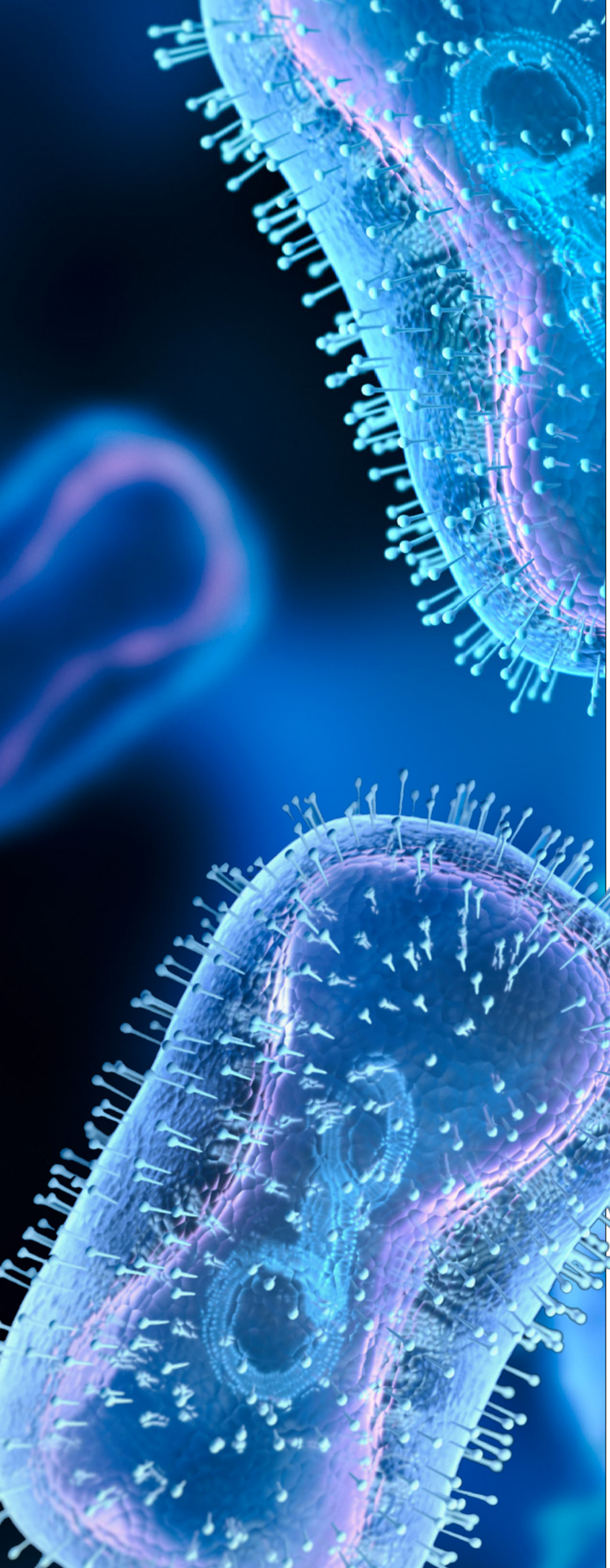


AMERICAN SOCIETY FOR MICROBIOLOGY

AMERICAN ACADEMY OF MICROBIOLOGY
RECOGNIZING SCIENTIFIC EXCELLENCE

Impact Assessment of Research on Infectious Agents

www.asm.org

Workshop Participants

Steering Committee

Michael Imperiale, Ph.D. *(Chair)*, *University of Michigan*

Arturo Casadevall, M.D., Ph.D., *Johns Hopkins Bloomberg School of Public Health*

Stacey Schultz-Cherry, Ph.D., *St. Jude Children's Hospital*

Vanessa Sperandio, Ph.D., *University of Wisconsin–Madison*

Susan R Weiss, Ph.D., *University of Pennsylvania*

Participants

Ron Fouchier, Ph.D., *Erasmus Medical Center*

Gigi Gronvall, Ph.D., *Johns Hopkins University*

Jo Handelsman, Ph.D., *University of Wisconsin-Madison*

Joseph Kanabrocki, Ph.D., *University of Chicago*

Filippa Lentzos, Ph.D., *King's College London*

Marc Lipsitch, D.Phil., *Harvard University*

Megan Palmer, Ph.D, *Ginkgo Bioworks*

Stanley Perlman, M.D., Ph.D., *University of Iowa*

Angela Rasmussen, Ph.D., *University of Saskatchewan*

David Relman, M.D., *Stanford University*

Kanta Subbarao, M.B.B.S., MPH, *WHO Collaborating Centre for Reference and Research on Influenza and the University of Melbourne*

ASM Staff

Stefano Bertuzzi, Ph.D., MPH, *Chief Executive Officer*

Catherine Ort-Mabry, M.A., *Chief Marketing & Communications Officer*

Allen Segal, J.D., *Chief Advocacy Officer*

Aleea Khan, *Director, Science Communications*

Nguyen K. Nguyen, Ph.D., MBA, *Director, American Academy of Microbiology*

Mary Lee Watts, MPH, *Director, Federal Affairs*

Amalia Corby, M.S., *Manager, Policy Development*

Ashley Hagen, M.S., *Scientific and Digital Editor*

Joanna Urban, *Public Relations Manager*

Rachel Burckhardt, Ph.D., *Senior Specialist, Scientific Analysis*

Preamble

Throughout history, the quest to seek scientific truth has often evolved through discussions and debates based on the data and known evidence at the moment. The rigorous scientific process and the commitment to follow the evidence have been the key attributes that secure scientific and societal progress. Thankfully, that approach remains effective in allowing us to resolve many complex issues that we face in science and society.

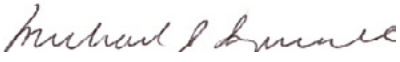
Today, as the world emerges from a pandemic, one of the topics on top of the mind of many researchers and the public is potential pandemic pathogen research. There have been many debates on this topic that started decades ago. The main focus has been on how to ensure scientific research is conducted safely and securely, to protect researchers and the general public, while maintaining strong support for scientific discovery. Government agencies in the United States and globally have provided guidance and policies in this area. However, many knowledge and implementation gaps related to the current situation remain to be filled.

As one of the largest life science societies in the world, we, ASM, decided to take on the convener role to facilitate a scientific conversation to assess the impacts of infectious agents and potential pandemic pathogen research, by organizing a workshop on this topic. Our goal was to leverage the diverse expertise and perspectives of experts on this topic to examine the evidence, communicate our current understanding of the issue to the rest of the scientific community and the public, and provide recommendations for improving how this research is planned, conducted, and managed. Through this effort, we hope to promote partnership, transparency, and trust in the scientific process that is fundamental to society.

This report aims to provide context to the issue and capture the discussion of the participants at the workshop. Like any scientific proceedings, the report focuses on the topics that were considered at the workshop, and is not a comprehensive review. The report presents the spectrum of opinions regarding the topic of research involving enhancing pathogens with pandemic potential. It does not endorse or refute any particular position of any of the participants as to whether and how such experiments should be performed. The recommendations in this report, which were agreed upon by all the workshop participants, can help inform the public, policymakers, the scientific community, and ASM in future policy positions or programmatic activities.

Finally, we would like to thank the American Academy of Microbiology for organizing this workshop; the Steering Committee for designing and developing the workshop and this report; and the many ASM staff, especially Dr. Nguyen Nguyen, Director of the American Academy of Microbiology, and Dr. Rachel Burckhardt, Senior Specialist, Scientific Analysis, for their partnership, contributions, and support in making the workshop and report possible.

Sincerely,



Michael J. Imperiale, Ph.D.
Chair, Steering Committee

Stefano Bertuzzi, Ph.D. MPH
Chief Executive Officer, ASM

EXECUTIVE SUMMARY

Infectious agents are a major source of death and disease worldwide. Research with infectious agents has provided many societal benefits but also has introduced concerns about the potential for negative impacts of modified pathogens on public health. There is an ongoing debate about what oversight, regulations and, potentially, legislative provisions are needed for a small subset of research with infectious agents commonly called gain of function research of concern (GOFROC) or enhanced potential pandemic pathogen (ePPP) research. To develop a deeper scientific understanding, gathered from different perspectives of leading scientists who possess expertise on this issue, the American Society for Microbiology hosted a workshop. The goal of the event was to review the benefits and risks of GOFROC or ePPP research to science and society. The deliberation prompted three overarching recommendations from participants: (i) the need for standardized research terminology and practices, (ii) increased engagement and transparency with the public on infectious agents research, and (iii) strengthened biorisk management systems for safe, secure, and responsible research.

KEY INSIGHTS

1) Research on infectious agents is necessary for understanding, monitoring, and developing treatments and prevention measures against these agents. Moreover, basic research provides knowledge and insights that may prove useful in the future in ways unknown at the present. For example, basic coronavirus and mRNA vaccine research starting in the 1980s and 1990s enabled the rapid development of vaccines for COVID-19 in the 2020s.

2) Gain of function research of concern or enhanced potential pandemic pathogen research makes up a very small fraction of all biological research. However, this category of experiments raises concerns about biosafety and biosecurity risks.

3) Clearly defined terminologies for research of concern should be developed by the scientific community to avoid public confusion and highlight its practical benefits.

4) Harmonized biorisk management standardization, training, mentoring, and reporting can help improve safety and security for laboratory workers and the public.

5) Expanded engagement and collaboration of scientists with policymakers and the public, including increased transparency on the risks and rewards of research with infectious agents, is needed.

INTRODUCTION

What are Infectious Agents and Why are They Important?

Infectious agents are among the leading causes of death globally. Infectious agents include bacteria, fungi, viruses, and parasites that are capable of producing infection or infectious disease. They cause a significant share of the overall burden of disease, especially in developing countries (https://www.who.int/data/stories/leading-causes-of-death-and-disability-2000-2019-a-visual-summary). In 2019, more than 2.6 million people died because of lower respiratory tract infections, according to the World Health Organization (WHO) (https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death). Thus, biological research on infectious agents, as well as the development of treatments and vaccines against infectious agents, is critical to reduce the impact on humanity caused by disease worldwide.

Infectious agents:
organisms capable of causing disease in humans, animals, or plants

Biological research aims to understand all aspects of living organisms. At times this involves modifying the organism's genome in an attempt to learn how a particular metabolic pathway or infection process works or how a specific protein functions. Sometimes modifying a genome alters the function of an organism or a cell in such a way that it may be able to do more than it used to do. This type of research is referred to as **gain of function** and can encompass many experimental approaches aimed at understanding mechanisms and processes of organisms, including basic research on microbes that do not cause disease (National Academies of Sciences, Engineering, and Medicine et al. 2015; Shi et al. 2021). For example, researchers have engineered the common bacterium *Escherichia coli* to degrade plastic and other research teams have modified mosquitoes to block transmission and infection of dengue virus to humans (Buchman et al. 2020; Shi et al. 2021).

Gain of function research of concern (GOFROC):
generation of pathogens with properties that do not exist in nature that may be more pathogenic and/or transmissible than the natural pathogen; this research is a very small subset of gain of function research

For infectious agents, gain of function research may be used to understand the mechanisms that infectious agents use to infect or colonize a host and cause disease, identify possible routes to block disease progression and symptoms, or develop vaccines. While gain of function approaches are widely used, there is a very small subset of gain of function experiments in which genetic modifications may enhance an infectious agent's transmissibility or virulence in humans. Very rarely, these types of experiments are conducted with **potential pandemic pathogens (PPPs)**, which are infectious agents that are "likely highly transmissible and capable of wide, uncontrollable spread in human populations and

highly virulent" (https://www.nih.gov/news-events/research-involving-potential-pandemic-pathogens). For example, as will be discussed below, H5N1 influenza A virus has been passaged in ferrets to determine whether it is capable of transmitting between mammals by an airborne route (Hertst et al. 2012; Imai et al. 2012). The latter type of research is sometimes labeled as gain of function research of concern or research on enhanced potential pandemic pathogens (https://www.nih.gov/news-events/research-involving-potential-pandemic-pathogens). U.S. federally funded "proposed research that is reasonably anticipated to create, transfer, or use PPPs resulting from the enhancement of a pathogen's transmissibility or virulence in humans" is currently deemed ePPP research and requires a higher level of review and is subject to strict laboratory protocols (https://www.phe.gov/s3/dualuse/Pages/ResearchReview-PPP.aspx).

Enhanced potential pandemic pathogen (ePPP) research: research that may be reasonably anticipated to create, transfer, or use potential pandemic pathogens resulting from the enhancement of a pathogen's transmissibility and/or virulence in humans

There are several existing regulations and oversight protocols for the small percentage of research deemed ePPP research (https://www.nih.gov/news-events/research-involving-potential-pandemic-pathogens). For ePPP research funded by the U.S. government, there are ongoing debates regarding how much risk an individual considers reasonable, how risks and benefits should be weighed, who will make the decision to review and to approve or not approve funding for and conduct of such research, and what processes should be in place to enhance safety and security and ensure scientific progress. Similar questions apply in other countries and for non-government-funded ePPP work in the U.S., and the WHO has published a document addressing this topic (https://www.who.int/publications/i/item/9789240011311). These value-based questions are complex to answer because they are subject to the prudential judgment of individuals and not solely dependent on scientific facts. Such complexity underpins an ongoing debate among scientists, policymakers, and the public. One of the goals for the workshop was to discuss these issues.

On behalf of the American Society for Microbiology, the American Academy of Microbiology, the society's scientific leadership group and think tank, convened a workshop on 12 May 2023 with leading scientists about gain of function research on pathogens with pandemic potential to discuss both the benefits and risks of this research to science and society. The workshop focused on human pathogens but the participants acknowledged that similar concerns apply to animal and plant pathogens. The workshop was conducted in a roundtable format where each topic was introduced by a framing presentation followed by active exchange among the participants. The participants discussed the benefits, risks and current policies and procedures for this research. The group came to agreement in several areas, including the need for improved standardization of biosafety and biocontainment norms internationally, increased engagement and transparency with the public, and strengthened systems designed to protect the safety of the public and laboratory workers. The participants recognized there were several unanswered questions that remained to be addressed that will require further research and discussion to reach solutions. The analysis and recommendations in this proceeding reflect the views of the scientific experts attending the workshop and are not intended to reflect official positions of the American Society for Microbiology.

Early history of gain of function research debates in the U.S.

Debates about what type of science should or should not be done have always occurred. In the early 2000s, the spread of the highly pathogenic avian influenza A H5N1 virus sparked debates about gain of function research. The experience with H5N1 influenza and the resulting transmission experiments is useful to frame the types of gain of function and ePPP debates that are being discussed today.

At the start of the 21st century, global public health officials were concerned that the influenza A/H5N1 virus might pose a risk of sparking a new influenza pandemic. Infections in fewer than 500 people had been reported to the WHO, mostly after direct contact with infected animals, and among those people the case fatality rate was over 50% (https://www.who.int/publications/m/item/cumulative-number-of-confirmed-human-cases-for-avian-influenza-a(h5n1)-reported-to-who-2003-2022-5-jan-2023). Fortunately, very few cases of human-to-human transmission were documented (Ungchusak et al. 2005; Kandun et al. 2006). However, there was concern that if the virus evolved to be able to transmit easily between humans, it could cause a severe and deadly pandemic. To address this question, researchers performed experiments to determine whether this virus could become transmissible in ferrets, which are a model for transmission among humans, with the assumption that adaptation to ferret transmission would involve similar mutations to those permitting transmission in humans. The researchers hoped doing so would help determine if such a phenotype was possible and, if so, the necessary characteristics for transmission among mammals. Proponents of these studies argued that if these markers were detected in the circulating virus population in avian species, it would help alert public health professionals to enforce stronger containment methods and could make a difference in preventing pandemic spread (Schultz-Cherry et al. 2014; Davis et al. 2014). Others argued, however, that this knowledge was unlikely to be beneficial in this manner, for several reasons including the possibility of a different evolutionary path with different mutations in the natural reservoir species and the possibility that by the time such mutations were detected, it would be too late to contain the virus (Lipsitch and Galvani 2014).

Independently, two research groups discovered that a small number of mutations in key influenza genes made the resulting strain more transmissible in ferrets and submitted their findings for publication in late 2011. The U.S. National Science Advisory Board for Biosecurity (NSABB), a federal advisory committee on **biosecurity**, requested a halt on publishing the details of the teams' findings due to national security concerns of publishing the genetic modifications to make the viruses more transmissible.

> **Biosecurity:** implementation of procedures that ensure safe use, control, and accountability of high-consequence biological agents, materials, and information, with a focus on protecting them from theft, loss, or misuse.

The NSABB worried that open access to the identity of the mutations responsible for transmission or the methods to construct the viruses could lead to bioterrorism using an influenza-based biological weapon or to accidental release of this virus by other investigators elsewhere now empowered to synthesize and produce these new viral variants in their laboratories, and initially recommended redaction of the mutation and method information from the manuscripts (Berns et al. 2012). The NSABB was told by the National Institutes of Health (NIH), however, that redaction was not an option:

the manuscripts needed to be either published in full or not published at all. After additional deliberation, the NSABB recommended full publication. This incident sparked a broader debate about what research on infectious agents should or should not be done and what oversight is needed, with subsequent discussions emphasizing the risk of accidental release in addition to the concerns about deliberate misuse that figured prominently in the debates over publication. These experiments, as well as the result of the NSABB review, raised concerns among a portion of the scientific community and led to a self-imposed one year pause in early 2012 on avian H5N1 research that could lead to enhanced transmissibility in mammals by the scientists conducting these experiments (Fouchier et al. 2012). The NIH later enacted its own pause of funding gain of function experiments, which was in effect from 2014 to 2017 (https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-lifts-funding-pause-gain-function-research).

In 2017, the U.S. Department of Health and Human Services (HHS) implemented the Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO) policy (https://www.phe.gov/s3/dualuse/documents/p3co-finalguidancestatement.pdf). This policy outlined a review and reporting process aimed at limiting the possibility of accidental or deliberate release of a pathogen capable of causing widespread harm to public health from U.S. federally funded research. Since the P3CO policy implementation, three research projects have been reviewed in the past six years and all three have been approved, though one project was ultimately modified so that it did not involve ePPP research (https://www.phe.gov/s3/dualuse/Pages/ResearchReview-PPP.aspx). HHS has not released details on its process for deciding whether research projects should undergo review, nor has it specified the nature of the review or the deliberations leading to the approval of these projects. Concerns have been raised by individuals across the spectrum of the debate about a lack of transparency.

The Known and Unknown Benefits and Risks of Research on Pathogens with Pandemic Potential

Potential Benefits and Risks of ePPP Research

Research with ePPPs is argued to provide both scientific benefits and public health risks. Proponents argue that scientific and public health achievements can come from ePPP research. They think this type of research allows researchers to understand how infectious agents cause disease with a high degree of detail and specificity that could be useful for therapeutics, vaccines, or surveillance, but others do not think key insights into infectious agents are achieved by these experiments or that the risks of certain experiments are worth the potential benefits. For example, the avian influenza transmission experiments described earlier provided detailed and specific information about genetic modifications that could lead to mammalian transmissibility. Some think this information is relevant and helpful for knowing the likelihood that the current H5N1 outbreak in birds will spill into human populations, while others have argued that the benefit to surveillance is negligible (or nonexistent).

There are risks associated with gain of function research on PPPs. Modifications that result in increased host range, transmissibility, or pathogenicity, or the ability to escape medical countermeasures, are the research areas of most concern (Warmbrod et al. 2021). These concerns are about both **biosafety** and biosecurity. As noted above, those who favor more comprehensive oversight or restrictions on ePPP research worry that an infectious agent with a broader host range or higher transmissibility or pathogenicity that inadvertently escapes laboratory containment or that is purposefully developed and released by a nefarious actor could cause significant harm to society by causing a pandemic.

Biosafety: is the use of safety practices, safety equipment, specially designed building, operations and policies to minimize potential risks of working with biological materials in laboratories.

Like the natural infectious agents themselves, modified infectious agents are also a concern for the researchers studying and handling them. Laboratory-acquired infections (LAIs) with infectious agents have been documented all over the world. Although so far they have been usually limited to a few exposed people, onward transmission has been documented in some cases (Wurtz et al. 2016; Rozo and Gronvall 2015; Pappas 2022; Liang et al. 2006) (http://wjw.lanzhou.gov.cn/art/2020/9/15/art_4531_928158.html). It has been difficult to obtain an accurate count of the number or frequency of such accidental exposures, probably due to underreporting. To date there has been no known LAI with an ePPP.

Because of the biosafety and biosecurity concerns, some scientists argue there are few reasons to work with ePPPs. In addition, it has been argued by some that ePPP research is generally relatively expensive because of the multiple safety and containment practices that are needed. As an alternative, they propose that those investments could be made on other approaches that are perceived to be less risky (Lipsitch and Galvani 2014). On the other hand, some scientists argue the potential benefits of gaining new knowledge by performing research

with an ePPP outweighs the risks. They argue that using the modified pathogenic strain is often the best way to understand how that pathogen causes disease, which will better inform development of preventative measures, treatments, and vaccines specific to the pathogen's mode of infection (Schultz-Cherry et al. 2014; Davis et al. 2014).

The results of ePPP research raise a related concern as they are considered an information hazard where "risk arises from the dissemination of (true) information that may cause harm or enable some agent to cause harm" (Bostrom 2011). In an interconnected digital and increasingly global world, results describing how to increase the pathogenicity of an infectious agent are now accessible to a much larger audience. This includes those with malevolent intentions or those without the necessary training or access to proper containment facilities. Thus, the deliberate misuse of ePPP research results, or conduct of legitimate research in subpar facilities, is a real concern.

Scientific research is a long-term endeavor. Many times, the benefits of basic research are not fully realized until many years after the experiment is over. As noted in the National Academies of Sciences, Engineering and Medicine report *Potential Risks and Benefits of Gain of Function Research*, "the benefits of basic biomedical research for medical practice and public health may be long term and their value not immediately evident. The results of particular types of research cannot always be predicted, and benefits are sometimes serendipitous" (National Academies of Sciences, Engineering, and Medicine et al. 2015). These unexpected and difficult-to-quantify potential benefits and risks complicate the ePPP research debate for some, though others argue that alternative research approaches that could be undertaken instead of ePPP research would equally carry unanticipated benefits (Lipsitch and Galvani 2014). Some argue that the potential public health risks entailed by ePPP research require a higher standard of short-term public benefit to justify doing such work.

Unknowns of ePPP research

In addition to these debated potential benefits and risks of ePPP research, there are unknowns. First, it is hard to estimate the potential "opportunity cost" to science and society if ePPP research does not take place. It has been suggested that increased regulations and reduced funding can slow down scientific progress and "prevent discovery of very beneficial but yet unanticipated knowledge" (Marchant and Pope 2009). On the other hand, it is possible that alternative approaches can get to the needed answer in some cases. Again, concerns about not performing the research must be balanced against risks associated with performing the research, and these must be compared to the potential benefits and risks of alternative research approaches. Both types of risks (i.e., either performing or not performing the experiment) are extremely difficult to quantify. Thus, scientists and others are questioning what is morally and ethically acceptable to publish and make available to the world (Rotblat 1999).

Another area of uncertainty relates to the process by which proposed experiments ought to be reviewed. Because high-level expertise is needed due to the complicated nature of the issue as discussed herein, some review entities, such as local institutional biosafety committees, may not have sufficient expertise to understand fully the benefits and risks of the alternatives or even of the original approach. Therefore, the review process needs to be developed carefully for it to be effective.

Another big unknown is the effectiveness of current ePPP research regulations in keeping laboratory workers and the broader public safe. This is a major hurdle in updating or crafting evidence-based regulations. Data that could inform this process, including but not limited to data collected by the U.S. government on laboratory safety lapses or potential laboratory acquired infections, are not widely available (https://www.nih.gov/news-events/research-involving-potential-pandemic-pathogens; https://www.selectagents.gov/index.htm). As noted, laboratory-acquired infections have occurred throughout the world (Wurtz et al. 2016; Henkel et al. 2012). However, LAI reporting is mostly voluntary, and the data that are collected by the U.S. government are not shared, making it difficult to know the real risk that this research poses to laboratory workers and their communities (Henkel et al. 2012). In the U.S., proposed legislation to exempt anonymous reporting of laboratory accidents and near accidents from being requested through the Freedom of Information Act will exacerbate the lack of information on laboratory safety; instead, such requests should be redacted as in other cases to protect confidential informants.

Understanding the Current Biocontainment and Biosafety Procedures in the U.S.

Research with infectious agents has many safeguards in the U.S., with multiple layers of oversight and review at both the institutional and sponsor level (Goodrum et al. 2023). Research institutions are required to have environmental health and safety officers and institutional biosafety committees that must review, modify if needed, and approve the details of experiments to ensure proper biosafety measures are being taken. HHS and the U.S. Department of Agriculture (USDA) oversee federal regulations for research involving plant, animal, and human pathogens. While not statutory, there are policies and guidance in place for recombinant DNA research, research with ePPPs, and **dual-use research of concern**, though some have raised concerns about their application and the risk of conflict of interest when these rules are being applied and adjudicated by the funding agencies. There are fewer, if any, policies and guidelines for non-government-funded research. Figure 1 details the different institutional and federal regulations. Reviews by institutional and federal regulators must occur before any research is conducted.

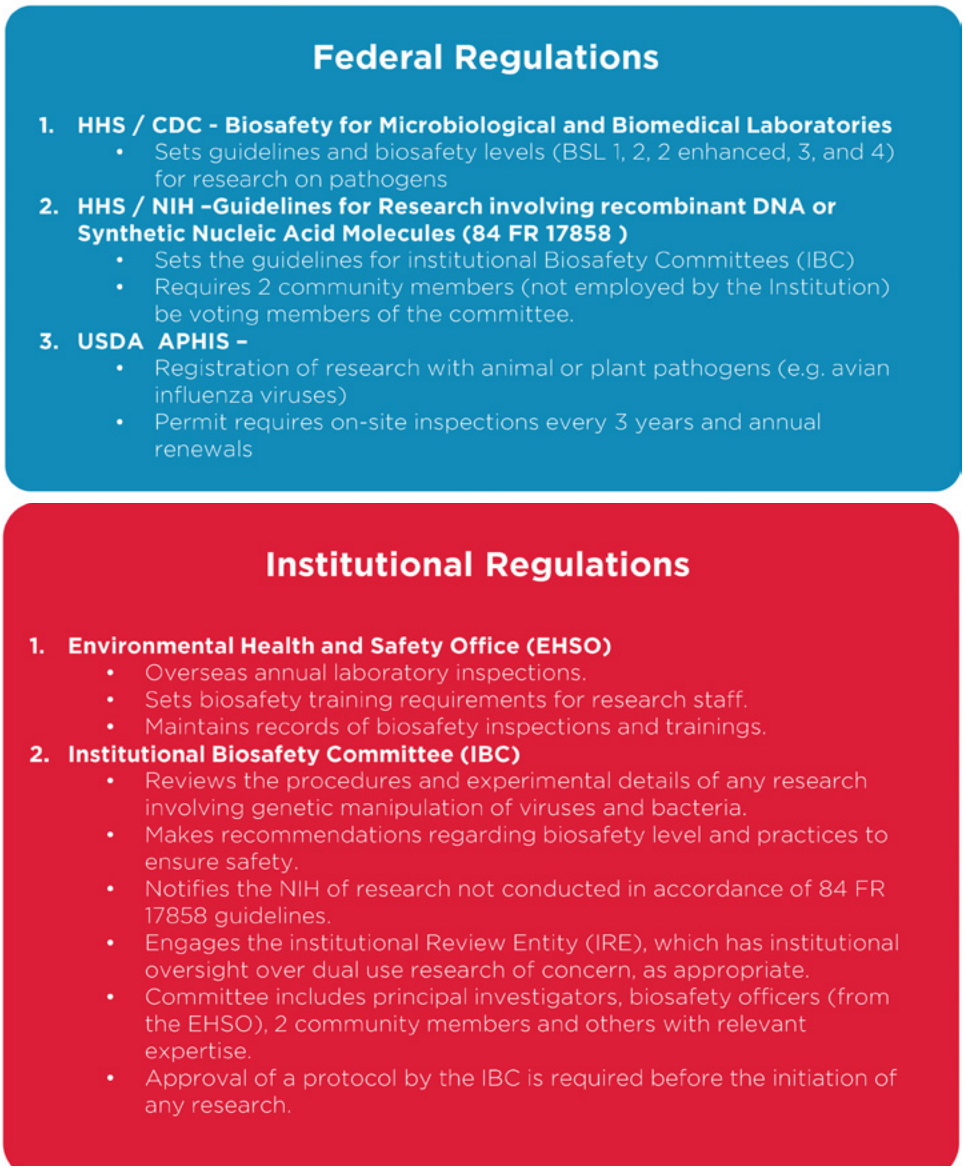


FIG 1 *Federal and institutional regulations (Goodrum et al. 2023).*

Biological research uses many engineering and procedural layers to contain infectious agents, known as biocontainment. Microbiology laboratories in the U.S. are guided by the Centers for Disease Control and Prevention's (CDC's) "Biosafety in Microbiological and Biomedical Laboratories" (BMBL) (https://www.cdc.gov/labs/BMBL.html). The BMBL recommends best practices for keeping workers safe in biomedical and clinical laboratories, but adherence is voluntary. The BMBL categorizes levels of containment based on the pathogen's "infectivity, severity of disease, transmissibility, and the nature of the work being conducted." These biosafety levels (BSLs) are numbered 1 through 4, with BSL-4 having the highest biosafety containment procedures and protocols. Figure 2 displays the different biosafety levels.

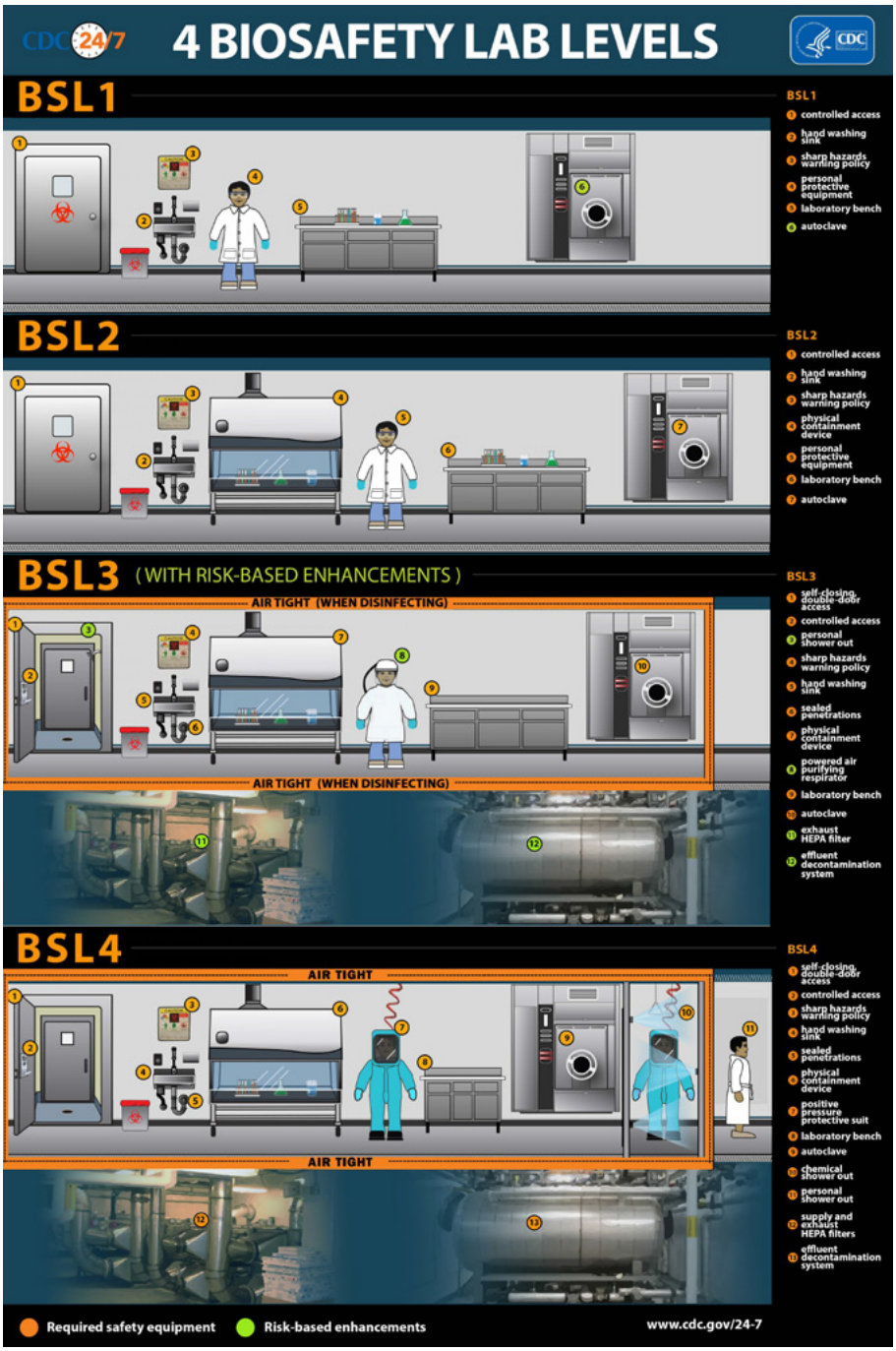


FIG 2 *Infographic of four biosafety laboratories (*https://www.cdc.gov/orr/infographics/biosafety.htm*).*

Containment practices include wearing personal protective equipment such as gloves and goggles, hand washing to slow the spread of microbes, proper airflow and filtration, and controlling access with restricted access doors and external security systems. The majority of microbiology research occurs at the lowest levels, BSL-1 and BSL-2, but research with PPPs is usually conducted in higher biosafety level laboratories (i.e., BSL-3 and BSL-4) that include enhanced biocontainment features including the following:

- Protective suits or respirators to prevent pathogens infecting a laboratory worker.
- Seals, HEPA filters, and effluence decontamination systems to prevent pathogens leaving the laboratory in the air.
- Self-closing double doors and decontamination showers to prevent pathogens leaving the laboratory on clothing.
- Facility safeguards such as directional airflow, specialized waste management systems, and generators to prevent the accidental release of a pathogen from the laboratory.

To work in any U.S. microbiology laboratory, a person must receive training. For higher biocontainment laboratories, there is intensive training and supervision required. Researchers must complete months of online training modules and in-person mentoring sessions before being allowed in higher biosafety level laboratories. This training ensures workers know the proper way to work with and dispose of infectious agents that limits the risk of such research to the laboratory workers and the local community. While safety requirements are not uniform globally, most developed nations have similar precautions and training in place as well.

Laboratories studying infectious agents, including PPPs, are monitored for their biosafety and biocontainment practices. This may include daily inspections by laboratory personnel and institutional officials of essential containment and life support systems and regular inspections by federal health and safety officers in the case of the highest containment levels. Occupational health services such as regular health monitoring and available immunizations for infectious agents in the laboratory are additional layers of biosafety for laboratory workers. When properly implemented, current biosafety guidance is considered by many as effective in reducing risks from experiments with infectious agents and PPPs to acceptable levels. Even so, there remain intrinsic unknowns that cannot be fully covered or predicted, including the possibility of human error, and as discussed above, LAIs do happen. Continuous monitoring, frequent data sharing, research on the effectiveness of biosafety measures, and periodic updating of these measures are needed to ensure the scientific community is informed and safely conducts these experiments.

Recommendations

The workshop participants shared their views on the benefits and risks as well as the current policies and procedures for reviewing ePPP research. The participants agreed on three main areas that warrant further focus to enhance **biorisk management** of ePPP research.

More Precise Terminology and Standardized Practices

A major challenge in this debate is the lack of clear, well-defined terms. The term *gain of function* in particular, but also gain of function research of concern (GOFROC) or enhanced *potential pandemic pathogen* (ePPP), can have different meanings based on the context or the audience. This makes it difficult for scientists to communicate with policymakers, the public, or even other scientists. Therefore, clear definitions will allow the scientific community to gain a better understanding of the advantages and disadvantages of a proposed experiment. It was strongly recommended that a new term(s) with a clear definition(s) is critical to improve clarity and reset expectations.

Besides terminology, standardization of biorisk management protocols and practices for both the U.S. and international communities is needed. The world lacks an international standard for regulating research on infectious agents in general, much less for ePPP research. Each country develops its own review and regulatory process, adding to the lack of clarity. For example, some infectious agents are classified at different biocontainment levels in different countries, which can make it problematic when examining the safety practices to contain these agents around the globe. An agent that is on the **Select Agent List** in the U.S. may be endemic elsewhere. The WHO recently published a relevant framework for this process (https://www.who.int/publications/i/item/9789240011311) (see Box). As more high-containment laboratories are built around the world, consistent protocols will be important to ensure safe and secure working conditions with infectious agents everywhere (https://www.globalbiolabs.org).

In terms of oversight, some of the workshop participants felt that broad, blanket regulations are not always helpful because each experiment is unique—the pathogen, biocontainment facilities, and research design will always be different. Debates about oversight should focus "less on quantity and more on quality," with the goal of designing

regulations that are effective at keeping the world safe and secure. It was suggested the scientific, policy, funder, and other stakeholder communities could "define circumstances" under which ePPP research could or could not be done safely, securely, and responsibly and then incorporate this into a framework for reviewing the proposed research. Some workshop participants felt that current levels of regulation and procedures for review were inadequate to address the considerable risks posed by ePPP research in the U.S.

Strengthened Reporting and Occupational Health Systems

The safety of both laboratory workers and society is imperative, and workshop participants noted that more can be done. Increased multistakeholder dialogue on risk-benefit considerations for ePPP research, along with funding for research on biosafety measures, biorisk management training, occupational medicine services, improved facilities and protocols, and personal protective equipment can ensure biorisk management is taken more seriously and effectively across institutions and laboratories. Such discussions must also include the issue of potential risks to the public.

Scientists working in high biocontainment laboratories (BSL-3 and BSL-4) can help shape standard biocontainment and biosafety protocols by sharing best practices. Mentoring programs specific to biosafety and biocontainment could also be beneficial for researchers working with infectious agents.

The current system relies on reporting of accidents by the people who experience or detect them. However, existing incentives and assessment systems for laboratory safety have some flaws. It was pointed out that current administrative responses to accidents are often viewed as punitive rather than constructive. This can lead to reticence in reporting laboratory accidents to institutions. A better system would encourage reporting with an eye towards learning from those accidents, along with refresher training. Overall, there was a call to support expanding reporting systems and whistleblower protections, with both anonymous and direct ways to report laboratory safety.

More reporting allows for more data collection, or "science of science," on laboratory accidents, which would help to constrain uncertainty in risk-benefit analysis that oversight committees must weigh. The limited studies there have been to date indicate low rates of laboratory infections, though a paucity of data makes assessing the effectiveness of current safety measures difficult (Lipsitch and Inglesby 2014). In 2022, the Australian Health and Medical Research Council re-reviewed approved gain of function research of concern studies (17 in total from the previous 10 years) and found that risks were managed and monitored well, with "no reported incidents" from working with the infectious agents (https://www.nhmrc.gov.au/about-us/publications/gain-function-research-review-report). A similar study from the EU concluded that existing rules and processes are in place, but also noted the importance of broader stakeholder engagement (https://easac.eu/fileadmin/PDF_s/reports_statements/Gain_of_Function/EASAC_GOF_Web_complete_centred.pdf) (European Academies Science Advisory Council 2015). It should be noted, however, that the number of experiments that are likely to have raised concern is very small and one must be cautious interpreting these studies. More large-scale analysis studies of biorisk management and regulatory procedures would be useful to know what procedures work well to better inform future biosafety efforts.

Increased Transparency and Public Engagement

A key pillar of science is transparency. While sharing of results and methods is useful to scientists, jargon and highly technical details can prevent effective communication of this information to the public or policymakers. This is especially true for ePPP research, as noted above.

Recent debates by the public and policymakers have focused on the risks of ePPP research, with some worried this research may be too dangerous. To help address these concerns, scientists need to acknowledge risks more clearly and candidly and explain and justify why using a perceived risky approach is necessary to answer certain research questions. A consensus was reached that scientists must do a better job of communicating risks involved in doing science as well as procedures in place to do science safely.

However, unidirectional communication in which scientists do all the talking without genuine engagement with policymakers or the public is generally viewed as unproductive. To make an impact, scientists should work with, rather than talk at, policymakers and interested members of the public about the risks, benefits, safety layers, and historical accidents to give a fuller picture. This includes communicating the difference between short-term and long-term benefits as well as acknowledging that some benefits or concerns will not be known until well after the experiment is over. It was also recognized that risk-benefit judgments may change over time. For instance, during times of pandemics or public health emergencies, there may be more tolerance for experiments focused on increased transmissibility or escape from treatments in the hopes of better understanding of, and responding to, an ongoing infectious agent threat.

Science engagement, then, should be the approach taken by scientists. This includes engaging in discussions with others and acknowledging not only risks and benefits but also the unknowns. Being as open as possible about what scientists do and do not know is an important component of building trust; otherwise, the public can lose trust in and challenge the credibility of scientists if theories change over time, which is common as scientific knowledge evolves. Open dialogues where scientists listen, appreciate, and act to address the concerns of the public allow scientists and their public partners to co-create a research ecosystem that reflects the values and judgment of their community. These steps can help to build public trust in science.

Is International Consensus Possible?

Science is a global enterprise, and scientists overall share the goal of making the world a better and safer place regardless of national borders. However, many regulations about science and research are made at local or national levels. The workshop participants recognized that it would be challenging to reach an international consensus on ePPP research oversight.

In lieu of international oversight, it is vital for scientists to coordinate and set norms that can be translated across countries or adapted to local needs. Examples of ongoing initiatives include the "WHO Global Guidance Framework for the Responsible Use of the Life Sciences," the World Organization for Animal Health "Guidelines for Responsible Veterinary Research," and the "Tianjin Biosecurity Guidelines for Codes of Conduct for Scientists" (https://centerforhealthsecurity.org/our-work/research-projects/international-guidelines-for-biosecurity-ethics; https://www.woah.org/app/uploads/2021/03/a-guidelines-veterinary-research.pdf; https://www.who.int/publications/i/item/9789240056107). In addition, as noted above, developing biosafety mentoring programs, building improved systems for laboratory incident reporting, and increasing transparency in science communication and public engagement are all steps scientists can take to make the world safer (Table 1).

Unresolved Issues

While most scientists agree research on potential pandemic pathogens is important, current debates center on what types of ePPP experiments are justified given the risks and the details of how to do such warranted experiments safely. These debates provide opportunities to seek mutual understanding and co-create solutions. The workshop allowed participants to vocalize the benefits and risks of ePPP research, with all recognizing the challenge in figuring out the "when" and the "how." Analyzing the benefits and risks of ePPP research provides some clarity; however, decision-making relies on values and judgments that are sometimes not easily defined, although the WHO framework has suggestions for doing so (https://www.who.int/publications/i/item/9789240011311; Ficociello et al. 2023). Importantly, those who have concerns about ePPP research did not suggest a blanket halt to all ePPP studies. Rather, it is a call for more careful review and considerations of current procedures to guide policy decisions and avoid actions that may unintentionally slow down the progress of necessary scientific research while still mitigating potential risks and ensuring public safety. Similarly, supporters of ePPP research acknowledge that there will be experiments that should not be performed. As highlighted above and outlined in the group's recommendations, more study and discussion are needed to reach a broader consensus on the how.

The future of ePPP research oversight is still unresolved. Some argue more oversight is needed (in both scope and extent), some think there is too much oversight, and still others argue certain experiments with ePPPs should not be allowed at all. Currently in the U.S., lawmakers at both the federal and state levels are considering (and, in Florida, have already passed) legislation to prohibit or pause some gain of function research on "potential pandemic pathogens or related risky research with potentially dangerous pathogens" (https://www.congress.gov/bill/117th-congress/senate-bill/3012; https://buddycarter.house.gov/uploadedfiles/cart-ga0303.21.23.pdf).

For the oversight framework currently in place, there are also unresolved concerns over if or how it should be updated. In 2020, HHS charged the NSABB with reviewing and updating the P3CO guidance. Early in 2023, NSABB released their draft findings and recommendations, expanding the pathogens to which P3CO review applies and increasing transparency by funding agencies about their decision-making process (Reardon 2023). While the recommendations were not discussed at the workshop, the responses to these recommendations have varied: both support for and concern about a number of the recommendations have been raised, and it is hoped that the U.S. government will carefully consider these thoughtful opinions (https://centerforhealthsecurity.org/sites/default/files/2023-01/20230126-nsabbcomment.pdf; https://www.gao.gov/products/gao-23-105455) (Lowen et al. 2023).

The Future of Infectious Agent Research

The future of the governance of infectious agent research will require further dialogue and investment to seek clarity on the unresolved issues. Bans on research or additional layers of oversight can have significant impacts on the future of scientific research and knowledge expansion. Slowing scientific progress has a potential cost to society by making it potentially less prepared for the future. At the same time, a lack of effective oversight could lead to risks to public health including new highly consequential pandemics if an infectious agent is produced in a laboratory and inadvertently infects a community and then the world or is deliberately released by someone wishing to cause harm. Therefore, finding the balance of scientific progress and biorisk mitigation is critical for promoting responsible science.

It is not a question of if but when the world will face another pandemic of natural origin. Science is a key defense mechanism to protect us against and respond to pandemics. As the world emerges and learns from the COVID-19 pandemic, the workshop participants agreed it was a good time to build a framework aimed at preparing for and preventing another pandemic. This includes strengthening safety practices to prevent laboratory acquired infections, implementing security measures to prevent malicious actors from obtaining pathogens, establishing effective processes that assess the risk-benefit analysis of research with infectious agents, ensuring responsible research, and engaging with society more transparently about the benefits and concerns of research with infectious agents. Together, these actions will help build public trust in science and strengthen the scientific enterprise for the future.

In the end, although the workshop did not discuss exactly what oversight is needed, it highlighted helpful recommendations for the scientific community and society to consider going forward (Table 1). Scientists must engage with diverse stakeholders to ensure transparency, accountability, and trust, as the decisions to pursue this type of work have important societal implications.

The workshop displays the importance of a process in which the scientific community works together to seek a better understanding of each other's perspectives on controversial research and attempts to find a step forward. As stated at the workshop, to make progress on this important goal, scientists need to be willing to acknowledge the uncertainties and unknowns and acknowledge their mistakes. Moreover, the scientific discovery process takes into consideration more than just the scientific facts. Scientists are humans; thus, decisions about which areas of scientific research should be pursued include the individual's value judgments. These values also affect how an individual views the importance of the results. Therefore, it is important to inform the public and policymakers about the nature of scientific process, which is independent of the conclusions. This can strengthen public confidence in the scientific community and inform policy decisions on public and global health.

Table 1. Call to Action for the Scientific Community and the General Public

For the Scientific Community

- Develop accurate terminologies with clear definitions around ePPP research, gain of function and GOFROC.
- Develop guidance to help support scientists and institutions in the decision-making process when reviewing experiments that are deemed risky.
- Revisit the current pathogen frameworks to determine what types of decisions about infectious agents research are appropriately made at the institutional level and what should be elevated and decide on who is most qualified to make such decisions.
- Where needed, provide additional training and mentoring programs for biosafety and high-containment laboratory practices, especially in low and middle-income countries.
- Re-examine whether current reporting practices are still the best approach or other incentives should be considered to encourage safety reporting to aid in monitoring and prevention of future incidents.
- Establish guidance to harmonize reporting standards and methods to inventory and safely disseminate accounts of laboratory safety incidents for the purpose of monitoring and learning.
- Engage with policy makers and the public using language that is clear, recognizes uncertainties and demonstrates increased transparency about the risks and benefits of science.
- Continue frequent dialogues with diverse stakeholders about debated and unresolved issues with the intention to co-develop solutions and enhance public confidence in science

For the General Public

- Advocate for evidence-informed policies.
- Support funding for research on the effectiveness of biosafety measures, biosafety training and reporting programs.
- Participate in science cafes or citizen science projects to stay informed and engage in the dialogue.

Glossary

- **Biosafety:** is the use of safety practices, safety equipment, specially designed building, operations and policies to minimize potential risks of working with biological materials in laboratories
- **Biosecurity**: implementation of procedures that ensure safe use, control, and accountability of high-consequence biological agents, materials, and information, with a focus on protecting them from theft, loss, or misuse
- **Biorisk management**: effective management of risks posed by working with infectious agents and toxins in laboratories; it includes a range of practices and procedures to ensure the biosecurity, biosafety, and biocontainment of those infectious agents and toxins
- **Dual use research of concern**: research intended to provide a clear benefit but which could easily be misapplied to do harm
- **Enhanced potential pandemic pathogen (ePPP) research:** research that may be reasonably anticipated to create, transfer, or use potential pandemic pathogens resulting from the enhancement of a pathogen's transmissibility and/or virulence in humans
- **Gain of function (GOF) research:** broad term that can encompass almost any type of research that alters the function of an organism in such a way that it is able to do more than it used to do; this can include anything from activation of new receptors to development of growth advantages, enhanced resistance, and even increased transmissibility in animals and/or in humans
- **Gain of function research of concern (GOFROC)**: generation of pathogens with properties that do not exist in nature that may be more pathogenic and/or transmissible than the natural pathogen; this research is a very small subset of gain of function research
- **Infectious agents**: organisms capable of causing disease in humans, animals, or plants
- **Potential pandemic pathogens (PPPs)**: bacteria, viruses, and other microorganisms that are likely highly transmissible (capable of wide, uncontrollable spread in human populations) and highly virulent (likely to cause significant morbidity and/or mortality in humans
- **Select Agent List:** list of biological agents and toxins have been determined to have the potential to pose a severe threat to both human and animal health, to plant health, or to animal and plant products in the U.S; these select agents and toxins are regulated by the Federal Select Agent program.

References

National Academies of Sciences, Engineering, and Medicine, Board on Life Sciences, Division on Earth and Life Studies, Committee on Science, Technology, and Law, Policy and Global Affairs, Board on Health Sciences Policy, National Research Council, Institute of Medicine. 2015. Potential risks and benefits of gain-of-function research: summary of a workshop. National Academies Press, Washington, DC.

Buchman A, Gamez S, Li M, Antoshechkin I, Li HH, Wang HW, Chen CH, Klein MJ, Duchemin JB, Crowe JE, Jr, Paradkar PN, Akbari OS. 2020. Broad dengue neutralization in mosquitoes expressing an engineered antibody. PLoS Pathog 16:e1008103. 10.1371/journal.ppat.1008103.

Shi L, Liu H, Gao S, Weng Y, Zhu L. 2021. Enhanced extracellular production of IsPETase in Escherichia coli via engineering of the pelB signal peptide. J Agric Food Chem 69:2245–2252. 10.1021/acs.jafc.0c07469.

Herfst S, Schrauwen EJ, Linster M, Chutinimitkul S, de Wit E, Munster VJ, Sorrell EM, Bestebroer TM, Burke DF, Smith DJ, Rimmelzwaan GF, Osterhaus AD, Fouchier RA. 2012. Airborne transmission of influenza A/H5N1 virus between ferrets. Science (NY) 336:1534–1541. 10.1126/science.1213362.

Imai M, Watanabe T, Hatta M, Das SC, Ozawa M, Shinya K, Zhong G, Hanson A, Katsura H, Watanabe S, Li C, Kawakami E, Yamada S, Kiso M, Suzuki Y, Maher EA, Neumann G, Kawaoka Y. 2012. Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets. Nature 486:420–428. 10.1038/nature10831.

Ungchusak K, Auewarakul P, Dowell SF, Kitphati R, Auwanit W, Puthavathana P, Uiprasertkul M, Boonnak K, Pittayawonganon C, Cox NJ, Zaki SR, Thawatsupha P, Chittaganpitch M, Khontong R, Simmerman JM, Chunsutthiwat S. 2005. Probable person-to-person transmission of avian influenza A (H5N1). N Engl J Med 352:333–340. 10.1056/NEJMoa044021.

Kandun IN, Wibisono H, Sedyaningsih ER, Yusharmen, Hadisoedarsuno W, Purba W, Santoso H, Septiawati C, Tresnaningsih E, Heriyanto B, Yuwono D, Harun S, Soeroso S, Giriputra S, Blair PJ, Jeremijenko A, Kosasih H, Putnam SD, Samaan G, Silitonga M, Chan KH, Poon LL, Lim W, Klimov A, Lindstrom S, Guan Y, Donis R, Katz J, Cox N, Peiris M, Uyeki TM. 2006. Three Indonesian clusters of H5N1 virus infection in 2005. N Engl J Med 355:2186–2194. 10.1056/NEJMoa060930.

Schultz-Cherry S, Webby RJ, Webster RG, Kelso A, Barr IG, McCauley JW, Daniels RS, Wang D, Shu Y, Nobusawa E, Itamura S, Tashiro M, Harada Y, Watanabe S, Odagiri T, Ye Z, Grohmann G, Harvey R, Engelhardt O, Smith D, Hamilton K, Claes F, Dauphin G. 2014. Influenza gain-of-function experiments: their role in vaccine virus recommendation and pandemic preparedness. mBio 5:e02430-14. 10.1128/mBio.02430-14.

Davis CT, Chen LM, Pappas C, Stevens J, Tumpey TM, Gubareva LV, Katz JM, Villanueva JM, Donis RO, Cox NJ. 2014. Use of highly pathogenic avian influenza A(H5N1) gain-of-function studies for molecular-based surveillance and pandemic preparedness. mBio 5:e02431-14. 10.1128/mBio.02431-14.

Lipsitch M, Galvani AP. 2014. Ethical alternatives to experiments with novel potential pandemic pathogens. PLoS Med 11:e1001646. 10.1371/journal.pmed.1001646.

Berns KI, Casadevall A, Cohen ML, Ehrlich SA, Enquist LW, Fitch JP, Franz DR, Fraser-Liggett CM, Grant CM, Imperiale MJ, Kanabrocki J, Keim PS, Lemon SM, Levy SB, Lumpkin JR, Miller JF, Murch R, Nance ME, Osterholm MT, Relman DA, Roth JA, Vidaver AK. 2012. Policy: adaptations of avian flu virus are a cause for concern. Nature 482:153–154. 10.1038/482153a.

Fouchier RA, García-Sastre A, Kawaoka Y. 2012. Pause on avian flu transmission studies. Nature 481:443. 10.1038/481443a.

Warmbrod KL, Montague MG, Gronvall GK. 2021. COVID-19 and the gain of function debates: improving biosafety measures requires a more precise definition of which experiments would raise safety concerns. EMBO Rep 22:e53739. 10.15252/embr.202153739.

Wurtz N, Papa A, Hukic M, Di Caro A, Leparc-Goffart I, Leroy E, Landini MP, Sekeyova Z, Dumler JS, Bădescu D, Busquets N, Calistri A, Parolin C, Palù G, Christova I, Maurin M, La Scola B, Raoult D. 2016. Survey of laboratory-acquired infections around the world in biosafety level 3 and 4 laboratories. Eur J Clin Microbiol Infect Dis 35:1247–1258. 10.1007/s10096-016-2657-1.

Rozo M, Gronvall GK. 2015. The reemergent 1977 H1N1 strain and the gain-of-function debate. mBio 6:e01013-15. 10.1128/mBio.01013-15.

Pappas G. 2022. The Lanzhou Brucella leak: the largest laboratory accident in the history of infectious diseases?. Clin Infect Dis 75:1845–1847. 10.1093/cid/ciac463.

Liang WN, Zhao T, Liu ZJ, Guan BY, He X, Liu M, Chen Q, Liu GF, Wu J, Huang RG, Xie XQ, Wu ZL. 2006. Severe acute respiratory syndrome—retrospect and lessons of 2004 outbreak in China. Biomed Environ Sci 19:445–451.

Bostrom N. 2011. Information hazards: A typology of potential harms from knowledge. Rev Contemp Philos 10:44–79.

Marchant GE, Pope LL. 2009. The problems with forbidding science. Sci Eng Ethics 15:375–394. 10.1007/s11948-009-9130-9.

Rotblat J. 1999. p 45–49. Science and human values. Proceedings of the World Conference on Science in Budapest.

Henkel RD, Miller T, Weyant RS. 2012. Monitoring select agent theft, loss and release reports in the United States—2004–2010. Appl Biosaf 17:171–180.

Goodrum F, Lowen AC, Lakdawala S, Alwine J, Casadevall A, Imperiale MJ, Atwood W, Avgousti D, Baines J, Banfield B, Banks L, Bhaduri-McIntosh S, Bhattacharya D, Blanco-Melo D, Bloom D, Boon A, Boulant S, Brandt C, Broadbent A, Brooke C, et al. (2023). Virology under the microscope—a call for rational discourse. mSphere 8:e0003423. 10.1128/msphere.00034-23.

Lipsitch M, Inglesby TV. 2014. Moratorium on research intended to create novel potential pandemic pathogens. mBio 5:e02366-14. 10.1128/mBio.02366-14.

European Academies Science Advisory Council. 2015. Gain of function: experimental applications relating to potentially pandemic pathogens. EASAC policy report No. 27. ISBN: 978-3-8047-3481-4.

Ficociello B, Giordano D, Incoronato F, Farinella A, Pietrangeli B. 2023. WHO Laboratory biosafety manual: a new approach to security. Ann Work Expo Health 67:425–429. 10.1093/annweh/wxac086.

Reardon S. 2023. Stricter US guidelines for 'gain-of-function' research are on the way—maybe. Nature 614:206–207. 10.1038/d41586-023-00257-0.

Lowen AC, Casadevall A, Alwine JC, Enquist LW, Goodrum FD, Imperiale MJ, Lakdawala SS. 2023. Oversight of pathogen research must be carefully calibrated and clearly defined. mBio 14:e0032323. 10.1128/mbio.00323-23.