

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.

<p>1. Gain of function as defined in the original moratorium announcement: “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].</p>
<p>2. Gain of function research as defined in the recent National Science Advisory Board for Biosecurity report: “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:</p> <ul style="list-style-type: none">• The pathogen generated is likely to be highly transmissible and likely to be capable of wide and uncontrollable spread in human populations. . . .• The pathogen generated is likely to be highly virulent and likely to cause significant morbidity and/or mortality in humans” [pp 41–2].
<p>3. Not gain-of-function research of concern:</p> <ul style="list-style-type: none">• Surveillance activities, including sampling and sequencing• Activities associated with developing and producing vaccines, such as generation of high-growth strains• Studies to characterize the virulence and transmission properties of circulating pathogens

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

coronavirus and Middle East respiratory syndrome coronavirus provided the key motivation for our review. Although some experiments were ultimately allowed to proceed, to date, no clear criteria have been defined for when moratoria should be placed [1, 2]. We, therefore, set out to provide an overview of the varied definitions of GOF research—updated since the publication of our review [3] (Table 1)—and an outline of its risks and benefits for the biomedical research and clinical medicine communities, as well as for society at large.

The continued ambiguity on the process of evaluating GOF research, even after years of public discussion and a final report by the National Science Advisory Board for Biosecurity [4], makes it probable that another impasse will occur in the future. Given the high likelihood that dangerous pathogens will continue to emerge, the biomedical research community requires the creation of a permanent review body that has broad representation and a transparent process of governance on the use of agents of concern to global health. Such a path forward will ensure public safety in preventing the accidental or intentional release of dangerous pathogens but also in avoiding unnecessary holds on research that could lead to important countermeasures to emerging public health threats.

Note

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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