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Virology—the path forward

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ABSTRACT In the United States (US), biosafety and biosecurity oversight of research on viruses is being reappraised. Safety in virology research is paramount and oversight frameworks should be reviewed periodically. Changes should be made with care, however, to avoid impeding science that is essential for rapidly reducing and responding to pandemic threats as well as addressing more common challenges caused by infectious diseases. Decades of research uniquely positioned the US to be able to respond to the COVID-19 crisis with astounding speed, delivering life-saving vaccines within a year of identifying the virus. We should embolden and empower this strength, which is a vital part of protecting the health, economy, and security of US citizens. Herein, we offer our perspectives on priorities for revised rules governing virology research in the US.

KEYWORDS COVID-19, virology, SARS-CoV-2, oversight, biosafety, emergence

A systematic study of pathogens is the only way to assess the risks they pose and develop medical countermeasures to mitigate those threats. However, on the heels of the COVID-19 pandemic, increased concern due to the possibility that SARS-CoV-2 may have emerged from a research-related accident has hindered progress in essential pathogen research. Most viruses emerge through zoonotic spillovers from animals to people. In the case of SARS-CoV-2, multiple lines of evidence are consistent with a zoonotic origin in association with the wildlife trade (1–4). Nevertheless, and without any credible evidence, widespread speculation that SARS-CoV-2 was introduced into humans through a laboratory accident persists (5).

Heightened fears that virology research may either create or propagate viruses with disease-causing or pandemic potential have resulted in calls for restrictions on virology research. At the request of the US Government (USG), the National Science Advisory Board for Biosecurity (NSABB) developed a series of recommendations that would modify and expand existing oversight over virology research (6). We are concerned that the proposed NSABB oversight rules are not compatible with the realities of implementation, will not achieve the stated goals of increased safety or security, and will ultimately slow research progress to the overall detriment of pandemic preparedness. In the first 23 years of the 21st century, we have already been confronted with two pandemics (H1N1

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influenza virus and COVID-19) and at least four major viral outbreaks (SARS, MERS, Zika, and Ebola). Well-developed and implemented oversight in pathogen research is crucially important; however, implementation of the proposed NSABB recommendations will leave the US more vulnerable to future viral outbreaks. New oversight must not impede the scientific mission of identifying and addressing well-evidenced natural threats.

CURRENT OVERSIGHT

There is no such thing as zero risk in any endeavor, but virology research in the US functions within multiple overlapping safety systems that effectively mitigate risk. Microbes are classified into risk groups, and standard biosafety protocols designed to protect both personnel and the community are applied to each group. Oversight and governance of research at all biosafety levels are provided by Institutional Biosafety Committees (IBCs) and Environmental Health and Safety Offices (EHSO) at institutions where microbiology research is conducted. Institutions, in turn, follow federal regulation and oversight, which is administered by the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the US Department of Agriculture (USDA) (5), as examples. The federal guidelines implemented by institutional biosafety committees are described in the CDC publication *Biosafety in Microbiological and Biomedical Laboratories* (BMBL). In addition, federal law regulates institutions, facilities, and personnel performing research on select agents (biological agents and toxins determined to pose a severe threat to human, animal, or plant health) (7). Finally, biosafety is considered during the review of grant proposals and research publications. These systems work in concert to make US virology among the safest, well-regulated, and strongest in the world. Importantly, no reported external outbreak of a human or agricultural virus has resulted from a US-based laboratory in the modern era of biosafety practices. Nevertheless, there are opportunities to increase engagement from institutions, subject matter experts, and other key stakeholders to best empower science to meet existing and emerging viral threats.

Balancing important scientific objectives with ensuring the safety of experimentalists has always been a central concern of scientific research. Scientists conducting experiments in a laboratory are at the frontline of any potential risks. In virology laboratories, investigating pathogens with unknown or heightened risk of transmission or disease in humans carries enormous responsibility for the safe conduct of research. Sample collection from animals in the field requires risk mitigation measures commensurate with the greatest anticipated risk. Importantly, however, these are needs that can be readily met. Decades of research on diverse viral pathogens tell us that the risks posed by even presently unknown pathogens are highly mitigatable. As one example, all viral pathogens can be completely inactivated by standard laboratory reagents and practices, including autoclaving, bleach, or other chemical disinfectants.

THE RISKS OF ILL-SUITED POLICY TO SCIENCE AND HUMAN HEALTH

The current NSABB recommendations for revised research oversight, if adopted as proposed, could significantly and adversely affect how microbiological research is conducted in the US. As written, categorical and broad restrictions will impair this nation's ability to respond to the rapidly changing landscape of infectious disease threats. We believe that increasing oversight across virology or all microbe research would represent a misdirection of resources and would fail to provide a commensurate increase in safety or security. The proposed NSABB rules would isolate American research internationally and discourage collaborations in other countries with fewer resources to bear increased laboratory and administrative burdens. In many cases, foreign institutions will be unable or unwilling to comply with regulations designed for US institutions or those that violate their intellectual property rights, and these are not required from their American counterparts, such as providing US regulators unfettered access to laboratory notebooks or proprietary data. The loss of international collaborations would greatly restrict our ability to detect emerging pandemic threats, which can arise in any region

of the globe. In addition to diminishing readiness for pandemics, direct implementation of the NSABB recommendations would harm surveillance, antiviral discovery, monitoring for resistance to antivirals and vaccines, and other critical efforts required to mitigate the substantial health and economic burdens annually brought by endemic pathogens.

Even in the absence of an outright ban, cumbersome oversight policies will deter essential research as investigators and institutions choose to focus their efforts elsewhere. For example, elevating SARS-CoV-1 to a select agent in 2009 resulted in many research institutions abandoning research on this pathogen due to the added administrative and infrastructure burdens. The resulting contraction of this field was detrimental to our understanding of coronaviruses and left us less well-prepared for the emergence of SARS-CoV-2. Similarly, poorly targeted oversight will dissuade the next generation of scientists from entering affected fields, accelerating their contraction.

Even without implementation, the NSABB recommendations are already having a chilling effect on virology research. The uncertainty generated by these proposed rules is causing scientists and their institutions to avoid research that is likely to be affected, including the development of vaccines and therapeutics. Work has preemptively been rejected by the NIH even after passing potential pandemic pathogen care and oversight (P3CO) review for biosafety and often after delays of months or years. As a result, many scientists are no longer proposing work anticipated to undergo this process, affecting both NIH-funded researchers in the US and foreign researchers who depend on collaborative awards to build capacity and maintain laboratories essential for early detection of emergent pathogens. Consequently, essential research around the world is being curtailed even before the NSABB recommendations are translated into new policies. Some of these setbacks have been reported in the lay press (8). This overwhelmingly negative trend will likely continue as concerned parties promote the most onerous and broadest implementation of the NSABB regulations without critical technical knowledge or experience with best practices in biosafety and biosecurity (9). Exclusive focus on the handling of viruses in the laboratory and the field leaves us vulnerable to the well-evidenced and increasing threat of zoonoses.

DEVELOPMENT OF POLICY

Assessing the risk of virology studies to biosafety and biosecurity requires specialized knowledge and an oversight framework offering precise definitions and transparent review. Oversight must start with a "bottom-up" approach with "boots on the ground." Investigators and their institutions are and should continue to work together to evaluate risks, benefits, and biosafety concerns. With a goal of consistent interpretation, intended outcomes of policy should be made clear to all stakeholders through the provision of many example scenarios. Additionally, to assist institutional bodies on an ongoing basis, a national network of IBCs should be established to enable sharing of best practices and standardization of risk assessments across institutions. Within this network, IBC representatives would offer their particular expertise where it is needed—similar to peer review of research publications. These decentralized approaches should be coupled with appropriate "top-down" federal guidance and oversight. Any new oversight of virology will bring significant cost to both institutions and the USG and must therefore be properly resourced to support implementation and training. Any USG entity established to administer and regulate pathogen research must include sufficient investment to carry out its mandate efficiently and effectively. A failure to do this will create confusion and bottlenecks that will multiply during review and will, as a result, stop research in its tracks.

Development of policy would benefit from a 1975 Asilomar-like conference similar to that used to develop guidelines for the use of recombinant DNA technology (10). This conference would comprise key stakeholders, including a broad range of scientists with technical expertise in virology. The Asilomar conference weighed the risks of genetic engineering with its considerable promise for science and medicine through

public discussion in the crafting of science policy. In the end, a structure of oversight was created to assign risk to experiments that then dictated the type of laboratory appropriate and the need for additional oversight. As a result, many recombinant DNA experiments inconceivable in 1975 have been carried out across the world safely.

The rationale for and the anticipated outcomes of new regulation must be specific, nuanced, and iterative. In developing policy, it must be understood that variables such as virulence and transmissibility are difficult to measure in the laboratory and apply to real-world situations. In fact, there is no absolute measurement for virulence or transmission potential; these properties are both species-specific and always measured relative to something else (e.g., as a comparison between strains). For example, viruses that are selected to replicate more efficiently in the laboratory are sometimes said to have increased virulence. However, in many cases, these viruses actually have a fitness disadvantage in nature. One example of this is in the preparation of the measles vaccine (11). Prior to widespread vaccination, measles claimed the lives of 1–2 million children annually in developed countries. Work in laboratories resulted in a virus that replicated to much higher yields. Technically, this represents a "gain of function," indicating increased replication, but in practice, the virus had reduced capacity to cause disease in people and was therefore suitable for use as a vaccine. Two immunizations protect 95% of susceptible children and effectively eliminated measles in vaccinated populations. Similarly, the initial attempts to develop a vaccine for the herpesvirus, human cytomegalovirus (CMV), involved passage of the virus in cultured cells, again resulting in a virus that replicated to much higher yields in the laboratory compared to CMV strains freshly isolated from humans (12). Despite this replicative advantage, the culture-adapted virus was incapable of causing disease or inducing immunity in humans. While the virus generated did not prove useful as a vaccine, it became a valuable research tool to investigate the biology of infection, identify determinants of CMV pathogenicity, and define viral mechanisms of immune evasion. CMV is a high priority for vaccine development as it is the leading cause of birth defects and causes life-threatening disease in transplant recipients. This research informs ongoing efforts to develop this much-needed vaccine and additional antivirals.

In microbiology, there are many routine experimental manipulations that alter pathogen phenotypes but do not present heightened risk to humans. A revised oversight policy should acknowledge this by avoiding or building policy around ambiguous terminology, including "gain of function." Risk should be evaluated based on the pathogen being studied at the outset of the work and iteratively reassessed as new experimental results indicate a change in risk.

SCOPE OF POLICY

NSABB recommendations, if adopted as proposed, would sweep much of virology research into new oversight by unnecessarily expanding oversight to pathogens that pose little risk. Concerns addressed by a new policy must be based on evidence so as to not unnecessarily burden or slow research. Furthermore, in considering evidence of risk, it is important to understand both the utility and limitations of model systems used to examine pathogen phenotypes and of correlates used to assess disease or pandemic potential.

Given that work with higher risk group agents is already subject to in-depth review, the expansion of oversight would most greatly impact research on Risk Group 2 agents. This risk group includes most viruses that circulate routinely in the human population, such as seasonal influenza, herpesviruses, adenoviruses, papillomaviruses, human respiratory syncytial virus (RSV), etc. These viruses present less of a threat, given that these viruses are already well-established in humans, with population immunity, vaccines, and antivirals available to many, and the exposure risk that they present to laboratory personnel is readily mitigable. Any new oversight system would likely identify such risk group 2 research as low risk. However, the need to complete redundant and unnecessary safety reviews will be highly detrimental in these fields simply because

administrative processes are slow and would be overburdened. The design of new policy must be thoughtful about the potential to disrupt research on everyday human pathogens.

New policy must grapple with the reality that it is exceptionally difficult to "reasonably anticipate" (as per NSABB recommendations) concerning experimental results, as defined by the Government Accountability Office, or that research is "likely to pose a severe threat to public health." Predictions of research results are plentiful and highly varied and are only as valuable as experimental validation allows. What one researcher may anticipate and see as predictable, another may not. In one dual-use research of concern example, the 2001 surprise finding of Jackson et al. that the introduction of the IL-4 gene into ectromelia virus (mousepox) allowed the virus to evade the vaccine (13) was countered by Mullbacher et al. suggesting that it could have been predicted (14). Furthermore, while H5N1 influenza virus has been considered a potential pandemic threat for decades, some researchers had predicted that it would not be possible for the virus to become transmissible between mammals because it lacked the genetic potential for mammalian transmissibility. This prediction was disproven in the laboratory and in nature (15–19).

In light of the challenges inherent to predicting biological outcomes, new policy should focus on observed outcomes of concern. Investigators should be tasked with alerting oversight bodies to experimental results that may pose heightened risk to humans. In nuclear physics, researchers adhere to such a notification regime. To address findings of concern, a no-fault reporting structure with a peer review component should be established. Ensuring review in the context of appropriate expertise, without automatic moratoriums or restrictions on necessary follow-up of critical findings, is important to promote a culture of compliance and to maintain a robust research enterprise. Such an approach would have the benefit of producing a well-curated set of research examples, ideal for informing further refinement of oversight policy.

Vaccine development and viral surveillance have typically been excluded from enhanced potential pandemic pathogen (ePPP) oversight. However, NSABB recommendations would remove exemptions that currently enable timely research that is immediately relevant to public health. It is not clear that the production of a vaccine within a year of SARS-CoV-2 identification would have been possible if exclusions for vaccine development were in place as they might have restricted or completely blocked the work required to adapt viruses for testing in small animal models of pathogenesis. Without the ability to adapt viruses by serial passage or molecular cloning for experimental challenge studies, essential preclinical testing would have been delayed by months or years. Even if additional review is expedited, it will impede the timely surveillance and characterization of emerging viruses and variants, thereby affecting vaccine development. These activities are critical for responding to infectious disease outbreaks and offer little benefit to public health if carried out retrospectively. Surveillance must be able to keep pace with pathogen spread. Vaccine development should ideally outpace pathogen spread and be rapid enough to allow updating of vaccines in response to pathogen evolution. Further, exemptions should be included to allow for resistance testing in the development of novel therapeutics. In evaluating the utility of a drug, it is essential to know how readily a pathogen will evolve resistance. Omitting this analysis limits our ability to exclude therapeutic avenues that will ultimately not be effective, thereby diluting effort and resources. The potential negative impact of revised oversight on core public health activities needs to be carefully considered. Well-designed exemptions are a valuable tool for avoiding unintended consequences of new policy.

Finally, well-nuanced policy cannot necessarily be restricted based on the mode of transmission. While respiratory viruses such as coronaviruses, paramyxoviruses, and influenza virus are certainly important human pathogens, it is worth noticing that pathogens with other transmission routes also fall into higher-risk categories. For example, poliovirus is an enteric virus that can persist in the environment for long

periods and presents a serious transmission risk to unvaccinated populations. Furthermore, HIV-1, which unleashed an ongoing pandemic, is transmitted only through the transfer of infected bodily fluids. While respiratory pathogens are easily transmitted through social interactions, oversight of any highly pathogenic virus should be considered regardless of the route of transmission.

CONCLUDING REMARKS

On the heels of the COVID-19 pandemic, most developed nations are fortifying their commitment to pathogen research. However, current political discourse and proposed restrictions suggest that the US is in retreat. It is critical that we ensure that US microbiological research is safe, secure, and socially responsible and that we enable American scientists to set the standards for pathogen research and safety. This is especially crucial as pandemics by definition transcend national borders. Preventing the next pandemic, or at least limiting its destructive impact, critically depends on scientific flexibility, speed, and collaboration. Adopting vague and problematic oversight rules will not advance these goals, but instead it will threaten to derail US progress, leadership, and technical competitiveness across a wide scope of biotechnology research and development. Subjective, poorly conceived rules of oversight will hamstring US scientists, devastating their ability to lead and influence safety practices at the international level. Meanwhile, other nations will take the lead in understanding important characteristics of emerging pathogens that are critical for effective responses and vaccine development. International norms will be set by them, not by US scientists. Moreover, this will leave the US beholden to potentially adversarial countries for data and information to mount responses and develop vaccines.

Virological research has resulted in life-saving vaccines and treatments for a myriad of viral diseases (5). Each vaccine or antiviral treatment rests on decades of research conducted by countless scientists all over the world to understand the biology of specific pathogens and the development of countermeasures. These investigations have informed and advanced science and human health far beyond the field of virology. Virologists led the discovery of oncogenes and tumor suppressors. Recombinant DNA technologies, which ushered in the molecular age for the development of targeted therapies and molecular understanding of pathogenesis, were born in virology laboratories. Discoveries in fundamental biology, such as the synthesis of RNA from DNA templates and use of RNA for protein expression, have resulted from virology research (20). Unrefined or poorly guided oversight will impede many areas of science focused on human health that are driven by virology, including novel cancer therapies, next-generation vaccine platforms, and gene therapy.

Future viral outbreaks are certain. Viruses most often emerge in the human population through zoonotic events. The frequency of virus emergence is increasing as the human population, urbanization, climate change, and habitat destruction all increase (21. Eight pandemic viruses have emerged, all from animals, in the nearly 100 years since the 1918 H1N1 influenza pandemic. It is contrary to the interests of public health to focus policy on handling of viruses in the laboratory and in the field without addressing the well-evidenced and increasing threat of zoonoses. Virology research determines whether or not we can identify, monitor, and prepare for emergent threats. Applying oversight that is ill-defined and fails to account for technical realities will have a chilling effect on virology and a devastating impact on public health and pandemic preparedness. In the event of a major infectious disease outbreak, the cost of poorly devised policy could be paid in tens or hundreds of millions of lives.

As we recover from the collective trauma of the SARS-CoV-2 pandemic, we must not lose sight of the real threat by disarming one of our best defenses—virology research—from operating in a safe and effective way. In the era of inevitable pandemics, pathogen research must be empowered to address emergent threats around the world, lest we find ourselves less prepared for the next pandemic than we were for SARS-CoV-2.

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