

**Comment on “Gain-of-Function Research and the Relevance to Clinical Practice”**

TO THE EDITOR—Kilianski et al [1] highlight clinical applications of gain-of-function (GOF) research on viruses and suggest that the present US government funding moratorium hinders progress in such research. Those concerned about biosafety risks of certain GOF experiments have used the term “potential pandemic pathogens” to denote the small subset of GOF research that poses a risk of widespread transmission of a highly virulent pathogen [2, 3]. The National Science Advisory Board on Biosecurity refers to this small subset as GOF research of concern (GOFROC) [4]. The funding pause, which initially covered 18 National Institutes of Health (NIH)–funded influenza virus and coronavirus projects, was reduced to 11 projects by December 2014. For comparison, a search of the NIH Reporter Database shows well over 200 projects naming influenza virus or coronaviruses in the title or abstract; thus the funding moratorium affects <5% of research on these viruses funded by the NIH.

Kilianski et al cite 5 categories of GOF research that can have clinical benefits. First they mention the development of animal models for coronaviruses. However, development of an animal model of MERS coronavirus infection was specifically removed from the funding pause [5], and SARS coronavirus GOF studies

(not designed for the development of an animal model) have been published during the pause [6] with US government funding.

Next, they mention vaccine development. While enhancement of vaccine strains to enhance production is technically a GOF, it is widely agreed to be low risk, high benefit, and not GOFROC [4]. This distinction has been noted by the Infectious Diseases Society of America, among others [7].

Next, they describe the generation of escape variants from therapeutics or immunity as a form of GOF that can be important to development of treatments or preventive measures. Such efforts may be valuable, but I am unaware of any such experiments that have been blocked by the present funding pause. Some such experiments might be risky and considered GOFROC and might pose particularly challenging test cases for risk-benefit analysis.

Finally, they cite the use of the results from GOFROC experiments to inform disease surveillance, prioritizing surveillance, and perhaps prevention and control measures for strains that show genetic changes that have been observed to confer increased transmission in ferrets during GOFROC experiments. Indeed, public health officials from the United States have indicated [8, 9] that they use the mutations identified in the noted GOFROC experiments on influenza A(H5N1) virus [10, 11] to prioritize surveillance. Given

that no pandemic of A(H5N1) influenza has occurred, there is no rigorous way to identify whether incorporating that information has improved the outcome of surveillance. Indeed, there are reasons to think that prioritizing strains showing those mutations might in some cases be misleading (Table 1). Moreover, each of the variants identified as potential risk indicators in the GOFROC experiments had previously been identified as such in safe, non-GOFROC studies by using alternative approaches [24], as shown in Table 1.

GOF is undeniably a valuable technique for microbiological research, including applied research with direct benefits for public health. This fact is accepted by most, if not all, critics of GOFROC or potential pandemic pathogen research. When weighing the benefits of GOFROC against those of alternative approaches [25], the issue is not whether GOF can be useful, which it often can be, but whether the risks of GOFROC are justified by unique benefits that cannot be achieved by safe approaches. Of the examples of public health or clinical benefits cited by Kilianski et al, some are not the result of GOFROC. Of those that are, the surveillance benefits at least can and have been achieved through alternative, safer means.

**Notes**

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**Table 1. Prior Studies That Identified Mutations of Concern That Were Later Identified in GOFROC Studies, And Exceptions to The Idea That They Are Associated With Increased Risks**

| Mutation Identified to Prompt Enhanced Concern That Was Derived From GOFROC Studies [8, 9] | Prior Studies Not Involving PPP Creation That Identified These Mutations | Exception  |
|--|--|--|
| Hemagglutinin (HA) Q222L (influenza A(H5N1) virus)   | [12–18]  | Context dependence: changes do not quantitatively shift receptor binding in related H5 influenza virus strains [18]                  |
| HA S133A, S135N, S123P, S155N  | [14, 19]   | ...  |
| HA T156A, Q222L (influenza A(H7N9) virus)  | [20, 21]   | ...  |
| Polymerase B2 subunit PB2 E627K, D701N   | [22]   | Misleading inference: both absent in 2009 pandemic influenza A(H1N1) virus [23]; could have led to its misclassification as low risk |

Abbreviations: GOFROC, gain-of-function research of concern; PPP, potential pandemic pathogen.

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## Reply to Lipsitch

TO THE EDITOR—We appreciate Lipsitch’s thoughtful comments on gain-of-function (GOF) research; however, we disagree with his general thesis that “the surveillance benefits [of GOF research] at least can and have been achieved through alternative, safer means.” On the contrary, we have found that, despite years of debate, there continues to be a lack of scientific consensus on the value and risks of GOF research. Research on each pathogen of concern requires a tailored, comprehensive assessment by experts across multiple disciplines, who consider the broad implications of conducting or curbing such research. Thus, current and future moratoria on such research should only be implemented with input and consensus from a wide spectrum of stakeholders, including the community of clinicians and other healthcare providers who are the end beneficiaries and users of such research but who have historically been underrepresented in the policy discussions on this topic.

The initial absence of broad debate on the research moratorium for highly pathogenic avian influenza virus, SARS

**Table 1. Gain-of-function definitions.**

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| 1. Gain of function as defined in the original moratorium announcement:<br>“New [US government] funding will not be released for gain-of-function 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” [5].                               |
| 2. Gain of function research as defined in the recent National Science Advisory Board for Biosecurity report:<br>“To be considered [gain-of-function research of concern], the research must, in a single step or over the course of multiple manipulations, be reasonably anticipated to generate a pathogen with both of the following attributes:<br>• The pathogen generated is likely to be highly transmissible and likely to be capable of wide and uncontrollable spread in human populations. . . .<br>• The pathogen generated is likely to be highly virulent and likely to cause significant morbidity and/or mortality in humans” [pp 41–2]. |
| 3. Not gain-of-function research of concern:<br>• Surveillance activities, including sampling and sequencing<br>• Activities associated with developing and producing vaccines, such as generation of high-growth strains<br>• Studies to characterize the virulence and transmission properties of circulating pathogens   |

Abbreviations: MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome.