discussions regarding this important new pathogenic human coronavirus.

Sincerely,

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Sent: Tuesday, November 25, 2014 6:26 AM

To: National Science Advisory Board for Biosecurity (NIH/OD)

Subject: NSABB Public Comment

Hello!

Some conservative back-of-the-envelope calculations might help this discussion.

If we assume there is a 1 in 10,000 chance per year of an accident occurring that results in a pandemic, and that the pandemic is typical for flu (infecting some 20% of the world's population), and has a case fatality rate of 0.05%, we get some 700 deaths per year in expectation.

Should we condone an experiment in which 700 people were expected to die per year?

Of course, some of these experiments might push the case fatality rate up by orders of magnitude. The utility of these experiments will need to be exceptional in order to justify thousands of deaths per year (in expectation).

All the best,
Andrew

--

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From: Laura H. Kahn [lkahn@Princeton.edu]

Sent: Tuesday, November 25, 2014 10:26 AM

To: National Science Advisory Board for Biosecurity (NIH/OD)

Subject: NSABB Public Comment

Attn: Carolyn Mosby

NSABB Public Comment

In 2004, the National Academy of Sciences report, "Biotechnology Research in an Age of Terrorism," listed seven "experiment of concern" in which altered microbial agents could pose significant public health risks if released from the laboratory.

The experiments include:

1. Make a vaccine ineffective
2. Confer resistance to antibiotics or antiviral agents
3. Enhance a pathogen's virulence or make a non-virulent microbe virulent.
4. Increase transmissibility of a pathogen
5. Alter the host range of a pathogen
6. Enable a pathogen's ability to evade diagnostic or detection modalities
7. Enable weaponization of a biological agent or toxin

Gain of function studies clearly fall into one or more of these categories and should not be supported by the NIH. I have written about this issue in my online column in the Bulletin of the Atomic Scientists.

Sincerely,

Laura Kahn
http://www.nap.edu/catalog/10827/biotechnology-research-in-an-age-of-terrorism The Bulletin (http://thebulletin.org/going-viral)

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