Infectious Diseases Society of America and Gain-of-Function Experiments With Pathogens Having Pandemic Potential

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(See the review article by Kilianski, Nuzzo, and Modjarrad on pages 1364–9.)

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The rapid pace of technological advances in the life sciences has provided powerful tools for understanding and managing human-microbe interactions. These new capabilities can aid the development of vaccines, diagnostic tools, and therapeutic interventions. These same capabilities, especially the ability to manipulate genomes and, therefore, the properties of bacteria, viruses, and other infectious agents, could also pose important risks. Efforts to study and/or predict the natural evolution and emergence of pathogenic microbes by deliberately creating, in the laboratory, pathogens with enhanced disease-causing or transmission-promoting properties pose the greatest concern. Examples of this type of gain-of-function (GOF) research include the recent creation of highly pathogenic avian influenza viruses with altered host range, enhanced transmissibility, and/or the ability to evade certain forms of human immunity.

As Infectious Diseases Society of America (IDSA) members, most of whom are involved in direct patient care, research, and public health responses, we recognize that some of the same laboratories, technologies, and types of research that have given rise to concern are also essential to protect public health. Just as we have an ethical responsibility to first do no harm to our patients, we are also responsible for ensuring that we do no harm to the public, either through unnecessarily dangerous scientific experimentation or, conversely, by unduly burdening and delaying scientific work that serves essential clinical and public health purposes. This responsibility means we must identify those experiments whose potential benefits to scientific knowledge and public health clearly outweigh the risks they pose to the public and could not be achieved by safer means.

In fall 2014, the US government issued a pause of GOF research projects of concern and tasked the National Science Advisory Board for Biosecurity (NSABB), a federal advisory committee formed at the request of the US government to address issues related to biosecurity and dual use research of concern, to establish recommendations on how GOF research of concern should be assessed for its risk and benefit to public health. The NSABB recently developed a framework to guide its efforts and is working with a contractor to undertake a risk-benefit assessment (RBA) of the paused GOF projects. Given the robust public discussion about this topic, the NSABB plans to engage with stakeholders as it continues to develop its final recommendations [1–4].

In their review in this issue of The Journal of Infectious Diseases, Kilianski et al remind us of the importance of including the clinician perspective in any conversation about how best to assess the risk and benefit of GOF research [5]. Infectious diseases specialists will be among the physicians who will respond to any microbial disease outbreak and care for affected individuals, be it of natural origin or laboratory engineered through accidental or deliberate means. Infectious diseases specialists are also among those leading research efforts to counter these disease threats. Accordingly, they are especially well positioned to understand...
the risks and benefits posed by potentially
dangerous experiments involving patho-
genic microbes and can be valuable advi-
sors for those who will need to undertake
the complex RBA for GOF research.

The IDSA appreciates the NSABB’s
efforts on the GOF debate and its willing-
ness to engage with the public as it devel-
ops its final recommendations. We agree
with Kilianski et al that this effort repres-
ents a key opportunity for clinicians to
join the discussion about GOF research.
To that end, we highlight below 6 key rec-
mendations that the IDSA recently
shared with the NSABB as we discuss how
best to assess the benefits and risk of GOF
research of concern.

**FOCUS ON THE GOF
EXPERIMENTS OF SPECIAL
CONCERN**

The IDSA remains concerned that the
NSABB framework’s broad definition of
GOF research of concern may inadver-
tently capture areas of research that pose
a lower risk to the public. For example,
while the NSABB recognizes the benefit
of research aiding the development or se-
lection of new or more-effective vaccines,
its framework still targets influenza vac-
cine production methods that rely on ad-
aptation of vaccine candidate viruses for
improved growth in culture as GOF re-
search. The adaptation and manipulation
of wild-type influenza virus for growth in
eggs or mammalian cell lines is critical
to vaccine manufacturing. This approach
to producing high-growth vaccine can-
didates has been practiced since the 1940s [6,
7] and is essential to protect the public from
both seasonal and pandemic influenza.

The IDSA strongly urges the NSABB to
narrow its definition of GOF research to
be considered for risk-benefit assessment
(RBA), to avoid this inadvertent capture
of low-risk research, which is not men-
tioned in the White House Office of Sci-
ence and Technology Policy’s original
description of the types of research that
should be included in the deliberative
process. We recommend that the RBA pro-
cess focus on research that is reasonably
anticipated to result in a pathogen that
combines a high risk of transmissibility
with severe pathogenicity in humans, as
this combination poses the greatest risk
to public health. Such research may
involve enhancing one of these properties
in a pathogen already possessing the other
or simultaneously enhancing both proper-
ties. Whereas other types of GOF research
are also of concern, notably those involving
increased resistance to known medical
countermeasures, they are secondary to
the two properties described above. The
IDSA believes that this definition strikes a
balance between impeding experiments
with a lower public health risk that society
has accepted for many years while ensuring
that experiments of special concern are as-
essed appropriately.

**ADDRESS THE UNCERTAINTY IN
ESTIMATING BOTH RISK AND
BENEFIT**

The risk assessment process to be used by
the NSABB will use estimated data in the
models, as it will have to make assumptions
on both risks and benefits. Although the
IDSA understands that assumptions are
necessary to assess risk and benefit, we
urge the NSABB to hold robust discus-
sions with experts about the uncertainty
of its estimates of risk. We also recom-
pend that the NSABB ensure that any
analysis of uncertainty not only include
uncertainties in the outcome of the re-
search, such as the pathogenicity changes
in a GOF organism, but also the uncer-
tainties in the assessments of the likeli-
hood of misuse of the science, as well as
the consequences of accidents, misuse,
and regulations on the conduct of the
science. Whereas the NSABB will use a
qualitative assessment of the benefits of
GOF research, we urge that the uncer-
tainties about the benefits of research be
explicitly considered. Finally, the IDSA
recommends that the NSABB consider
communicating specific assumptions
used in its modeling as well as error due
to uncertainty to assist other policy
makers in better understanding the risk/
benefit estimates.

**SEEK A WIDE BREADTH OF
EXPERTISE TO AID IN THE RBA
PROCESS**

The NSABB has indicated that it will in-
terview subject-matter experts to obtain
additional input to aid its RBA efforts.
The IDSA strongly supports these actions
and also urges the NSABB to consider
seeking additional perspectives to inform
the RBA process, including those of a
range of experts in vaccine development,
microbial risk assessment, and public
health response; physicians whose work
is primarily clinical; and the public. In ad-
dition, the moral and ethical implications
surrounding GOF research have not been
adequately addressed in the NSABB fram-
ework [8]. Several experts in this field are
actively engaged in the GOF research de-
bate, and their unique viewpoints can be
valuable to the RBA process.

Some stakeholders have expressed con-
cern that the experts best positioned to
evaluate the risk and benefits of GOF re-
search are in some cases the ones who are
actively conducting the research. The
IDSA agrees that this potential conflict
of interest is an issue that should be con-
sidered and strongly believes that, while
this RBA evaluation needs as many ex-
pert perspectives as possible, those per-
spectives must be transparent, with all
relevant interests disclosed.

**RISK SHOULD ACCOUNT FOR THE
IMPACT ON THE PUBLIC
PERCEPTION OF SCIENCE**

One important type of risk that is not in-
cluded in the NSABB framework is the
ethical, reputational, and credibility risk
for science with the public. The recent lab-
atory mishaps at some of the nation’s
most prestigious laboratories have placed
a strain on the public’s trust for scientific
research. Should a US government–fund-
ed GOF study result in an accident or a de-
liberate act that places the public at risk,
the credibility of science as a whole may
suffer. This occurrence, in turn, could
lead the public to question the quality of
public stewardship of biomedical funding
and the reliability of scientific and medical
advice on risk. Such a loss of public trust could significantly impair science’s ability to inform evidence-based policy decisions. The IDSA recommends that the NSABB consider recruiting additional perspectives, such as those from individuals with expertise in sociology and ethics, to assess this risk, as the NSABB develops its final recommendations.

RISK SHOULD ACCOUNT FOR THE IMPACT OF ANY NEW GOF FRAMEWORK ON THE COURSE OF SCIENCE

The ability of humanity to protect itself against pathogens with pandemic potential rests on a vigorous and healthy scientific enterprise. Some, including IDSA members, have raised the concern that as controversy swirls around GOF experiments, investigators might abandon certain types of scientific approaches that are powerful tools of scientific inquiry [9]. Furthermore, the concern has been raised that the best and brightest researchers will avoid these areas of inquiry simply because of the weight of regulation, the uncertainty in planning careers in areas subject to moratoriums and increased scrutiny, and the controversial nature of the work [10]. If this happens, humanity will be more vulnerable to future threats. The IDSA recommends that the possible risk of regulation to the scientific enterprise and, in particular, to certain fields of inquiry be factored in the overall RBA.

CONSIDER RECOMMENDATIONS ON HOW TO MAKE GOF RESEARCH SAFER

In the NSABB’s assessment approach for GOF research benefit, it states that it will evaluate “other GOF experiment types” in addition to alternative approaches. The IDSA believes these efforts will yield valuable information that may be useful in developing constructive recommendations on how GOF research may be conducted more safely. For example, during the December 2014 National Academies of Science discussion on the pause in GOF research, one researcher presented data on how to engineer high-risk influenza virus strains to only generate productive infection in experimental animals, posing minimal risk to public health [11]. This search for pragmatic solutions that lower the risk of GOF has not been widely discussed, and the IDSA urges that such solutions be a more prominent component in the NSABB’s final recommendations.

The IDSA is committed to ensuring that the broader scientific and science policy community participates in efforts to guide GOF research appropriately. To complement the NSABB’s efforts, the IDSA calls for a continued series of transparent, broad discussions on GOF research and dual use research of concern among stakeholders, including scientists, healthcare workers, policy makers, ethicists, and representatives from the public. These discussions should include a consideration of RBA methods, governance models, classified research, and social responsibilities of scientists and journal editors; increased vigilance of biosafety and security concerns; and societal values. The discussions should also solicit international input. We look forward to working with the public, as well as with the US government, to ensure that GOF research of concern is conducted appropriately and only when the risk is outweighed by the benefit to public health.

Note

Potential conflicts of interest. P. R. D. was an employee and shareholder in Novartis Influenza Vaccines during the drafting of this manuscript, is a Pfizer employee and shareholder, and is listed as an inventor on multiple influenza and vaccine-related patent applications and patents. M. L. has received grants from Pfizer and Path Vaccine Solutions on vaccine modelling, A. T. P. has received royalties from Antimicrobial Therapy, honoraria from WebMD for CME materials preparation, and compensation from Biofire Diagnostics for advisory board participation. All other authors report no potential 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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