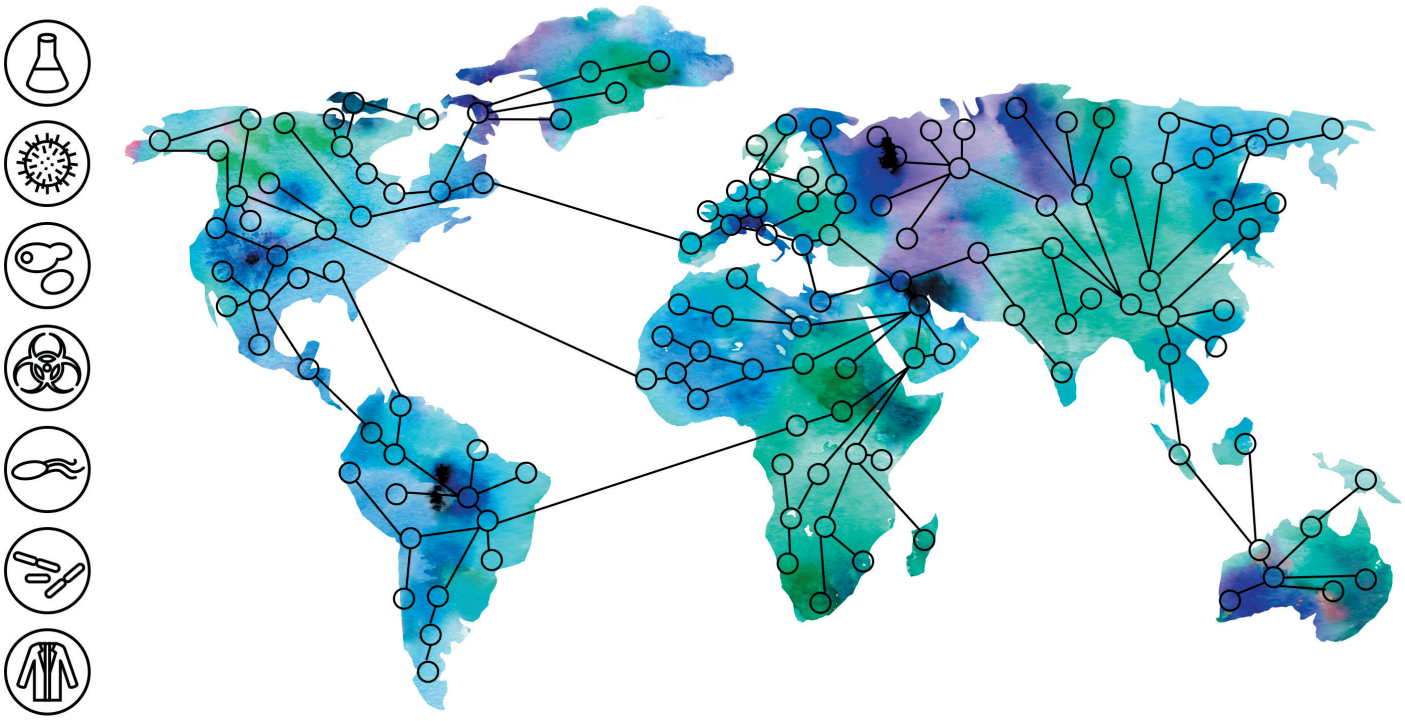
THE BIORISK MANAGEMENT CASEBOOK:

Insights into Contemporary Practices

FEBRUARY 2023



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Authors: Daniel Greene*, Kathryn Brink*, Melissa Salm*, Connor Hoffmann, Sam Weiss Evans, Megan J. Palmer

**These authors contributed equally to this work*

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REPORT RATIONALE

International advisory boards, national academies, professional societies, and members of the scientific community have called on organizations involved with life science research to manage the biosafety and biosecurity risks that can accompany discovery and innovation. As a result, several initiatives have proposed biorisk management strategies in generalized frameworks and guidance documents. However, the breadth of biorisks and the diversity of life science research pose challenges to the development, adaptation, and consistent implementation of management frameworks. Moreover, organizations lack access to concrete examples of how extant frameworks are or have been implemented in practice, hindering their ability to learn from one another about what works and under which circumstances.

The goal of the Visibility Initiative for Responsible Science (VIRS) is to share information about the value of biorisk management and how life science stakeholder organizations approach the issue. The Initiative aims to help organizations initiate biorisk management, learn from their peers, establish norms, and improve their practices over time. *The Biorisk Management Casebook* is an initial effort by researchers and policy experts at Stanford University, Harvard University, and NTI | bio to serve the goal of VIRS by compiling and summarizing case studies and interviews with leading organizations in the field. The primary aim is to highlight the variety of practices organizations currently employ to manage biorisks related to life science research and thereby showcase what is and is not working on the ground. Future visibility initiatives may help identify emerging best practices.

By providing concrete details of real practice, VIRS uniquely complements other initiatives that have developed high-level recommendations for biorisk management. The approach adopted in VIRS is distinct from, and complementary to, related efforts because (i) it is grounded in original qualitative research and (ii) it serves as a pilot for using case studies as mechanisms for knowledge sharing. VIRS begins from the assumption that the details are important, both as a source of information for others to learn from and as a normative signal that sharing is safe and valuable.

WHAT YOU WILL FIND IN THE CASEBOOK

This report synthesizes the observations from our research, expert consultations, interviews, and case studies and organizes them into four sections:

- **Key Challenges & Opportunities:** Cross-cutting observations on biorisk management gathered through VIRS that apply broadly to organizations across the life science research ecosystem and to the ecosystem itself.
- **Detailed Findings:** Summarized observations of biorisk management practices collected from our case studies and interviews, describing (i) the conditions organizations describe as important for establishing their practices, (ii) the practices they use, and (iii) the mechanisms they may use when coordinating their efforts with other stakeholders.
- **Suggested Initiatives:** Descriptions of options for future initiatives to further improve biorisk management and information sharing.
- Additional resources and details about the methods used in the report.

BIORISK MANAGEMENT CASE STUDIES

This report is also associated with, and draws from, a collection of eight case studies containing descriptions of organizations' practices. Links to the full individual case studies are available in Appendix 3. Participating case study organizations included:

- *American Society for Microbiology Journals*
- *Centre for Biosecurity and Biopreparedness*
- *Colorado State University Biosafety Office*
- *International Genetically Engineered Machine Foundation*
- *Massachusetts Institute of Technology Broad Foundry*
- *National Institute for Public Health and the Environment Biosecurity Office*
- *Science*
- *United States Department of Energy Joint Genome Institute*

KEY CHALLENGES & OPPORTUNITIES

This section provides a set of cross-cutting insights that apply broadly to organizations across the life-science research ecosystem and to the ecosystem itself. Each insight draws out common challenges we observed, examples of how those challenges have been or are beginning to be addressed, and opportunities to help overcome them.

1. **Assigning responsibilities:** There is ambiguity regarding which responsibilities for managing biorisks can or should be assumed by different stakeholder groups, both across the research ecosystem and within a given organization. Clarifying the responsibilities of different stakeholder groups and providing support, whether financial or programmatic, could help organizations overcome barriers to the adoption and improvement of biorisk management practices.

2. **Adapting frameworks to context:** Many organizations conduct biorisk assessments according to frameworks that are based on lists of concerning agents and/or experiments, and by adapting those to their local needs, capacities, and constraints. Organizations seeking to go beyond agent- and/or experiment-based lists could benefit from being exposed to frameworks that have been expanded to include other outcome-based concerns.

3. **Accessing relevant expertise:** Some organizations struggle to identify and access the expertise they believe is relevant for biorisk review. Opportunities for improving access to expertise include the cultivation of cross-disciplinary professional networks, the training of new experts, and the creation or promotion of services to support or supplement organizations' internal biorisk reviews.

4. **Codification and documentation of practices:** Organizations with established biorisk management practices rarely document them formally. Efforts to facilitate documentation and codification of biorisk management practices, as well as to strengthen and multiply mechanisms to share tacit knowledge, could enable organizations to learn about emerging norms and current conduct in the life science research ecosystem.

5. **Learning from examples:** Some types of biorisks are novel or arise infrequently in an organization's scope of work. As a result, organizations have little practical experience managing these risks. Collecting examples of how organizations manage ambiguity around novel, challenging, or infrequent biorisks could identify and highlight useful practices and facilitate collective learning.

6. **Fostering trusted networks:** Organizations are reluctant to share information about their biorisk management practices, particularly publicly, but also find value in learning about the practices of others. This points to a need to form trusted networks, perhaps in place of or complementing formal standards. Creating trusted networks can facilitate sharing and catalyze further adoption and improvement of practices among organizations.

DETAILED FINDINGS

Our detailed findings summarize case studies and interviews with representatives from a diverse set of organizations that fund, conduct, support, and/or publish life science research and manage their attendant risks. We identified 380 organizations through literature review and expert consultations, narrowed to 52 candidates with some evidence of a biorisk management practice, and reached out to 33 with the goal of creating a diverse set of case studies. We received responses from 22 and were able to develop complete case studies with nine, of which eight are included in this report. We summarize these case studies below, along with non-attributed interviews from 12 additional organizations.

Findings are organized into three parts:

- **Part I** describes the *conditions* organizations designate as important for establishing a biorisk management practice. These include an internal or external impetus to review projects and programs for risks (Section 3.1.1), a clear delegation of responsibilities (Section 3.1.2), access to the necessary expertise to assess and mitigate risks (Section 3.1.3), and the capacity to engage and communicate with researchers whose projects are under review (Section 3.1.4).

- **Part II** describes the *practices* organizations use to conduct biorisk management. These include choosing a scope of risks to consider (Section 3.2.1), assessing potential project and program risks within that scope (Section 3.2.2), creating and following plans to mitigate those risks (Section 3.2.3), and periodically reviewing and improving their approaches (Section 3.2.4).

- **Part III** describes the challenges organizations face and the strategies they use when *coordinating their risk management efforts* with other organizations. These include the challenge of assigning responsibility for risk management as projects develop from funding proposals to publication (Section 3.3.1) and the challenges and opportunities related to sharing information about biorisk management practices among organizations (Section 3.3.2).

In each section we present **background information** reflecting current normative guidance for biorisk management, our **findings** depicting the approaches that occur in practice, and in some cases, a **vignette** illustrating one or more of the ideas presented in the section.

SUGGESTED INITIATIVES

We suggest three complementary initiatives that could be pursued to improve and promote knowledge sharing about biorisk management and to strengthen ecosystem-wide attention to biorisks. While this project and casebook focus on how individual organizations understand and enact their responsibilities for biorisk management, these initiatives address how to support efforts across the ecosystem and between organizations. Where possible, they leverage the materials and insights from the VIRS as well as those of complementary efforts. Each initiative addresses one or more challenges related to biorisk management, as noted in Section 2, Key Challenges and Opportunities, that could be tackled separately or in combination. The initiatives would:

- Enhance project-level risk assessment transparency through adoption of a structured reporting framework.
- Improve organization-level practices visibility by developing mechanisms to support knowledge sharing in trusted networks.
- Increase the availability of expertise through professional activities and formal resources that facilitate network development.

Implementing these initiatives will require resources and support. NTI's Biosecurity Innovation and Risk Reduction Initiative (BIRRI) efforts, including those launched through the International Biosecurity and Biosafety Initiative for Science (IBBIS), are actively soliciting suggestions for, and seeking to direct resources toward, improving biosafety and biosecurity practices and would be well-positioned to support implementation of the initiatives suggested here. We also suggest other potential partners or lead organizations as implementers, noting that these suggestions are meant to be illustrative and not exhaustive.

Contributors & Acknowledgments

PROJECT LEADERSHIP

The VIRS leadership team developed the VIRS project and this report.

- Megan J. Palmer, Stanford University
- Sam Weiss Evans, Harvard University
- Daniel Greene, Stanford University
- Kathryn Brink, Stanford University
- Melissa Salm, Stanford University
- Connor Hoffmann, Stanford University
- Jeffrey Ladish (research assistant)
- Geetha Jeyapragasan (research assistant)

NTI | BIO

The NTI | bio team provided financial support, guidance, and oversight to the project.

- Jaime Yassif, NTI | bio
- Hayley Severance, NTI | bio
- Aparupa Sengupta, NTI | bio
- Jacob Eckles, NTI | bio
- Chris Isaac, NTI | bio
- Gabby Essex, NTI | bio

CASE STUDY CONTRIBUTORS

The following contributors co-developed case studies (see Appendix 3) through a combination of interviews, written responses, and reviews.

- Melissa Junior, American Society for Microbiology (ASM) Journals
- Line Gylling, Centre for Biosecurity and Biopreparedness (CBB) (Denmark)
- Katja Nyholm Olsen, Centre for Biosecurity and Biopreparedness (CBB) (Denmark)
- Heather Blair, Colorado State University (CSU)
- Nicole Marlenee, Colorado State University (CSU)
- Rebecca Moritz, Colorado State University (CSU)
- Joanie Ryan, Colorado State University (CSU)
- Miranda Harmon-Smith, Joint Genome Institute (JGI)
- Nathan Hillson, Joint Genome Institute (JGI)
- Lisa Simirenko, Joint Genome Institute (JGI)
- Tessa Alexanian, International Genetically Engineered Machine (iGEM) Foundation
- Piers Millett, International Genetically Engineered Machine (iGEM) Foundation
- Arturo Casini, MIT-Broad Foundry
- Ben Gordon, MIT-Broad Foundry
- Diederik Bleijs, National Institute for Public Health and the Environment (RIVM) (Netherlands)
- Stella Hurtley, *Science*

INTERVIEW PARTICIPANTS

The project conducted interviews with the following participants to gather insights about their organizations' practices, but specific practices were not attributed to particular organizations within this report. Participants who agreed to have their responses attributed to them are marked with an asterisk (*).

- Eric Perkins, Addgene
- Ali Asy, Africa CDC, Animal Health Research Institute (Egypt)
- John Inglis, Cold Spring Harbor Laboratory Press, bioRxiv, medRxiv*
- Anna Friden, Committee for Technological Innovation and Ethics (Komet) (Sweden)
- Charlotte Hall, Committee for Technological Innovation and Ethics (Komet) (Sweden)
- Maike Scharp, Bill & Melinda Gates Foundation
- Monica Arevalo, Howard Hughes Medical Institute (HHMI)
- Laura Carmona, Howard Hughes Medical Institute (HHMI)
- Ashok Gopala-Rao, Howard Hughes Medical Institute (HHMI)
- Neva Kassis, Howard Hughes Medical Institute (HHMI)
- Samantha Houston, Howard Hughes Medical Institute (HHMI)
- Joshua Russell, Howard Hughes Medical Institute (HHMI)
- Chalinee Kongsawat, National Center for Genetic Engineering and Biotechnology (BIOTEC) (Thailand)
- Vipaporn Leewattanapisarn, National Center for Genetic Engineering and Biotechnology (BIOTEC) (Thailand)
- Boonhiang Promdonkoy, National Center for Genetic Engineering and Biotechnology (BIOTEC) (Thailand)
- Aamer Ikram, National Institute of Health (Pakistan)
- Edgar Sevilla Reyes, National Institute of Respiratory Diseases (Mexico)
- Chris Somerville, Open Philanthropy Project
- Heather Youngs, Open Philanthropy Project
- Daniel Cohen, Tel Aviv University
- Joseph Kanabrocki, University of Chicago
- + 3 individuals that did not wish to be named

EXPERTS CONSULTED

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- Kavita Berger, AAAS Center for Science Technology and Security Policy
- Leonora Nusblat, Administración Nacional de Laboratorios e Institutos de Salud (ANLIS Malbrán)
- Talkmore Maruta, Africa Centres for Disease Control and Prevention (Africa CDC)
- Indira Nath, All India Institute of Medical Sciences
- Mayra Ameneiros, Argentine Normalization and Certification Institute (IRAM), Argentinian Association of Microbiology
- Renée Wegrzyn, ARPA-H
- Todd Kuiken, Ask a Biosafety Officer, North Carolina State University
- Sacha Wallace-Sankarsingh, Caribbean Public Health Agency (CARPHA), GHSA—Action Package on Biosafety and Biosecurity
- Tim Errington, Center for Open Science
- Tim Trevan, CHROME Biorisk Management Consulting
- Justine Lacey, Commonwealth Scientific and Industrial Research Organisation (CSIRO)
- Fiona Napier, Commonwealth Scientific and Industrial Research Organisation (CSIRO)
- Claudia Vickers, Commonwealth Scientific and Industrial Research Organisation (CSIRO)
- Kodi Isparan Kandasamy, Genetic Modification Advisory Committee (Malaysia), Malaysian Biosafety Department (MBD)
- Gregory Koblentz, George Mason University
- Ryan Ritterson, Gryphon Scientific
- Gautham Venugopalan, Gryphon Scientific
- Maryrose Franko, Health Research Alliance (HRA)
- Bodo Stern, Howard Hughes Medical Institute (HHMI)
- Sinead Tuite, Innovation Science and Economic Development Canada (ISED)
- Peter McGrath, InterAcademy Partnership (IAP)

- Gigi Gronvall, Johns Hopkins University—Bloomberg School of Public Health
- Filippa Lentzos, Kings College-London
- Norwati Adnan, Malaysian Biosafety Department (MBD)
- Mohana Anthonysamy, Malaysian Biosafety Department (MBD)
- Samira Senouci, Morocco Health Ministry, Moroccan Biosafety Association (MOBSA)
- Katherine Bowman, National Academy of Science (NAS)
- Nariyoshi Shinomiya, National Defense Medical College (Japan)
- Gerald Epstein, National Defense University (NDU)
- Anastasia Trataris-Rebisz, National Institute for Communicable Diseases (South Africa)
- Faheem Tahir, National Institute of Health (Pakistan), Pakistan Biological Safety Association
- Matthew Chang, National University of Singapore
- Poh Lian Lim, National University of Singapore
- Jessica Tucker, NIH Office of Science Policy, National Institutes of Health (NIH)
- Sergey Netesov, Novosibirsk State University
- R. Alta Charo, Nuclear Threat Initiative (NTI) | bio
- Chris Bakerlee, Open Philanthropy Project
- Andrew Snyder-Beattie, Open Philanthropy Project
- David Santoro, Pacific Forum
- Patrice Binder, Pasteur Institute
- Genevieve Lacroix, Public Health Agency of Canada (PHAC) Centre for Biosecurity
- Zabta Shinwari, Quaid-i-Azam University
- Bradley Dickerson, Sandia National Laboratories
- Evan Michelson, Alfred P. Sloan Foundation
- Adam Elliott, Stanford University
- Drew Endy, Stanford University
- Judi Sture, Judi Sture Biosecurity Consultancy
- Abhi Veerakumarasivam, Sunway University
- Weiwen Zhang, Tianjin University Center for Biosafety Research and Strategy
- Alexander Hamilton, United Nations Interregional Crime and Justice Research Institute (UNICRI), International Network on Biotechnology
- Ernesto Gozzer, Universidad Peruana Cayetano Heredia
- Stephen Maurer, University of California Berkeley
- Iqbal Parker, University of Cape Town
- Hatem Fakhfakh, University of Carthage—Faculty of Sciences of Bizerte (FSB)
- Andrew Ellington, University of Texas—Austin
- Dave Franz, US Army, Retired
- Nancy Connell, US National Academies of Sciences, Engineering and Medicine
- Soatiana Rajatonirina, WHO Emerging Technologies Research Prioritisation and Support Research for Health—Science Division
- Anna Laura Ross, WHO Emerging Technologies Research Prioritisation and Support Research for Health—Science Division
- Emmanuelle Tuerlings, WHO Emerging Technologies Research Prioritisation and Support Research for Health—Science Division
- Jennifer Lasley, World Organisation for Animal Health (OIE)

Acronyms & Abbreviations

ABSA	Association for Biosafety and Biosecurity
Africa CDC	Africa Centers for Disease Control
APP3	Action Package Prevent-3 on Biosafety & Biosecurity
ASEAN	Association of Southeast Asian Nations
ASM	American Society for Microbiology
BAS	Biorisk Association of Singapore
BBIC	Biosafety and Biosecurity International Consortium
BIRRI	Biosecurity Innovation and Risk Reduction Initiative
BLZ4	Biosafety Level 4 Zoonotic Laboratory Network
BSL	Biosafety Level
BWC	Biological Weapons Convention
CARPHA	Caribbean Public Health Agency
CBB	Centre for Biosecurity and Biopreparedness (Denmark)
CISAC	Center for International Security and Cooperation
COS	Center for Open Science
CSR	Council on Strategic Risks
CSU	Colorado State University
DARPA	US Defense Advanced Research Projects Agency
DOI	Digital Object Identifier
DURC	dual use research of concern
EASAC	European Academies Science Advisory Council
EBRC	Engineering Biology Research Consortium
EBRF	European Biosecurity Regulators Forum
EBSA	European Biosafety Association
ePPP	enhanced potential pandemic pathogen
FAO	Food and Agriculture Organization
FAS	Federation of American Scientists
GoF	gain-of-function
GHSA	Global Health Security Agenda
GMO	genetically modified organism
HHMI	Howard Hughes Medical Institute
IBBIS	International Biosecurity and Biosafety Initiative for Science
IBC	institutional biosafety committee
ICGEB	International Center for Genetic Engineering and Technology
ICP	EU Internal Compliance Programme (ICP)
ICSU	International Council for Science
IEGBBR	International Experts Group of Biosafety and Biosecurity Regulators
IFBA	International Federation of Biosafety Associations
iGEM	international Genetically Engineered Machine
INER	National Institute of Respiratory Diseases
IRB	institutional review board
ISF	Israel Science Foundation
IUBMB	International Union of Biochemistry and Molecular Biology
IWG	International Working Group on Strengthening the Culture of Biosafety and Biosecurity and Responsible Conduct in the Life Sciences
JGI	Joint Genome Institute, Lawrence Berkeley National Laboratory, US Department of Energy
LMO	living modified organism
MDAR	Materials Design Analysis Reporting
MIT	Massachusetts Institute of Technology
MIT-BF	Massachusetts Institute of Technology Broad Foundry
MOBSA	Moroccan Biosafety Association
NASEM	National Academies of Sciences, Engineering, and Medicine
NATO	North Atlantic Treaty Organization
NIH	National Institutes of Health
NSABB	National Science Advisory Board for Biosecurity (United States)
NTI	Nuclear Threat Initiative
OIE	World Organization for Animal Health
P3CO	Potential Pandemic Pathogen Care and Oversight
PHAC	Public Health Agency of Canada
PPE	personal protective equipment
PPP	potential pandemic pathogens
PRs	principal investigators
RIVM	National Institute for Public Health and the Environment (Netherlands)
TMP	technology with misuse potential
TOP	Transparency and Openness Promotion
UN BWC ISU	United Nations BWC Implementation Support Unit
UNESCO	United Nations Educational, Scientific and Cultural Organization
UNICRI	UN Interregional Crime and Justice Research Institute
UNSC	United Nations Security Council
UNSCR	United Nations Security Council Resolution
USG	United States Government
VERTIC	Verification Research, Training and Information Centre
WHO	World Health Organization

1. Introduction

1.1 | GOAL

The goal of the Visibility Initiative for Responsible Science (VIRS) is to share information about how life science stakeholder organizations approach biorisk management and the value of assessing and managing biorisks. By sharing this information, we aim to help organizations initiate biorisk management programs, learn from their peers, establish norms, and improve their practices over time.

Various advisory boards, national academies, professional societies, and members of the scientific community have called upon organizations involved with life science research to manage the biosafety and biosecurity risks that can accompany discovery and innovation.[1–6] In order to successfully manage these risks, organizations need to learn about effective practices and how to apply them in their specific contexts, along with the justification to spend the required time and resources. To date, several initiatives have proposed biorisk management strategies in generalized frameworks and guidance documents. However, the breadth of biorisks and the diversity of life science research poses challenges to the development, adaptation, and consistent implementation of management frameworks. Moreover, organizations lack access to concrete examples of how extant frameworks are or have been implemented in practice, hindering their ability to learn from one another about what works, and under what circumstances. Unfortunately, organizations rarely document or share their biorisk management practices, and what is shared is done so ad-hoc and informally, which hampers the potential for systemic improvement.

The Biorisk Management Casebook describes an initial effort by researchers and policy experts at Stanford University, Harvard University, and NTI | bio to serve the goal of VIRS by compiling and summarizing case studies and interviews with organizations with biorisk management practices.

In order to successfully manage risks, organizations need to learn about effective practices and how to apply them in their specific contexts.

1.2 | CONTEXT

Life science research has the potential to cause harm through biological agents. The World Health Organization (WHO) defines "biorisk" as "the probability or chance that an event caused by accidents, inadvertent or deliberate misuse of the life sciences can adversely affect the health of humans, nonhuman animals, plants and agriculture, and the environment."[7] Biorisk can involve more or less well-known biological agents,[8] can unfold over the shorter- or longer-term, and can harm living beings directly or indirectly—for example, by contributing to societal inequities or economic disruption.[7,9] Biorisk also can be created not only by biological agents themselves, but by knowledge or information that enables access to those agents, commonly referred to as "information hazards."[10]

As life science and its associated risks evolve, so too should the governance tools and mechanisms for effective biorisk management. In September 2022, WHO released a technical and normative framework document called the *Global Guidance Framework for the Responsible Use of the Life Sciences* to set foundations for the development of national approaches to biorisk management.[7] In the document, WHO defines biorisk management as:

> An integrated, overarching approach to address the risks associated with the life sciences research enterprise, from accidents and inadvertent actions to deliberate misuse. Biorisk management relies on three core pillars: biosafety, laboratory biosecurity and the oversight of dual use research. Biorisk management involves the quantitative or qualitative forecasting and evaluation of the probability of harm occurring and subsequent consequences (risk assessment), together with the identification and implementation of technologies, measures, or practices to avoid or minimize their likelihood or impact (risk mitigation).[7]

With an eye to the near future, WHO determined that *"[b]uilding effective biorisk management systems will require experimentation and regular revisiting of tools and mechanisms and their implementation. It will also require the development of tools and mechanisms to exchange information among different stakeholders."*[7] **By directly taking this challenge, VIRS complements these and other ongoing initiatives with long-standing commitments to biorisk management (see Table 1 on page 12).**

There are many high-level frameworks and guidance documents for biorisk management,[11–16] but surprisingly little is known about which ones are implemented in practice and how. There is also little information available about how organizations conceptualize risks, adapt guidelines to fit local needs, or communicate and share information on biorisk management across research programs and throughout the research life cycle.

The appropriate level of public transparency around the management of biorisks has been a topic of policy discussions, such as those of the US National Science Advisory Board for Biosecurity (NSABB) in its recommendations on the development of, and revisions to, the dual use research of concern (DURC) policies and the potential pandemic pathogens care and oversight (P3CO) policies. However, policy discussions often focus on assessing the risks of sharing information and less so on the organizational needs and benefits of sharing.[17]

Several existing efforts are seeking to identify useful tools and mechanisms to manage biosafety and biosecurity risks. While most of these efforts focus on collecting and proposing general recommendations for biorisk management, others are beginning to identify the need to collect specific examples of practice and develop mechanisms for information-sharing among organizations. Examples of these efforts are highlighted in the table below, along with related initiatives to promote information-sharing for rigorous and reproducible research.

Table 1 | Selected examples of scientific transparency and/or visibility initiatives

EXAMPLE	DESCRIPTION
Advanced Research Workshop: Security and Resilience for Emerging Synthetic Biology and Biotechnology Threats[18]	A workshop held in 2019 organized by the North Atlantic Treaty Organization (NATO) for scientists and experts in the field of synthetic biology and biotechnology, risk assessment, management, and communication to discuss potential biosecurity governance strategies and offer perspectives for collaboration in oversight and future regulatory guidance
Biosafety Clearing-House[19]	A mechanism set up by the Cartagena Protocol on Biosafety to facilitate the exchange of information on Living Modified Organisms
CBRN CoE Project 18[20]	A program that ran between 2012–2014 for reinforcing a culture of biosafety and biosecurity by raising awareness of dual use concerns in biotechnology among universities and research institutes
Enhancing Scientific Reproducibility in Biomedical Research Through Transparent Reporting[21]	A workshop in 2019 organized by the National Academies of Sciences, Engineering, and Medicine (NASEM) to enhance transparent reporting of preclinical research findings across the biomedical research life cycle
GHSA Action Package Prevent-3 on Biosafety & Biosecurity (APP3)[22]	A collection of experts and leaders from countries and nongovernmental organizations that seek to advance global biosafety and biosecurity capacity under the auspices of the Global Health Security Agenda (GHSA)
The International Experts Groups of Biosafety and Biosecurity Regulators (IEGBBR) Mobile Application of Biosafety, Biosecurity and Dual-Use Oversight[23]	A publicly available reference tool for countries aiming to develop or strengthen their national biosafety, biosecurity, or dual use oversight by providing 11 detailed examples of the national oversight systems of the IEGBBR member countries
Materials Design Analysis Reporting (MDAR) Framework[24]	A policy framework launched in 2019 to promote transparent reporting that would support article-level application of the principles of the Transparency and Openness Promotion (TOP) guidelines (see below),[25] with a focus on implementation through journal policies and editorial practice
National Science Advisory Board for Biosecurity (NSABB) Meeting 2020[26]	A meeting convened in 2020 by the NSABB to discuss issues of security and public transparency when sharing information about research involving enhanced potential pandemic pathogens (ePPPs)
Nuclear Threat Initiative (NTI) Biosecurity Innovation & Risk Reduction Initiative (BIRRI)[27]	An initiative that began in 2018 to work with stakeholders around the world to mitigate the misuse of tools and technologies for biowarfare and to reduce the risks of high-consequence biological accidents
NTI Global Biosecurity Dialogue[28]	A forum that began in 2018 to bring together senior officials from ministries of foreign affairs, health, defense, agriculture, and other relevant sectors to advance international biosecurity
Open Scholarship Knowledge Base[29]	A platform for sharing open scholarship resources
Principles and Guidelines for Reporting Preclinical Research[30]	A workshop in 2014 hosted by the National Institutes of Health (NIH) with the Nature Publishing Group and Science on the issue of reproducibility, rigor, and transparency of research findings
Stakeholder Engagement Workshop on Implementation of the USG Policy for Institutional Oversight of Life Sciences DURC[25]	A public workshop in 2017 hosted by the US government to engage with stakeholders and facilitate information sharing among research institutions regarding their approaches to, and experiences with, implementing the USG policy for oversight of DURC
Transparency and Openness Promotion (TOP) Guidelines[31]	Published by *Science* in 2015, the TOP Guidelines are an initiative of the Center for Open Science (COS) that provides a suite of tools to guide journals and funders in the implementation of better, more transparent research
WHO Ensuring Responsible Use of Life Science Research[32]	An initiative that began in 2020 with a series of dialogues and consultative meetings, and the establishment of expert working groups that led to the development of the global guidance framework for the responsible use of the life sciences. It identifies a set of mechanisms to support responsible life science research, including the creation of research oversight mechanisms, framework, and policies such as international regulations, professional codes of conduct, and educational campaigns to raise awareness

1.3 | OUR APPROACH

VIRS was conceived by a multi-stakeholder group during the April 2019 working group meeting of NTI's Biosecurity Innovation and Risk Reduction Initiative (BIRRI) (see Appendix 1). The efforts reflected in this casebook serve to advance the VIRS concept by piloting mechanisms for knowledge-sharing to improve biorisk management in the life science ecosystems.

The work was undertaken in four parts:

1. Conducting interviews with life-science research stakeholders to gather insights about useful biorisk management strategies;
2. Partnering with stakeholders to co-develop case studies that describe the "how" and "why" of their biorisk management practices in more detail;
3. Conducting workshops to gather and share insights and foster connections among stakeholders;
4. Engaging in related efforts to develop guidance to support biorisk management, including the Global Biosecurity Dialogues, the Global Health Security Agenda Action Package Prevent-3, and WHO's consultative processes to develop the *Global Guidance Framework for the Responsible Use of the Life Sciences.*

This approach is distinct from many of the others listed above in Table 1 for two reasons:

First, it is grounded in original qualitative research. While VIRS complements other initiatives that have similarly adopted consultative and participatory multi-stakeholder approaches to endorse recommendations for biorisk management practice and compile lists of many different frameworks and tools, our approach uniquely provides concrete details of real practice. The details of actual biorisk management practices are important, both as a source of information for others to learn from and as a normative signal that sharing is safe and valuable.

To explore how to provide the necessary level of detail, we developed eight case studies in collaboration with a diverse set of organizations that practice biorisk management related to life science research. We pursued case studies from different regions and organizational types (e.g., oversight bodies, funders, service providers, and publishers) and across different focal areas of concern (e.g., biosafety, biosecurity, and dual use). The case studies are intended to stand alone as shareable learning tools, akin to business-school case studies. We complemented the case studies with consultations with biorisk experts and interviews with representatives from additional organizations. Their comments help to contextualize the information presented in the case studies, and inform key takeaways, summary findings, and suggested initiatives below.

The details of actual biorisk management practices are important, both as a source of information for others to learn from and as a normative signal that sharing is safe and valuable.

Second, our approach piloted the use of case studies and workshops as formal mechanisms for information-sharing. The central premise of VIRS is that formalizing and sharing risk management practices can help to establish norms and promote cross-organizational learning. We tested this premise by co-creating case studies and by hosting two workshops with case-study organizations (comprising life science researchers, funders, service providers, and publishers) and coordinating bodies such as NTI | bio and WHO to receive feedback on our approach. Effectively, the case studies captured the "how" and "why" of organizations' biorisk management practices in addition to the "what" of shareable information and "with whom." As we describe below, many of the organizations involved found the development of case studies to be a helpful exercise on its own. Through the workshops, they also discovered useful insights from other organizations' case studies and were interested in continuing to learn from one another to improve their practices.

1.4 | LIMITATIONS

This work provides an important starting point but does have some limitations and challenges worth noting as a direction for future work.

First, a primary goal of VIRS was to enable organizations to learn from one another by identifying and sharing "effective biorisk management practices." However, determining the efficacy of biorisk management practices is exceptionally difficult, given the contingencies of context and the lack of well-established standards and measures for systematic evaluation. Ultimately, this study relied on consultations with experts and on organizations' self-reporting to select practices *perceived as* effective for inclusion in this study. Additional work will be needed to evaluate their efficacy in the development of best practices.

A key limitation is "organizational imposter syndrome," where practitioners may have been reluctant to share their processes of biorisk management out of concern that they may be judged to be substandard in relation to their peers, even though their processes, in our analysis, could be considered as good or better than others with which we engaged.

While not explicitly a limitation, in the process of creating this casebook, we also broadened the scope of risks that we examined. VIRS originally focused on "dual use risk management." In international outreach we found unfamiliarity with, and inconsistency around, the meaning of the term "dual use." We also found very few examples of formalized dual use risk management practices specifically scoped to protect against the deliberate misuse of knowledge from research.[7,8] Instead, most organizations had practices intended to address a blend of biosafety and/or biosecurity concerns that might emerge from laboratory practices or from research information. As a result, we extended our scope to "biorisk management" to more explicitly capture this broader range of concerns.

Though VIRS participants represent a breadth of organizational types and regional contexts, the ability to draw general conclusions from our findings is limited by our small sample size. Despite extensive international outreach efforts, organizations based in the United States ultimately are overrepresented, reflecting the networks in which the authors were already embedded. This may have influenced our interpretation of key challenges and opportunities and impact the relevance of our findings for other regional and regulatory contexts, particularly those with less developed life science research or biorisk management capacities. Another limitation is that we did not engage with organizations in industry. Future initiatives to examine and incentivize the implementation of systemwide biorisk management practices should seek to broaden the scope achieved by VIRS (see Part 4, Suggested Initiatives).

VIRS aimed to make biorisk management practices visible where possible but did not focus extensively on reasons why transparency currently is limited. Future work to examine the incentives and disincentives that affect knowledge sharing about biorisk management could enable future visibility initiatives to reach a broader range of organizations. A particular area in need of attention is around what one of the reviewers of this casebook called "organizational imposter syndrome," where practitioners may have been reluctant to share their processes of biorisk management out of concern that they may be judged to be substandard in relation to their peers, even though their processes, in our analysis, could be considered as good or better than others with which we engaged.

Additional limitations arose, in part, from the context in which VIRS was conducted. In particular, our efforts coincided with the start of the COVID-19 pandemic. On the one hand, COVID-19 reminded the world of the power of biological threats to cause profound disruption and loss of life. On the other hand, it required key stakeholders in charge of biorisk management, in some cases, to shift attention and resources from improving research risk management to the immediate needs of COVID-19 response. Some of the organizations we initially contacted also became more reluctant to share their biorisk management practices, likely as a result of the geopolitical climate created by uncertainty over the origins of SARS-CoV-2. We discuss these dynamics in more detail throughout the Findings sections of this report.

1.5 | RELATED EFFORTS

There are several concurrent efforts related to the VIRS project that our work may inform and inspire. First, in February 2022 NTI | bio proposed the establishment of a new international organization, the IBBIS, to "strengthen global biosecurity norms and develop innovative, practical tools and incentives to uphold them."[33] IBBIS is well-positioned to leverage insights from VIRS to further develop and recommend a set of best practices for biorisk management among life science stakeholder organizations worldwide. IBBIS also could facilitate ongoing exchanges among and between organizations that practice biorisk management and organizations that seek to develop biorisk management practices, which could include efforts to advance norms around sharing of biosafety and biosecurity risk management practices, where possible. NTI also may help incubate and drive new initiatives and pilot projects via the ongoing BIRRI, which helped conceive of and launch VIRS (see Part 4, Suggested Initiatives for further details).

Second, the Science Division of WHO is working with Member States, partners, and a broad range of multidisciplinary stakeholders from around the world to support responsible life sciences research. It has conducted a series of "DURC dialogues" with various stakeholders, and in September 2022 released its updated *Global Guidance Framework for the Responsible Use of the Life Sciences.*[7,34–36] The framework provides global perspectives on principles, tools, and mechanisms the detailed case studies and insights developed in VIRS may complement.

Finally, there are many different efforts specific to certain regions or types of organizations in the life science research ecosystem that may carry on this work, such as those led by the Africa Centres for Disease Control and Prevention (Africa CDC) and Engineering Biology Research Consortium (EBRC).

1.6 | CASEBOOK STRUCTURE

This report synthesizes the observations from our research, expert consultations, interviews, and case studies and organizes them into four sections:

- **Key Challenges & Opportunities:** Cross-cutting observations on biorisk management gathered through VIRS that apply broadly to organizations across the life science research ecosystem and to the ecosystem itself;
- **Findings:** Summarized observations of biorisk management practices collected from our case studies and interviews, describing (i) the conditions organizations describe as important for establishing their practices, (ii) the practices they use, and (iii) the mechanisms they use when coordinating their efforts with other stakeholders;
- **Suggested Initiatives:** Descriptions of options for future initiatives to further develop improvements in biorisk management and information sharing;
- **Methods:** Additional details on the research methods and process used to develop the casebook;
- **Appendices:**
  - *Appendix 1*— Original VIRS Concept Paper: Original paper proposing the VIRS concept and describing the problem it addresses, its goals, and opportunities for pilot programs;
  - *Appendix 2*—Case Study Template: Structured template used to develop case studies, including section descriptions and guiding questions;
  - *Appendix 3*—Case Studies: Digital Object Identifiers (DOIs) for individual case studies;
  - *Appendix 4*—Interview Questions: Questions used to guide non-attributed interviews;
  - *Appendix 5*—Additional Resources: Curated compilations of useful information on current biorisk management guidance documents, models, tools, and policies, as well as a list of public statements by diverse stakeholder groups advocating for or pledging to conduct biorisk management.

This report is also associated with and draws from *The Biorisk Management Case Studies,* a collection of eight case studies containing detailed descriptions of organizations' biorisk management practices.

1.7 | NOTES FOR READERS

The casebook is not a biorisk management manual nor a rigorous assessment of the efficacy of specific practices. Its primary aim is to make visible the variety of practices organizations currently employ to manage biorisks related to life science research, not to drive the development of specific international standards and best practices for biorisk governance. Case studies describe conditions at one point in time, yet the nature of biorisks and of organizations' biorisk management practices continue to evolve. More data on the evolution and efficacy of these practices across a larger sample of organizations will be required to promote any of them as a best practice.

By showcasing what is and is not working on the ground, the casebook develops initial evidence of *potential* best practices and emerging norms upon which biorisk management standards could one day become formalized. For now, strategies to promote and strengthen biorisk management should focus on making visible what is being tried, not just what seems best. We encourage readers to use the casebook as a signpost to other biorisk management resources, a starting point in understanding the current state of biorisk management in practice, and an inspiration for future work to safeguard the life science research enterprise moving forward.

For now, strategies to promote and strengthen biorisk management should focus on making visible what is being tried, not just what seems best.

Different types of readers may find different forms of value in the casebook. For example:

- **Biorisk management practitioners, including life scientists,** might review the Findings section and relevant individual case studies (Appendix 3) for the granular detail necessary to update or improve their practices. Case studies contain extensive detail about when and how risks are assessed and mitigated, and how risk management systems are reviewed and improved over time. Practitioners might also find value in using the case study template (Appendix 2) to document and reflect on their own biorisk management practices;
- **Policymakers** might review the Key Challenges & Opportunities and Findings sections to learn about how current risk-management policies are implemented, identify their limitations, and take inspiration for potential improvements. For example, Section 3.2.1 notes the influence of policy frameworks on the scope of biorisks that organizations consider, and Section 3.3.1 describes the importance of government policy and legal frameworks for empowering organizations such as Denmark's Centre for Biosecurity and Biopreparedness (CBB) to review research projects across the life science research life cycle;
- **Advocates** promoting the development and promulgation of biorisk management norms might connect with the individuals and organizations identified in the Contributors section and review proposed future work in Section 4, Suggested Initiatives.

We also note that when we refer to "research projects" throughout this document, they are to be considered across many scales—from a specific grant, protocol, or manuscript to an overall research program. When we refer to organizations, we mean life science research stakeholder organizations that have or could have processes in place to manage biorisks. These organizations are further composed of individuals who can have distinct responsibilities based on their roles within the organization. Organizations can include groups that fund research or that conduct oversight, journals that publish research, institutions that conduct research, service providers that support research, and organizations that have hybrid or other roles.

1.8 | SUMMARY OF PARTICIPATING ORGANIZATIONS

Bold type = case study
Normal type = interview (specific practices not attributed to specific organizations)

While a much broader network was involved in initial expert consultation and outreach (see Contributors), the following organizations listed in Table 2 participated in case studies and interviews about their practices that formed the principal materials for our findings.

Table 2 | Summary of participating organizations

Oversight / Advisory	**Centre for Biosecurity and Biopreparedness (CBB)—*Denmark*** **National Institute for Public Health and the Environment (RIVM) Biosecurity Office—*Netherlands*** Committee for Technological Innovation and Ethics (Komet)—*Sweden*
Funder	Open Philanthropy—*United States* Bill & Melinda Gates Foundation—*United States* Howard Hughes Medical Institute (HHMI)—*United States*
Research Performer (often combined with other roles including funding, management, and biosafety oversight)	**Colorado State University (CSU) Biosafety Office—*United States*** **Massachusetts Institute of Technology-Broad Foundry (MIT-BF)—*United States*** University of Chicago—*United States* Tel Aviv University—*Israel* National Institute of Respiratory Diseases (INER)—*Mexico* National Institute of Health (NIH)—*Pakistan* National Center for Genetic Engineering and Biotechnology (BIOTEC)—*Thailand* Animal Health Research Institute—*Egypt*
Publisher	***Science*—*United States*** **American Society for Microbiology (ASM) Journals—*United States*** bioRxiv—*United States*
Service Provider / Other	**Joint Genome Institute (JGI)—United States** **International Genetically Engineered Machine (iGEM) Foundation—France** Addgene—*United States*

2. Key Challenges & Opportunities

This section provides a set of cross-cutting insights that apply broadly to organizations across the life-science research ecosystem and to the ecosystem itself. Each insight draws out common challenges we observed, examples of how those challenges have been or are beginning to be addressed, and what opportunities exist to help overcome them. These insights are drawn from and build upon the more detailed findings that compare specific elements of biorisks management found in Section 3, Detailed Findings.

2.1 | ASSIGNING RESPONSIBILITIES

There is ambiguity regarding which responsibilities for managing biorisks can or should be assumed by different stakeholder groups, both across the research ecosystem and within a given organization. Clarifying the responsibilities of different stakeholder groups and providing support, whether financial or programmatic, could help organizations overcome barriers to the adoption and improvement of biorisk management practices.

Clarifying the responsibilities of different stakeholder groups and providing support, whether financial or programmatic, could help organizations overcome barriers to the adoption and improvement of biorisk management practices.

Challenges

Organizations require dedicated staff and resources, as well as support from top management, to implement biorisk management practices. Support from top management is critical not only for the allocation of financial and human resources, but also for process approvals, infrastructure investments, and ensuring that processes are sustainable. However, these resources are not always readily available, especially for organizations (i) with smaller budgets, (ii) in institutional environments or geographical regions where biorisk management is not prioritized, or that (iii) prioritize biosafety risk management to the exclusion of biosecurity risk management. Advisory documents recommending laboratory research best practices from a biosafety perspective, such as the US Centers for Disease Control & Prevention (CDC)'s *Biosafety in Microbiological and Biomedical Laboratories,* clearly define the responsibilities of top level management for managing biosafety risks; however, ambiguity remains regarding their responsibilities for managing biosecurity risks, which often appear more distant and diluted. When stakeholder groups lack clear assignments of responsibility and when organizations lack resources to provide support, they may opt to forgo aspects of biorisk management or do so minimally even in instances when individuals or leadership within the organization would like to do more.

Organizations that do not identify biorisk management as their responsibility may opt not to implement it. The scientific community has called upon multiple stakeholder groups—ranging from funders, research performers, publishers, service-providers, and regulatory and oversight bodies—to develop proactive measures for mitigating risks that may arise during the research and development process. In practice, however, research institutions seem to bear much of the oversight responsibility; in some cases, other stakeholders specifically rely on research institutions to fulfill key oversight functions.

Bright spots

Organizations with more developed biorisk management practices describe them as being useful. Commonly cited benefits include protecting staff and communities from biological risks and shielding the organization against liability or external criticism. For example, one interviewee described a dramatic reduction in laboratory accidents following the implementation of enhanced biorisk management protocols at their organization (Interviews). Another organization used the data captured through their biorisk management system to identify gaps in current biosecurity education and governance as well as to determine priorities for applied biosafety and biosecurity research (Case: iGEM).[37–39]

Opportunities

Financial resources and programmatic support could be developed to help organizations implement or improve biorisk management practices. For example, grant programs could be established to provide multi-year financial support for capacity-building activities, such as hiring or training staff, or twinning programs could be developed or expanded to foster knowledge sharing between organizations with more and less established practices. This could help to identify and support leaders within organizations who are willing to champion both biosafety and biosecurity management practices.

Additional resources could be allocated for more empirical research into the barriers to implementation organizations presently encounter.

Clarifying the responsibilities of stakeholders throughout the research life cycle could catalyze improvements, especially among organizations with under-developed protocols. WHO *Global Guidance Framework for the Responsible Use of the Life Sciences* presents one recent attempt to enumerate key stakeholder groups and their unique responsibilities for managing biorisks related to life science research.[7] Additional resources could be allocated for more empirical research into the barriers to implementation organizations presently encounter, including ambiguities about how to implement practices as well as concerns about the perceived costs of implementation. Not only could this generate strategies for reducing barriers to implementation, but it could yield additional insight into which stakeholder groups and organizations can or should take on responsibility for diverse aspects of biorisk management. Policymakers or regulatory authorities could then use this information to create and enforce laws or policies that more explicitly specify the respective responsibilities of different life science research stakeholders.

2.2 | ADAPTING FRAMEWORKS TO CONTEXT

Many organizations conduct biorisk assessments according to frameworks based on lists of concerning agents and/or experiments, and adapting those to their local needs, capacities, and constraints. Organizations seeking to go beyond agent- and/or experiment-based lists could benefit from being exposed to frameworks that have been expanded to include other outcome-based concerns.

Challenges

Biorisk management requires more than a one-size-fits-all approach. Organizations with developed biorisk management practices adapt general frameworks for identifying, assessing, and managing biosafety and biosecurity concerns to the specificities of their organizational contexts; the types of changes required may vary depending on an organization's stage in the research life cycle and the types of life science research they conduct or support. Acknowledging that what works well in one context may differ in another, it is unclear how difficult it could be to establish a general code of best practice.

Bright spots

Existing frameworks provide useful starting points for organizations to develop individualized biorisk management practices. In addition to or as part of compliance with statutory regulations, several organizations use and adapt agent-specific guidance, such as lists of high-risk agents and toxins (e.g., Australia Group Common Control Lists[40] or US Select Agents and Toxins List[41]), and experiment-centered guidance, such as the seven areas of concern elaborated in the 2004 Fink Report,[8] to develop their biorisk management practices. Some organizations expanded the risks they considered beyond those represented in agent- and experiment-based lists to include potential societal, environmental, economic, and public health consequences, even when this was not explicitly required (Case: iGEM, JGI, RIVM). Moreover, research institutions generally establish biosafety and/or biosecurity oversight committees to assess risks and develop mitigation plans (Interviews, Case: CSU, MIT-BF).[7,42–44]

Opportunities

Organizations could benefit from the promulgation of frameworks that further expand upon agent- and experiment-centered lists. Agent- and experiment-based lists can provide useful starting points for organizations that are new to biorisk management; however, their limited scope may prevent recognition of the broad range of risks that can accompany life science research. Where possible, organizations should be encouraged to use frameworks that expand on or move beyond agent- and experiment-centered lists. For example, the RIVM Dual-Use Quickscan[45] supports the identification of agent- and experiment-based risks, but also includes questions that enable organizations to consider the ecological, economic, and societal consequences of potentially risky research (Case: RIVM). Dual-Use Quickscan could be a useful starting point for organizations looking to define an initial scope of risks or to broaden the scope of risks they consider during biorisk assessment. Alternatively, MIT-BF risk assessment matrix (Case: MIT-BF) and the Public Health Agency of Canada (PHAC) Decision Tree for the Identification of Dual-Use Potential in Life Sciences Research[46] take outcome-based approaches that could likewise be useful for evaluating a broad spectrum of risks related to life science research. WHO *Global Guidance Framework for the Responsible Use of the Life Sciences* also provides a checklist and six-step approach that can be adapted broadly.[2] There is an opportunity for policy-directed interventions to investigate the utility and efficacy of these frameworks within and across different organizational contexts.

Organizations could benefit from the development of region-specific frameworks. Global-level guidance aims to be sufficiently general to apply across diverse contexts. However, region-specific frameworks may be easier to adapt, given that research economies are organized and coordinated differently across regions in ways that impact organizations' local needs and responsibilities. Africa CDC is one example of a regional coordinating body working to develop guidance that specifically addresses biorisk management in the African life-science research ecosystem. The IEGBBR mobile app[23] lists examples of biosafety, biosecurity, and dual use oversight systems from 11 countries and could be consulted as a resource in the development of regional or national frameworks.

2.3 | ACCESSING RELEVANT EXPERTISE

Some organizations struggle to identify and access the expertise that they believe is relevant for biorisk review. Opportunities for improving access to expertise include the cultivation of cross-disciplinary professional networks, training of new experts, and creation or promotion of services to support or supplement organizations' internal biorisk reviews.

Challenges

Organizations face uncertainty in assessing which expertise is relevant for biorisk management, in general or for specific projects. Life science research can engender an exceptionally broad range of biorisks that depend on the specific activities being undertaken. Additionally, biorisks evolve continually alongside technological advances. In light of this, current guidance recommends leveraging multidisciplinary expertise for project review. Accordingly, the types of expertise most relevant for different reviews will vary. Some organizations may not recognize which type of expertise is useful or necessary for conducting assessments; others may discount the expertise they already have. In practice, however, the input of life scientists tends to be overrepresented when compared to other potentially relevant disciplines or professions, such as policy, public health, security, or social science. This suggests that organizations may not realize the value in, or lack adequate access to, cross-disciplinary networks of expertise.

Opportunities for improving access to expertise include the cultivation of cross-disciplinary professional networks, training of new experts, and creation or promotion of services to support or supplement organizations' internal biorisk reviews.

Organizations are concerned about their ability to steadily identify and/or access suitable experts for conducting biorisk review. Currently, organizations rely on small pools of individuals to provide expert consultations and to make important judgment calls, with the same individuals sometimes being consulted across multiple organizations. These individuals are often volunteers and may have competing responsibilities, which presents a challenge to efforts aimed at scaling and sustaining biorisk management systems. In addition, relying on a handful of well-known and highly regarded experts limits the diversity of perspectives that are incorporated into biorisk review and concentrates decision-making authority, perhaps inadvertently, among a select few. Further, there may be qualified individuals whose perspectives are underrepresented or underutilized because they are not well integrated into the professional networks of those seeking biorisk management expertise.

Professional communities of biorisk experts are under-developed in some regions. To adapt biorisk management frameworks to context, organizations may benefit from access to local or regional biorisk experts. However, in some regions, biorisk management expertise may be scarce or experts may not be fully integrated into an accessible professional community. Some organizations also may encounter difficulties connecting with experts outside of their region due to language barriers, further limiting the pool of experts accessible to them.

Bright spots

Several organizations we engaged with successfully implemented multidisciplinary and cross-sectoral review. For example, iGEM's review committee includes biosafety officers, former weapons inspectors, practicing researchers, public health officials, and science and technology studies scholars that each contribute differing perspectives to the review process (Case: iGEM). Similarly, CBB leverages experts across domains that include microbiology, bioweapons dispersal or manufacturing processes, and synthetic biology (Case: CBB). MIT-BF involved policy experts, synthetic biologists, law enforcement, international safety and security experts, United States government defense and intelligence community members, and local staff in their Biosecurity Advisory Committee (Case: MIT-BF).

There are multiple avenues for sourcing expertise. Some organizations rely primarily on their extensive in-house expertise (Case: ASM, CBB). Others successfully rely upon collegial networks to recruit external experts formally or informally as needed (Case: iGEM JGI, MIT-BF, *Science;* Interviews). In other cases, paying external consultants is a viable strategy for recruiting the necessary expertise. For example, iGEM has evolved from using voluntary experts to now including both paid full-time staff that coordinate volunteers as well as paid consultants (Case: iGEM).

Opportunities

Cultivating cross-disciplinary networks of experts and connecting them with life science organizations could reduce barriers to accessing expertise. There are professionals both in the life sciences and in external disciplines whose expertise may be currently under appreciated or undersought. For example, policy, public health, security, and social science experts are underrepresented among the individuals organizations consulted. These professionals could be identified and incentivized to participate in biorisk management via honoraria or based on mutual benefit, when participating in biorisk management overlaps with individuals' core duties or responsibilities. When multiple experts are involved, mechanisms should be implemented to enable decision-making in cases of disagreement, such as concentrating ultimate authority in a single individual. Additionally, investing in professional biorisk management education, training, and accreditation[47–50] or developing or expanding programs that feature hands-on, practical experiences with biosafety and biosecurity could further increase the pool of experts available for biorisk consultations or review. Such programs could facilitate networking opportunities and coordinators could develop regularly maintained databases of experts that organizations can draw from for biorisk management expertise.

There are professionals both in the life sciences and in external disciplines whose expertise may be currently under appreciated or undersought.

Regional or national capacity-building programs could increase accessibility to biorisk management expertise where professional communities are currently under-developed. As described above, such capacity-building programs could include education, training, and accreditation opportunities or hands-on experiences designed to cultivate biosafety and biosecurity expertise. Experts with specialized knowledge of regional or national contexts may be particularly well-suited to helping organizations adapt more general biorisk management frameworks to their local contexts. Regional or national efforts could also help to reduce the impact of language barriers as a challenge to accessing expertise.

The creation of a service, or promotion of existing services, that can supplement organizations' internal capacities for project review could lower barriers to implementation of biorisk management practices. While third-party experts may be less familiar with the norms and contexts specific to each organization, these services could help streamline expert engagement, create cross-organizational databases of risk management examples from which to learn, standardize project review, and reduce the burden on organizations to develop their own practices *de novo.* This also could help create external mechanisms of accountability and ensure institutional knowledge about biorisk management is not lost.

2.4 | CODIFICATION & DOCUMENTATION OF PRACTICES

Organizations with established biorisk management practices rarely document them formally. Efforts to facilitate documentation and codification, as well as to strengthen and multiply mechanisms to share tacit knowledge, could enable organizations to learn about emerging norms and forms of current conduct in the life science research ecosystem.

Challenges

Certain aspects of biorisk management, such as relationship-building and discussion, are highly context-dependent and thus difficult to codify. Organizations near universally describe "discussion" as essential to the biorisk review process and the development of mitigation measures. In practice, however, it is difficult to codify the specifics of how to conduct or structure said discussions since they often rely upon tacit knowledge and interpersonal relationships.

Without formal documentation of biorisk management practices, protocols for managing risks cannot be easily codified.

Biorisk management processes may be well-established within an organization but not formally documented. Reasons for a lack of documentation vary. In some instances, organizations may perceive documentation development to be overly resource-intensive and to offer limited benefits. Responsible parties may avoid detailed documentation of their processes because of the perception that, should an adverse event occur, and documented processes have been followed imperfectly, the responsible party or the organization as a whole might face greater consequences. Without formal documentation of biorisk management practices, however, protocols for managing risks cannot be easily codified. On the one hand, the lack of formal documentation may enable organizations to more readily adapt to emerging concerns or swiftly tailor their biorisk management practices as long as tacit knowledge is maintained. Conversely, the lack of documentation presents barriers to an organization's ability to preserve biorisk management knowledge over time as well as to its ability to share information readily with other organizations.

Bright spots

Organizations are able to articulate their biorisk management practices even if they lack formal documentation. This ability suggests that organizations have biorisk management practices that they are ultimately able to reflect upon and that may be at least partially codified. Consequently, future documentation of many elements of their processes is highly possible.

Organizations found the VIRS case study development and interview process to be useful mechanisms for reflecting on their biorisk management practices. For case study organizations, VIRS provided a structured template that enabled them to document their practices, in several cases for the first time. Both case study organizations and interviewees described having achieved greater clarity about the design decisions, successes, and shortcomings of their own processes by virtue of discussing them with a third party. This suggests that organizations can find value in codification and documentation and could be incentivized to invest more in doing so.

Opportunities

Facilitating documentation and codification of organizational protocols and practices could enable multiple stakeholder groups to learn about emerging norms and forms of current conduct in the life science research ecosystem. Internally, this would enable organizations to record, benchmark, learn from, and improve their processes over time. Cross-organizationally, this would allow diverse stakeholders to communicate and coordinate strategies more easily with one another. More broadly, it would enable norm-setting bodies to put forth recommendations that are responsive to emerging best practices, including organizations' continual experimentation with different approaches to biorisk management. Promulgation of the VIRS case study template could empower organizations to document their practices or serve as inspiration for the development of other forms of documentation. A service where organizations could talk through their existing practices with the aid of a consultant, akin to the VIRS case study development process, could be useful for documenting practices methodically while facilitating reflection that could enable improvements.

Promulgation of the VIRS case study template could empower organizations to document their practices or serve as inspiration for the development of other forms of documentation.

For aspects of biorisk management that are not easily codified, developing mechanisms to share tacit knowledge could enable organizations to learn internally and from one another more readily. Interpersonal relationships are essential to biorisk management, particularly during the review and mitigation stages during which reviewers and researchers come to an agreement about the measures required to undertake research safely and responsibly. Discussion and relationship-building may be codified as components of any given biorisk management protocol; however, it would be difficult and perhaps ill-advised to develop highly specific guidance on how to standardize them. In the absence of codification, organizations could learn from one another through hands-on training, shadowing each other's practices, or short-term exchange programs.

2.5 | LEARNING FROM EXAMPLES

Some types of biorisks are novel or arise infrequently in an organization's scope of work. As a result, organizations have little practical experience managing these risks. Collecting examples of how organizations manage ambiguity around novel, challenging, or infrequent biorisks could identify and highlight useful practices and facilitate collective learning.

Challenges

Organizations are reluctant to share examples of their decision-making processes and outcomes for specific projects. Privacy, liability, intellectual property, and security concerns all may dissuade organizations from publicly sharing detailed information about or comprehensive examples of individual projects, including how specific risks were managed therein. These barriers to sharing make it challenging to identify potential patterns across organizations and thus standardize practices for managing specific risks across the life-science research ecosystem.

While flexibility enables organizations to mold biorisk management practices to specific biorisks as they arise, it may ultimately reinvent management practices rather than building upon past experiences. Some types of biorisks are rare or arise infrequently in an organization's scope of work, such as DURC. Due to their low frequency, organizations have few of their own experiences to draw from when assessing these types of risks. In addition, organizations sometimes actively restrict access to records of prior reviews within their organization to protect the privacy of reviewers and researchers and intellectual property, further reducing the pool of examples from which to draw. Organizations build flexibility into their biorisk management systems so that they may respond to unique events. However, this is an imperfect solution to managing low-frequency risks that might better be solved by sharing examples of practice, including successes, failures, and lessons learned.

Bright spots

Sharing may be manageable under certain conditions. Some organizations internally or publicly share partial records of specific biorisk management instances already. For example, the High Council for Biotechnology of France (Haut Conseil des Biotechnologies) assesses the risks associated with the use of biotechnology and renders biosafety evaluations that are publicly available.[51] iGEM has published case studies of past projects in academic journals to improve biosecurity practices and to guide policy development. Other industries have successfully implemented mechanisms for sharing anonymous information on current practices, which could serve as a template for similar efforts to publish anecdotal data in biorisk management. For example, the US Federal Reserve publishes a "Beige Book"[52] that uses anecdotal information to describe current economic conditions. Elsewhere, the Aviation Safety Reporting System maintains a clearinghouse for aviation near-misses, where information can be submitted anonymously without fear of being implicated in subsequent investigations.[53]

Since organizations have a limited set of examples from which to draw, pooling their experiences could provide a more strategic vantage point to view the frequency of specific challenges.

Opportunities

Sharing specific examples of how organizations managed challenging or infrequent biorisks could facilitate collective learning over time. Since organizations have a limited set of examples from which to draw, pooling their experiences could provide a more strategic vantage point to view the frequency of specific challenges. Mechanisms to promote sharing would need to be sensitive to organizations' concerns, for example, by respecting privacy constraints. Facilitating the collection and curation of anonymous reports of decision-making processes for specific projects could simultaneously enable the collective identification of new classes of risks and the standardization of strategies for managing them. See Part 4, Suggested Initiatives, for more detail.

2.6 | FOSTERING TRUSTED NETWORKS

Organizations are reluctant to share information about their biorisk management practices, particularly publicly, but also find value in learning about the practices of others. This points to a need for the formation of trusted networks, perhaps more so than the formulation of standards. Creating trusted networks can facilitate sharing and catalyze further adoption and improvement of practices among organizations.

Challenges

Some organizations are reluctant to subject their biorisk management practices to public scrutiny. Liability, political sensitivities, and concerns about information hazards make organizations less willing to publicly disclose or even document their practices. Lacking other examples of practice, many organizations also are reluctant to share as a result of what one reviewer called "organizational imposter syndrome": a belief that their biorisk management practices are inadequate or inferior to those of others, even when this is not the case. This suggests that a high level of trust may be needed to get organizations to share information about their practices.

Other organizations may be incapable of entering trusted networks under the condition that shared information would not be made public. Organizations such as publicly funded universities or laboratories may be subject to open records laws that make records of their biorisk management process, as well as any retained information shared by other organizations in such networks, open to public scrutiny.

Lack of visibility into whether and in what ways organizations are practicing biorisk management makes it difficult to evaluate and improve upon the current state of play across the research ecosystem. This lack of transparency hinders the ability of oversight, regulatory, or coordinating bodies to identify and legitimize exemplary practices that could inform recommendations. It also contributes to a self-perpetuating problem in the research ecosystem wherein lack of information sharing begets further lack of sharing.

Bright spots

Organizations are willing to share information about their practices under conditions of minimal effort and non-attribution. Sharing information on processes with a high level of granularity, as represented in the VIRS case studies, was possible but required a third party (our research team) to invest significant time in building rapport, accompanying participants through the documentation process including multiple stages of review, and facilitating workshops among all participants to foster a smaller trusted network for sharing before moving to public release. When organizations were reluctant to engage in a full case study, a number of individuals consented to share information under a condition of non-attribution about their organizations' biorisk management practices via interviews that were less structured and less time intensive than case studies. This mode of engagement suggests organizations may be more willing to share when their concerns and constraints are considered.

Organizations find value in learning about others' biorisk management practices. Among organizations that co-developed case studies and individuals who participated in non-attributed interviews, many described a desire to learn more about others' practices. Organizations that participated in workshops also found sharing case studies to be valuable.

Opportunities

Fostering trusted networks can facilitate sharing and catalyze further adoption and improvement of biorisk management practices. Regularly convening semi-public or private fora can help organizations develop trusting relationships with one another, which could in turn build the conditions necessary for deeper knowledge-sharing. IEGBBR, for example, represents a small network of trusted regulators that share biorisk management practices with one another.[54] Other partially overlapping but broader networks, such as those convened by WHO via its DURC dialogues[34–36] with donors, science editors and publishers, and national academies, or the Global Biosecurity Dialogue, have successfully convened stakeholders to share information related to biorisks and could serve as inspiration for future initiatives. These networks could then be leveraged to create and promote more formal means of knowledge-sharing, for example, through the development and compilation of case studies that describe organizations' biorisk management practices and lessons learned.

3. Detailed Findings

Our detailed findings summarize case studies and interviews with representatives from a set of diverse organizations that fund, conduct, support, and/or publish life science research and manage their attendant risks. We identified 380 organizations through literature review and expert consultations, narrowed to 52 candidates with some evidence of a biorisk management practice, and reached out to 33 with the goal of creating a diverse set of case studies. We received responses from 22 and were able to develop complete case studies with nine, of which eight are included in this report. We summarize these case studies below, along with non-attributed interviews from 12 additional organizations.

Findings are organized into three parts:

- **Part I describes the *conditions* organizations designate as important for establishing a biorisk management practice.** These include an internal or external impetus to review projects and programs for risks (Section 3.1.1), a clear delegation of responsibilities (Section 3.1.2), access to the necessary expertise to assess and mitigate risks (Section 3.1.3), and the capacity to engage and communicate with researchers whose projects are under review (Section 3.1.4);
- **Part II describes the *practices* organizations use to conduct biorisk management.** These include choosing a scope of risks to consider (Section 3.2.1), assessing potential project and program risks within that scope (Section 3.2.2), creating and following plans to mitigate those risks (Section 3.2.3), and periodically reviewing and improving approaches (Section 3.2.4);
- **Part III describes the challenges organizations face and the strategies they use when *coordinating their risk management efforts* with other organizations.** These include the challenge of assigning responsibility for risk management as projects develop from funding proposals to publications (Section 3.3.1) and the challenges and opportunities related to sharing information about biorisk management practices among organizations (Section 3.3.2).

In each section we present **background information** reflecting current normative guidance for biorisk management, our **findings** depicting the approaches that occur in practice, and in some cases, a **vignette** illustrating one or more of the ideas presented in the section.

3.1 | ESTABLISHING THE CONDITIONS FOR BIORISK MANAGEMENT

3.1.1 | Deciding to implement a biorisk management practice

BACKGROUND

Organizations are expected to implement biorisk management practices to mitigate against threats that could cause harm to lab personnel, the public, the environment, and the scientific enterprise. To motivate the implementation of biorisk management practices, current guidance highlights high-profile lab accidents, biological attacks, and controversies. These include the 2001 American anthrax attacks,[42,55] the laboratory-acquired SARS-CoV infections of 2003–2004 in Singapore, Taipei, and Beijing,[56] and the reconstruction of the 1918 influenza A (H1N1) pandemic virus and ensuing controversies surrounding the publication of gain-of-function (GoF) research with pandemic potential pathogens, such as H5N1.[57,58] Organizations also are encouraged to practice biorisk management to increase public awareness of biological risks,[59] to protect valuable materials and safeguard the health of individuals in laboratory facilities,[56,59] to comply with laws, regulations, or policies,[44,55,60] and to temper the potential for public misunderstanding or sensationalism regarding risks associated with life science research.[61]

All members of the scientific community have roles to play in biorisk management. (See Appendix 5 for examples of expert statements about and organizational pledges to practice biorisk management.) Current guidance emphasizes that multiple stakeholder groups have different responsibilities to mitigate biosafety and biosecurity risks given the potential for biorisks to emerge and the differing options available to manage them at different stages during the research and development process.[7,62,63] Research institutions have historically been key sites for biorisk management,[59] but more recently, other stakeholder groups have attracted attention for their potential to play a critical role.[64–66] Funders have been encouraged to implement biorisk management practices to define general research guidelines for all life science research, flag concerning projects, and ensure responsible stewardship of funds.[57] Journal editors also have been encouraged by biosecurity experts to implement biorisk management practices to balance the dissemination of important scientific findings with a need for careful publication in the face of potentially harmful use.[67]

FINDINGS

Some organizations implement biorisk management practices to comply with legal frameworks, mandates, or funding conditions at the regional, national, or institutional level. For example, the CBB is the national authority that administers Danish biosecurity legislation. This legislation was passed in response to a biosecurity survey conducted in Scandinavia[68] and to fulfill Denmark's obligation to the United Nations Security Council (UNSC) Resolution 1540,[69] which was adopted in 2004 to develop and enforce legal and regulatory measures against the proliferation of chemical, biological, radiological, and nuclear weapons (Case: CBB). MIT-BF received funding through the US Defense Advanced Research Projects Agency (DARPA)'s 1,000 Molecules program and was required as a condition of participation to implement a formal process for addressing biosafety, biosecurity, and dual-use concerns with its work (Case: MIT-BF).

Other organizations mentioned the importance of protecting themselves and their field against liability and backlash in the event of accidents. For example, iGEM implemented its first formalized safety screening process nearly one year after encountering several particularly concerning student projects through ad hoc screening. Motivated to protect participating teams, the future of the competition, and the broader synthetic biology community from biorisks and liability risks, iGEM scaled up its project review process and hired outside consultants to conduct safety screenings.

Several organizations mentioned that external criticism acted as a trigger for them to implement or update their biorisk management practices. Biorisk management at Science came into focus in 2012, when it published a paper describing molecular changes in H5N1 avian influenza that would enable respiratory transmission among mammals.[70,71] The ensuing controversy prompted *Science* to pause publication while it conducted an additional dual use risk review in coordination with the authors and the US NSABB, and ultimately revise their risk assessment process (Case: *Science*). Another unattributed interview participant described how their institution effectively restructured its biosafety and biosecurity management system after laboratory–acquired infections led to audits. Finally, the JGI was prompted to develop an internal biorisk management practice in part because an audience member at a public presentation questioned them about the potential risks that could result from implementing one of their projects.

Organizations also mentioned a number of reasons why they could not or would not implement a biorisk management practice. Several mentioned that biorisk management can sometimes be time-consuming, costly, and/or constraining, and that risks can seem speculative or rare. Several interviewees claimed that the focal domains of life science research they supported through funding or other services were not particularly risky, and they assumed that research institutions driving those projects would take the lead in managing associated biorisks Interviews. Others perceived themselves to be unable to effectively manage certain types of risks, either because they would likely occur before the organization could intervene or because it lacked leverage to change researchers' practices. In these cases, organizations often pointed to others to take responsibility, such as funders or research institutions (see Section 3.3.1).

Finally, some organizations lack support from top management to acquire the financial, technical, and human resources they need to create a biorisk management practice. That said, several unattributed interview participants described how motivated individuals within an organization could overcome ambivalence from leadership to establish biorisk management practices that go beyond meeting minimal requirements or guidelines, albeit informally.

Motivated individuals within an organization could in some cases overcome ambivalence from leadership to establish biorisk management practices that go beyond meeting minimal requirements or guidelines, albeit informally.

3.1.2 | Distributing responsibilities within an organization

BACKGROUND

For biorisk management systems to be effective, organizations need a range of stakeholders to participate. Cross- and inter-organizational relationships are described in Section 3.3. Within an organization, roles and responsibilities can include the following:

- *Leadership* is responsible for establishing a biorisk management system and ensuring it is functional, including securing resources, assigning, or delegating responsibilities, communicating the importance of biorisk management, and promoting improvement;[56,72,73]
- *Biorisk professionals* (e.g., biosafety officers, biosecurity officers, biorisk management advisers) are responsible for developing, implementing, enforcing, and improving biosafety and biosecurity measures, as well as providing advice and training, conducting inspections, identifying risks, reporting issues, and communicating organizational policies;[42,43,55,72–74]
- *Biorisk management committees* should review research protocols, perform risk assessments, develop policies, arbitrate disputes, provide guidance, report issues, and communicate organizational policies.[42,56,61,72,73] Members of biorisk management committees can hold primary positions internally or outside an organization.[43] In some cases, committees may be wholly external to an organization;[44] commercial entities such as Clinical Biosafety Services[75] and Advarra[76] offer institutional biosafety committee (IBC) and/or institutional review board (IRB) services;
- *Principal investigators* are responsible for compliance with biorisk management policies, training and supervising their staff, and reporting issues;[42–44,72,77]
- *All scientists,* including research staff and trainees, are expected to identify and mitigate risks associated with their work.[7,61] Scientists also are often held responsible for reporting issues[42,55] and communicating organizational policies.[42]

Responsibilities for biosafety, biosecurity, and dual use review can be independent of, or coupled with, one another.[72] For example, in the United States, some research institutions use the same committees for evaluating biosafety and dual use concerns, whereas others have specialized committees for these purposes, reflecting implementation flexibility articulated within the US DURC policy and its associated guidance.[77,78] The specific roles of biorisk management committees (such as IBCs at research institutions) can vary considerably depending on the organization.

While committees can be useful for gathering a variety of perspectives on how to manage particular biorisks, guidance documents often recommend that top management have ultimate responsibility for an organization's biorisk management system.[55,56,72] Biorisk assessment and mitigation measures are often qualitative or subjective,[42,43] and committee members can disagree with

one another on what constitutes an appropriate outcome. Concentrating ultimate responsibility in a single individual, such as an organization's director or manager, is one mechanism for decision making when disagreements arise.

The use of group discussions reflects the fact that, typically, no one individual has sufficient expertise to make biorisk management decision.

Roles and responsibilities can be connected through a "chain of notification" that enables individuals within an organization to communicate about risks and access the resources necessary to manage them. In some cases, this chain of notification can extend beyond the organization itself to include other relevant stakeholders, such as oversight bodies.[43,44,77] The means for activating such a process is elaborated in the US government's DURC policy, for example.[78]

FINDINGS

Many organizations report having a designated individual who ultimately is responsible for making biorisk management decisions. However, these individuals work with larger groups to arrive at their decisions. Organizations use discussions within review committees, advisory committees, or other groups to inform their decision-making (Case: ASM, CBB, iGEM, MIT-BF, JGI). These groups can vary greatly in size from two to more than 40 individuals. They use different practices to make final decisions, including consensus agreement among the reviewer team (Case: iGEM, JGI, *Science*), a majority vote (Case: ASM), or a single final authority decision (Case: CBB, CSU, MIT-BF). In general, even when consensus is not required, case study organizations and interviewees seek group consensus on risk judgments whenever possible. Group discussions also can involve external consultants with specialized expertise as needed (Case: ASM, CSU, iGEM, *Science*). The use of group discussions reflects the fact that, typically, no one individual has sufficient expertise to make biorisk management decisions. Organizations value committee discussions for making careful biorisk management decisions, and expressed that they can be enjoyable (Case: ASM, MIT-BF; Interviews).

Individual "champions" sometimes proactively take on biorisk management responsibilities not formally assigned to them by leadership or mandated by law. These individuals may seek validation from other parties external to the organization to convince leadership to value and invest in biorisk management. Examples include relaying positive feedback from local community outreach events (Case: JGI) or hiring external consultants (Case: CSU). In addition, some of our interview participants engaged in international collaborations to receive training and increase awareness of biorisk management within their organizations.

Some organizations create dedicated systems specifically for identifying and managing biorisks. Others incorporate biorisk management into a broader decision-making process. Some organizations have specialized project submission or review processes dedicated to biosafety and/or biosecurity (Case: CBB , CSU, iGEM, MIT-BF). In other organizations, biorisk review is one component of a more comprehensive review process that can include elements such as: scientific merit, research integrity, and alignment with the organization's mission (Case: ASM, JGI, *Science;* Interviews).

Organizations value committee discussions for making careful biorisk management decisions, and expressed that they can be enjoyable.

To effectively flag issues and arrive at decisions about how to handle them, organizations have escalation routes that bring issues to the attention of parties with decision-making authority and that distribute accountability throughout the organization. For example, at ASM Journals, editorial staff, reviewers, and individual journal editors can alert the editor in chief to biosafety or biosecurity concerns, who can, in turn, convene a committee to provide an additional layer of review and make a final decision regarding publication and mitigations (Case: ASM). Similarly, when laboratory staff at MIT-BF raise issues to the director during lab meetings, the director can convene a committee for additional discussion and advice.

3.1.3 | Accessing expertise

BACKGROUND

Organizations need access to diverse and relevant expertise to adequately assess and mitigate risks associated with life science research. The specific expertise required depends on the mission and research scope of the organization, but can include:

- Sciences (e.g., molecular biology, microbiology, virology);[43,55–57,77]
- Health and medicine (e.g., public health, clinical medicine);[43,55,57,77]
- Agriculture;[57]
- Biosafety, biosecurity, and environment, health and safety;[42,43,56,57,77]
- Bioethics, social sciences, and humanities;[7,57,77]
- Regulatory compliance (e.g., export control);[77,78]
- Law (e.g., legal counsel, general counsel);[43,57,77]
- Communications (e.g., scientific editing;[77]
- Public policy and administration;[43,55,57,77]
- Organizational policies (e.g., research administration, management);[43,56,77,78]
- Facility operations (e.g., facility security, maintenance, information technology);[42,56,77]
- Law enforcement, national security, and intelligence;[42,56,57,77]

Guidance documents often recommend or require committees for structuring expert review of research projects.[42,43,56,61,72–74,77] For example, USG policies for oversight of DURC require research institutions to have a five-member committee with "breadth of expertise to assess the dual use potential of the range of relevant life sciences research."[78] While lists of relevant expertise, roles, or occupations are common, guidance documents provide little information about how to recruit individuals with relevant expertise to participate in biorisk management practices, how to train reviewers to conduct biorisk management assessments or to determine appropriate mitigations, or how to structure committee decision-making processes.

Relevant experts can be internal or external to the organization. For example, a research institution could rely on the expertise of its own principal investigators, biosafety or biosecurity officers, or committees to conduct routine biorisk reviews but may additionally consult government funding agencies for biorisk management advice.[44,78] Members of the public can also raise previously unappreciated concerns and/or ensure that public interests are reflected in risk assessment.[61,77]

FINDINGS

Organizations differ in the expertise they consider relevant to biorisk management; nearly all organizations include experts from the life sciences, while only some draw on expertise across a broader range of fields. While guidance highlights the need for multidisciplinary or diverse review committees, organizations interpret this guidance differently. Some organizations exclusively consult life scientists, though these experts may specialize in different disciplines or topic areas. For example, one interviewee specifically mentioned seeking advice from scientists with specialized expertise in whatever biological agent was being used in the project under review. Other organizations incorporate individuals with expertise in biosafety, bioweapons, law, policy, defense, intelligence, and/or law enforcement into their review processes (Case: CBB, iGEM, MIT-BF). At the same time, some organizations expressed having experienced uncertainty about the breadth of expertise that could be useful for biorisk management (Interview: bioRxiv, Case: MIT-BF).

Some organizations rely exclusively on in-house expertise, while others recruit external reviewers or consultants. Biorisk management assessments and decisions can include sensitive information, and relying on in-house expertise enables organizations to better keep this information confidential (Case: CBB). Organizations that have extensive expertise internally may also be less likely to seek outside help (Case: ASM). Conversely, organizations that struggle to find external reviewers with relevant expertise externally may rely on training in-house experts to meet their needs (Case: CBB). For organizations that incorporate external review, reviewers and consultants generally are volunteers and often are connected through informal personal and professional networks (Case: iGEM, JGI, MIT-BF, *Science*; Interviews). iGEM is a notable exception and hires paid, external consultants to perform its biosafety reviews because they are labor-intensive and involve evaluating hundreds of projects within a short period of time. Compensating reviewers might facilitate reviewer recruitment (Case: JGI).

Organizations note that recruiting external experts to participate in project review can be challenging. Challenges cited by organizations included difficulty accessing known experts with relevant expertise (Case: JGI) and the need for vetted, trustworthy contacts (Case: MIT-BF). Many organizations also emphasized that they are fortunate to have access to the experts they regularly consult and speculate that it could be difficult for other organizations to have comparable access to expertise. For example, ASM Journals has several staff members who formerly participated in the NSABB and, as a result, have extensive experience with issues related to dual use in the life sciences. Two interviewees suggested that the creation or expansion of for-hire review committees or biosafety professionals could pose an alternative solution for organizations that lack extensive networks; however, these external entities may lack relevant knowledge about organizational culture and norms.

Many organizations also emphasized that they are fortunate to have access to the experts they regularly consult and speculate that it could be difficult for other organizations to have comparable access to expertise.

Organizations provide reviewers with formal and informal training to maximize their efficacy. Organizations emphasize that significant tacit knowledge, including a sense of organizational norms, is acquired experientially by reviewing projects as well as interacting with more experienced colleagues (Case: Addgene, CBB, CSU, JGI). However, tacit knowledge can be difficult to maintain over time as individuals involved in biorisk management come and go (Case: *Science*). Access to previous risk assessments and decisions (Case: CBB) and formal training courses (Case: CSU) also are valuable for training reviewers. In addition, organizations that rely primarily on external reviewers often supply basic training materials to guide reviewers in their assessments (Case: ASM, iGEM, JGI).

3.1.4 | Engaging researchers

BACKGROUND

Researchers are the first, but not only, line of defense against emerging biorisks. Researchers, including principal investigators, laboratory staff, and trainees, have specialized knowledge about their projects, facilities, and personnel that can provide important context for risk assessments,[61,77] making them well-positioned to identify biorisks and raise concerns to relevant oversight entities.[44,59,77,79] Their participation also is clearly critical in implementing mitigation measures. However, researchers may lack training and awareness about biorisks[80,81] or be hesitant to raise concerns if they believe that doing so could slow their work.[77] It is important, therefore, for researchers to understand their work as part of a larger biorisk management system.

Maintaining good relationships with researchers helps biosafety and biosecurity professionals provide effective oversight of life science research.[55,77] To this end, guidance documents recommend including research staff in the development and improvement of biorisk management programs; they similarly encourage biosafety and biosecurity professionals to discuss biorisks and mitigation strategies with researchers so that they can better understand and appreciate each other's rationale.[61,72,77]

Training and awareness raising are critical to building a culture of responsibility among researchers.[61,79] Workshops, courses, curricula, and lectures can equip researchers with knowledge, skills, and awareness to enable them to identify and manage biorisks associated with their work.[73,74] Codes of ethics can provide researchers with a sense of professional conduct and norms with respect to biorisk management.[82] In addition to defining policy objectives, guidelines and regulations can also serve an awareness-raising function.[61,77] Organizations typically are held responsible for providing training and education to their staff as part of their biorisk management program.[72]

Research proposals are almost never rejected outright; instead, organizations work with researchers to identify biorisks and develop mitigation measures that enable research to proceed.

FINDINGS

Organizations prefer to adopt a discussion-based, constructive, and collaborative style of engagement rather than one of policing researchers. Research proposals are almost never rejected outright; instead, organizations work with researchers to identify biorisks and develop mitigation measures that enable research to proceed. For example, JGI offers opportunities for feedback, revision, and clarification during proposal review, and CSU Biosafety Office staff try to "be on the researcher's side," promoting casual researcher-biosafety officer interactions rather than framing laboratory visits as audits. Discussions also enable biorisk professionals to collect additional information and evaluate the extent to which researchers are taking biorisk concerns seriously (Case: CBB, JGI).

Organizations note that engaging researchers directly in biorisk management practices helps build a culture of responsibility. Self-assessments provide useful data for individuals responsible for oversight, but they also serve as an awareness-raising function by encouraging researchers to reflect about the risks of their research. In some cases, self-assessments serve as the basis for extended discussions with biorisk professionals (Case: CBB, RIVM) or colleagues (Case: MIT-BF) about research projects. Inviting researchers from across the organization to participate in project review meetings, whether as review committee members or more casual observers, is another mechanism for raising awareness and demonstrating to researchers the value of biorisk management practices (Case: MIT-BF; Interviews).

Some organizations invest in education, training, and awareness-raising opportunities for research performers. RIVM and CBB provide training and awareness-raising programs to relevant stakeholders within their respective countries, and iGEM offers courses to participants in the research competition. While research funders and publishers sometimes provide training to project reviewers, they often do not provide training to researchers, relying instead on research institutions to fill that role.

VIGNETTE

- The MIT-BF case study notes that "[t]he mechanisms that the Foundry put in place to foster a culture of responsibility involving all researchers in the lab—notably requiring biosecurity self-assessments, weekly discussions about biosecurity risks, and annual or biannual meetings with experts open for researchers to attend—should be replicable in other research environments. The Foundry welcomes broader adoption of these practices."

3.2 | CONDUCTING BIORISK MANAGEMENT

3.2.1 | Choosing a scope of risks to consider

BACKGROUND

Organizations need to decide the scope of risks they will or will not manage. To define their scope, organizations can consider several conceptual dimensions or categories of risk, such as the nature of the biological agent involved and whether harms are accidental or deliberate;[59] derived from physical materials versus knowledge or information;[10] could lead to physical damage to living beings or to other kinds of negative outcomes (e.g., contributing to societal inequities[83]); and whether potential negative consequences unfold in the shorter- or longer-term.[84] While organizations may be required by law or policy to manage certain types of risks (e.g., working with high-risk agents,[40,41] conducting DURC,[44,85] or experiments involving recombinant DNA or genetic modifications[43]), organizations can broaden the scope of risks they consider beyond those baseline requirements.[77]

Guidance documents have called for organizations to consider many different types of risk, including dual use concerns, concerns about specific types of dual use research such as potential pandemic pathogen or GoF research, risks of laboratory accidents, or theft or deliberate misuse of laboratory materials (see Appendix 5, Table A5.1 | Examples of Biorisk Management Guidance Documents for references). However, while risks associated with laboratory accidents are widely seen as the responsibility of research institutions, responsibility for other types of biorisks are not as clearly assigned (see Section 3.3.1).

One common way to categorize biorisks is as follows:

- *Biosafety risks:* risks of "unintentional exposure to biological agents or their inadvertent release," of biological agents and materials including but not restricted to pathogens;[79]
- *Biosecurity risks:* risks of "unauthorized access, loss, theft, misuse, diversion or release" of "biological agents, data or equipment, biotechnologies, skills and information related to their handling;"[79]
- *Dual use risks:* risks involving research that is, "conducted for peaceful and beneficial purposes, but has the potential to produce knowledge, information, methods, products or technologies that could also be intentionally misused to endanger the health of humans, nonhuman animals, plants and agriculture, and the environment."[79]

Other terms that have been used to describe categories of risks include:

- Biosafety Level (BSL) 1–4 and Risk Group 1–4: Two widely used schemas used to denote containment measures and agents associated with research that poses increasingly serious risk of harm to humans, animals, plants, and the environment.[42] The two are correlated but not equivalent—BSLs refer to sets of procedures, while Risk Groups refer to categories of biological agents. Similar terms such as "class," "schedule," and "group" are used internationally to circumscribe different sets of containment measures and agents;[23]
- Australian Security Sensitive Biological Agent (SSBA) Standards: List of biological agents deemed to pose security risks, grouped into several tiers of risk, and associated with a regulatory scheme for their proper management;[86]
- Dual use research of concern (DURC): US government policy originally defined DURC as "life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security."[44] In practice, US government policy currently only requires DURC assessment and mitigation for a subset of research at federally-funded institutions in which one or more of 15 high-risk "select agents" is used and one or more of seven particularly-concerning experimental designs are or will be implemented;[41,44]
- Gain-of-function (GoF) research: Life sciences research involving "the acquisition of new, or an enhancement of existing, biological phenotypes."[57] In the context of virology and synthetic biology, GoF research has been controversial for its potential to create or enhance PPPs;[87–89]

- Potential pandemic pathogens (PPPs): US government policy defines PPPs as pathogens that are "likely highly transmissible and likely capable of wide and uncontrollable spread in human populations" as well as "highly virulent and likely to cause significant morbidity and/or mortality in humans;"[60]

- Technology with misuse potential (TMP): Danish government policy defines TMP as "[t]echnology, which can be directly used for the development of biological weapons or for offensive usage of biological weapons."[85] Technologies in this case are considered to be intangible.

FINDINGS

Table 3 | Biorisk categories considered in-scope by case study organizations

CATEGORY	ORGANIZATIONS INCLUDING IN SCOPE
Biosafety risks	iGEM, CSU, JGI, MIT-BF
Biosecurity risks	iGEM, CBB, CSU, JGI, MIT-BF, RIVM
Dual use risks	iGEM, CBB, CSU, RIVM, MIT-BF, JGI, ASM, *Science*

Most organizations draw upon agent- and/or experiment-based lists to help them articulate scope, but some consider a broader range of risks than those formally identified in existing frameworks. Many organizations use existing risk assessment frameworks to guide the development of their own original frameworks. In particular, at least six out of eight case study organizations explicitly refer to lists of select agents and/or make use of typologies of dual use risks that resemble those elaborated in the Fink report[8] (Case: ASM, CBB, iGEM, JGI, MIT-BF, RIVM). However, most case study organizations also consider dual use risks beyond those identified in formal lists (Case: CBB, iGEM, JGI, MIT-BF, RIVM, *Science*). When identifying manuscripts that warrant additional review, ASM and *Science* both use the US government definition of DURC.[44] ASM additionally considers work with any agent on the US Select Agents and Toxins List.[41]

The scope of risks organizations define for themselves is partly constrained by their mandates—their guiding missions as established at their point of creation—and by their positioning in the research life cycle (see Table 3 above). When mandates and positioning allow it, organizations tend to consider a broad scope of risks. All the research institutions we engaged are mandated to guard against biorisks that would emerge from laboratory materials within the institution itself, but they are only sometimes mandated to consider dual use risks that might have indirect effects elsewhere (Case: CSU; Interviews). In contrast, the publishers we spoke to focus primarily on dual use information risks, rather than biosafety or biosecurity risks, because laboratory work already has been performed by the time it reaches the publisher (Case: *ASM, Science*; Interviews). The government oversight and advisory organizations we engaged are able to advise or influence projects early in development, and they have broad mandates that encompass risks from both laboratory materials and information (Case: CBB, RIVM). Similarly, the organizations we engaged that are sufficiently flexible in their mandates to determine their own scope and positioned to influence projects early in, or continuously throughout, the research and development process tend to consider a broader scope of risks (Case: iGEM, JGI, MIT-BF). Defining the boundaries of a broader scope can itself be an intensive process.

Scopes of risk that are broad or imprecisely defined may enable organizations to consider and capture more risks, but they also increase the resources required for project review. Broad and ambiguous scopes can enable organizations to identify risks across a wider range of categories and to identify novel risks that fall outside of existing categories, respectively. However, broader and more ambiguous scopes also increase the burden of review by capturing more risks that require attention (Case: CBB, iGEM).

VIGNETTE

- A 2009 executive order mandates that Denmark's CBB manage risks of any research deemed to be directly useful to the development, production, or use of bioweapons. CBB draws in part on lists of regulated biological agents and equipment originally developed for export control in outlining its scope of risks. However, CBB also pursues a more expansive, outcome-focused approach by regulating any technology that could have a strong enabling effect on bioweapons development, such as technologies that could aid in the dissemination of pathogens. Supplementing list-based approaches with those focused on potential adverse outcomes may enable organizations to identify and manage a wider array of risks.

3.2.2 | Assessing risks

BACKGROUND

Organizations need to identify biorisks in research projects and evaluate the significance of those risks to effectively manage them. For simplicity, in this section we refer to these steps collectively as "biorisk assessment." Biorisk assessment is used to make decisions about biorisk mitigation (discussed in Section 3.2.3) and does not necessarily need to result in an explicit judgment of a certain level or amount of risk.[90,91]

Projects requiring review can be flagged for biorisk assessment in a variety of ways. For example, principal investigators (PIs) or researchers can self-report project-specific issues to their local regulatory bodies;[42,43,77] biosafety officers can report issues with projects to their biosafety committee;[43] and funding applications or manuscripts can be flagged for further review as an element of standard submission and review process.[7]

There are many existing guidelines for performing biorisk assessment, and they tend to follow a similar set of general steps. In these guidelines, projects are submitted to a review body, which typically performs a preliminary review. If no concerns are flagged, the project is approved; otherwise, the project proceeds to a more in-depth review that could result in an approval, a rejection, a request for the proposer to revise and resubmit, or development of a plan to mitigate risks. For example, the US government's policy for managing DURC requires that federally funded academic institutions form committees to review life science research projects involving any of a set of listed agents and experiments.[44]

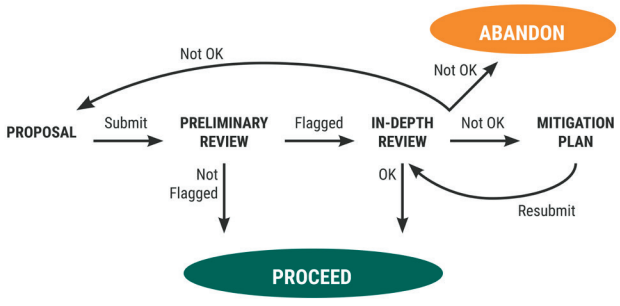

Figure 1 | An outline of a typical biorisk assessment process

Depending on the nature of the project, existing guidance recommends that in-depth reviews consider the following issues:

- The overall likelihood of harms as distinct from the potential consequences of harms;[59,72]
- The availability of feasible, equally efficacious, less risky alternatives to a project;[60]
- The balance of risks to benefits of research;[25,61,78]
- For biosafety and biosecurity risk assessment: the inherent risk of biological materials being used, the containment methods for those materials, their potential points of failure, and the current level of training and reliability of associated personnel;[42,43,59]
- For dual use risk assessment: the novelty of information relative to what is available, information dissemination channels, the generalizability of the information to new contexts or biological materials, and the ease or feasibility with which research might be misused.[78]

Guidance documents acknowledge that biorisk assessment typically involves some degree of qualitative and subjective judgment.[7,56,59,78] Biorisk assessment is challenging in part due to a lack of high-quality, empirical reference data to ground review.[92] Some organizations have developed tools like decision trees to attempt to reduce variability in approach and response to some risks.[23,46]

FINDINGS

Most, but not all, of the organizations we spoke to found it useful to have at least one well-defined channel through which to submit projects for biorisk assessment. For example, ASM and *Science* have standard intake processes when considering manuscripts for publication, and JGI incorporates biorisk assessment practices into its existing workflow for research project review. Some organizations have multiple channels by which they identify projects requiring review. iGEM, for example, requires all participating research teams to complete a safety form, which serves as the basis for an initial risk assessment for all teams. In addition, iGEM identifies projects in need of further review through supplementary forms teams are required to complete when pursuing projects with an elevated level of risk. CSU identifies projects for review through several channels, including IBC review, researchers reaching out with questions, and reports from other academic staff. CBB learns

about potentially concerning projects through institutions self-reporting work that could qualify for oversight, inspections of facilities that have pre-existing permits from CBB, and visits to facilities that do not currently have a permit but that might qualify for oversight based on their research and publication portfolio.

Forms are useful for facilitating rapid preliminary review, but interviews or discussions between researchers and reviewers can capture more detailed information about a project and its context.

Case study organizations seek to balance depth and speed throughout the risk assessment process. See Table 4 | Balancing Depth and Speed, for more detail.

Organizations use a variety of data collection mechanisms that differently weigh speed and depth. Case study organizations and interview participants use a wide range of methods to gather data about projects, including: checklists and highly structured forms (Case: CSU, iGEM, MIT-BF, RIVM, *Science*); open-ended writing and reflection questions (Case: iGEM, JGI); interviews (Case: CBB); group discussion among researchers at lab meetings (Case: MIT-BF); and asking researchers to declare potential dual use concerns in manuscript cover letters (Case: ASM). Not only do these approaches require varying amounts of time, but they also collect information at different levels of detail. For example, while checklists can quickly flag common issues, open-ended questions can capture additional information about uncommon risks, yet can be time-consuming to answer and analyze. Similarly, forms are useful for facilitating rapid preliminary review, but interviews or discussions between researchers and reviewers can capture more detailed information about a project and its context, including the extent to which the researcher proposing, conducting, or submitting the work is aware of biorisks.

Preliminary review processes enable organizations to quickly approve projects or flag them for subsequent in-depth review. Organizations utilize a variety of preliminary review mechanisms. Some use screening strategies like allowlist/blocklist—lists of approved and disapproved biological agents and experiments, respectively—in their preliminary review practice, which can help them process large numbers of projects (Case: ASM, iGEM; Interviews). Some organizations use self-assessment mechanisms, such as open response fields (Case: iGEM, MIT-BF, *Science*) or checkboxes (Case: iGEM, RIVM), as the primary data source indicating potential risks to review. In many cases, organizations allow a single project reviewer or small group of reviewers to read proposals and make qualitative judgments regarding whether a project requires further attention (Case: ASM, CSU, iGEM, MIT-BF; *Science*; Interviews). Some organizations may not implement preliminary review practices for biorisks but instead use other criteria to screen projects, such as scientific merit, prior to performing in-depth biorisk review (Case: JGI, *Science*).

***All* case study organizations with an in-depth review practice structure it as one or more informal small-group discussions, but the details of these discussions are difficult for case study organizations to report or systematize.** Organizations did not describe any standardized forms or templates for in-depth review. In-depth review processes vary between—and to a lesser extent within—institutions both in their number of steps and in how different stakeholders are integrated in the process (e.g., researchers, consultants, committees). Discussions can be:

- Between reviewers and researchers, to collect or clarify information about a project (Case: CBB, CSU, iGEM, JGI, MIT-BF, RIVM, *Science*);
- Among reviewers, or between researchers and reviewers, as part of biorisk assessment and to determine appropriate mitigations (Case: CBB, CSU, iGEM, JGI, MIT-BF, RIVM);
- Between individuals responsible for biorisk management at an organization and external consultants, who may be brought in on an ad hoc basis to contribute biosecurity expertise (Case: ASM, *Science).*

None of our case study organizations routinely and explicitly weigh the benefits of research against risks when they practice risk assessment; rather, they assess and mitigate risks in and of themselves. However, at least one organization (CBB) stated that it *would* weigh benefits against risks if it were necessary to resolve difficult decisions related to closing or blocking a research project, but that this has not happened for some time. In addition, several participants mentioned that their decision-making process, particularly prior to devising adequate mitigation measures, includes weighing potential risks against the scientific merit of a proposed project (Case: JGI, Interviews). For example, JGI only conducts biorisk review for projects that have passed their merit review process, which enables them to concentrate their biorisk management efforts on projects that they are more likely to fund or support (Case: JGI). Once projects are determined to have sufficient merit to proceed to risk review, the decision to pursue or halt a project largely is contingent on an organization's ability to implement adequate mitigation measures. Other organizations said they are not well-positioned to conduct risk-benefit or risk-merit analyses based on their role in the research life cycle (see Section 3.3.1).

Finally, all the case study organizations used a fundamentally qualitative and subjective process to assess risks. No organizations mentioned using a specific common unit of risk, such as the expected value of the number of lives endangered.

Once projects are determined to have sufficient merit to proceed to risk review, the decision to pursue or halt a project largely is contingent on an organization's ability to implement adequate mitigation measures.

VIGNETTE

- ASM uses a combination of automated keyword/phrase screening and reviewer evaluation to flag manuscripts for in-depth review by the editor in chief and/or an external committee of experts: "The screening phase is designed to be rapid and unobtrusive while at the same time identifying manuscripts that require discussion."[13]

BALANCING DEPTH AND SPEED

Table 4 | Organizations can face a trade-off between quickly screening for risks and catching edge cases that do not easily fit into existing categories

STRATEGY	BENEFITS	DRAWBACKS	OTHER CONSIDERATIONS	EXAMPLES
Use screening tools (e.g., lists) to identify risks	• Designed to be fast and easy to implement; • Flags projects requiring further review; • Clearer lines of what is inside and outside the scope of review	• Designed for specific use cases and may not adapt well to edge cases nor capture all possible risks; • Allow reviewers to avoid thinking carefully about risks.	• Screening tools may still require manual follow-up for flagged projects; • Screening tools can be based on lists of agents, functions, experiments, or outcomes, or a combination of these.	• RIVM Biosecurity Office developed the Dual-Use Quickscan tool; • iGEM uses allowlist for confirmed-safe materials and questionnaires (safety forms); • ASM uses automated word/phrase matching to trigger deeper review; • CBB uses a questionnaire; • CSU uses forms to evaluate projects likely to have elevated levels of risk.
Perform the most stringent review steps first to triage projects more quickly	• Projects can be disqualified early, saving reviewer effort; • Enables organizations to employ specialist biorisk reviewers instead of relying on generalists.	• Sequencing reviews of different types (rather than performing them in parallel) can increase review time.	• Works well when biorisk review is coupled with other review processes (e.g., scientific merit); • May not be relevant for all review processes.	• JGI and *Science* screen projects for technical feasibility and/or scientific merit *before* assessing safety and security risks.
Dialogue with researchers	• Adapts well to edge cases; • Enables access to additional project information among additional key stakeholders; • Enables access to investigators' risk attentiveness.	• Time-intensive; • Not easily standardized.	• Good relationships with investigators and strong interview skills can facilitate dialogue.	• CBB primarily sources information about a project through dialogue with researchers; • CSU, ASM, iGEM, MIT-BF, and JGI use dialogue as part of their risk management practices; • RIVM and MIT-BF encourage dialogue between researchers and biosafety officers.
Avoid overly detailed assessment frameworks	• Saves researcher and reviewer time; • Encourages reflection by reducing administrative burden for researchers and reviewers.	• May miss necessary or useful information.	• Piloting a review process can help to determine the right level of detail.	• JGI and MIT-BF use a short self-assessment form to make it less burdensome for researchers to reflect deeply on the risks of their work.

3.2.3 | Mitigating risks

BACKGROUND

The primary purpose of risk assessment is to decide whether and what mitigation measures are necessary. To improve biosafety, researchers can wear personal protective equipment (PPE), use lab equipment designed for safety such as a biosafety cabinet, or undergo training to foster safer work practices.[59,61] Biosecurity improvements can include physical lab security, personnel reliability assessment, procedures for inventory control, or redesigning research to reduce or eliminate the need for hazardous agents.[55,93] In the event of a biosafety or biosecurity threat, laboratories also can maintain response protocols such as exposure surveillance, worker health programs, incident notification, reporting, and follow-up investigation.[56,72] These often are grouped into standard practices that adhere to a given Biosafety Level.[7,42,43,93] Dual use issues stemming from life sciences research also present their own unique set of mitigation options. Strategies to mitigate these risks include heightening biosafety and biosecurity measures, evaluating the availability of medical countermeasures to a potential future threat, and developing a plan for responsibly communicating research findings.[25,78]

Halting research can virtually eliminate biosafety, biosecurity, and dual use risks. However, halting research is typically framed as a last resort. For example, the US government's DURC policy companion guide states that "it is anticipated that risks associated with the majority of DURC can be mitigated appropriately and that the research will still be conducted. The goal of the risk-benefit assessment process is to promote the responsible conduct and communication of DURC, not to restrict such research."[78]

When developing biorisk mitigation plans, the goal is to mitigate biorisks to an acceptable level; it is unlikely that biorisks can be eliminated entirely. What an organization considers to be an acceptable risk level is subjective and varies between organizations and across different jurisdictions. In some cases, organizations may choose to accept risks without mitigation. In these situations, the *ISO 35001 standard for Biorisk management for laboratories and other related organizations* recommends documenting accepted risks with an accompanying rationale.[72]

FINDINGS

Organizations pursue a range of mitigation strategies. The most commonly reported measures include requiring additional training for researchers; expanding biosafety or biosecurity procedures for a laboratory; developing strategies to responsibly communicate results for publication; and occasionally modifying the project's design, methods, or materials. See Table 5 | Risk mitigation strategies used by case-study organizations, below for a more complete account.

Almost all the case study organizations and interviewees seem to adopt the default assumption that biorisks can be mitigated through less extreme options than terminating a project.

It is rare for organizations to reject or stop a project altogether. As noted in Section 3.2.2, the decision to pursue or halt a project often hinges on the ability to adequately and feasibly mitigate identified risks. Almost all the case study organizations and interviewees seem to adopt the default assumption that biorisks can be mitigated through less extreme options than terminating a project. As one example, the CSU Biosafety Office generally "does not see prohibiting projects to be within its purview" and instead focuses on implementing appropriate mitigation measures for funded research projects (Case: CSU). Notably, some organizations also proactively mitigate against or limit the potential severity of risks by exclusively supporting lines of research that pose limited risk (Case: iGEM; Interviews).

Some organizations noted that follow-up reviews were important for understanding the risks of projects as they develop. Projects can change significantly from proposal through execution and new risks can emerge in the process. Organizations that review a project in an earlier stage can request or require a follow-up review later. However, organizations differ in their positioning to conduct follow-up reviews with researchers. For example, publishers typically only review research that already has been conducted. Funders and service-providers can also find it difficult to require researchers to participate in follow-up reviews after funding or services have been provided (Interviews). JGI and MIT-BF work around this problem by requiring researchers to explain up-front how they intend to manage future risks. The organizations that reported conducting follow-up reviews tended to review projects early and have authority over the conduct of the project via government mandate (Case: CBB) or local institutional oversight (Case: CSU; Interviews). iGEM's unique relationship with its researcher teams also allows it to follow up with projects across the development life cycle.

Institutional positioning and the availability of resources can constrain an organization's risk mitigation options. For example, publishers such as *Science* and ASM typically are unable to impose risk mitigation options related to laboratory practice since lab research usually is complete by the time a manuscript has reached them for review. Funders, service providers, and publishers also may have limited individual influence over research projects insofar as researchers could pursue funding or resources from other organizations of those types, including ones with less stringent or burdensome review practices. In another example, one individual that participated in a non-attributed interview reported that it sometimes was difficult for researchers to purchase new safety equipment if they lacked the necessary budget, so they pursued other routes to risk reduction, including stopping work on a project.

VIGNETTE

- iGEM sometimes requires teams to modify their experimental designs to reduce risks while preserving scientific benefit. One iGEM team sought to test engineered yeast in a stratospheric probe, but the iGEM Safety and Security Committee was concerned about the potential environmental release of genetically modified organisms (GMOs) in the stratosphere. After consultation, the team changed its experimental design and instead ran an experiment where it launched wild-type, non-engineered yeast instead. iGEM benefits from a position in which they are able to review projects from conception through publication/presentation, offering more possibilities and points for risk mitigation and evaluation of risk mitigation outcomes.

Table 5 | Risk mitigation strategies used by case study organizations

MITIGATION STRATEGY	ORGANIZATIONS CONFIRMED TO USE STRATEGY WITHIN THE CASE STUDY COLLECTION
Level: Materials and information	
Adapt lab facilities or require different facilities	CSU
Expand or implement new biosafety and/or biosecurity procedures	CBB, CSU, iGEM, MIT-BF
Secure project data	CBB, MIT-BF
Develop strategies to responsibly communicate research results (redacting information and/or providing added context)	ASM, CBB, iGEM, MIT-BF, *Science*
Level: Individuals	
Require researchers to articulate their own mitigation plan	CSU, JGI
Recommend vaccinations for researchers	CSU
Raise project team's awareness of risks / require appropriate training	CBB, CSU, iGEM
Exclude specific researchers from project	CBB, CSU
Ban researchers from future engagement with the organization	iGEM
Involve external experts/stakeholders to supervise, approve, or perform some work	iGEM, MIT-BF
Evaluate or restrict outside partners involved in the project	CBB, MIT-BF
Level: Projects	
Establish a process for follow-up assessment	CBB, CSU, JGI, MIT-BF
Modify the project design or methods	CBB, CSU, iGEM, JGI, MIT-BF
Stop, block, or reject the project entirely	ASM, CBB, iGEM, JGI, MIT-BF

3.2.4 | Improving risk management practices

BACKGROUND

There is widespread agreement among biorisk experts that organizations should continually review and improve their own biosafety and biosecurity risk management systems to ensure ongoing effectiveness.[42,59,72] Improvement efforts often are represented in repeated cycles of assessment, reflection, and revision, such as "Plan-Do-Check-Act" cycles.[59,72] Regular performance evaluation and improvement can enable organizations to avoid costly biosafety and biosecurity incidents and to streamline their responses to risks that would previously have required time-intensive in-depth review.[42,59] Continuous improvement also may be necessary to address novel risks that can emerge as life science tools and techniques advance. Guidance indicates that performance analysis and improvement efforts should be pursued both proactively and in response to obvious biorisk management failures.[42,59]

Guidance documents emphasize the importance of including individuals across all levels of an organization in improvement efforts.[42] For example, WHO recommends that improvement efforts be based on input from scientific directors, Principal Investigators, biosafety officers, research and administrative staff, and law enforcement.[73]

Organizations require data to determine where improvements are needed and how to implement changes, but collecting such data is inherently difficult. There are many options for data collection, including interviews, training evaluations, incident reports, and questionnaires.[59] *Laboratory Biorisk Management*[59] emphasizes the importance of both outcome ("lag") measures, such as accident rates, and activity ("lead") measures, such as external audits of safety practices. Although they are important for measuring performance, useful outcome measures can be challenging to acquire because harmful biological events are rare and effective biorisk management makes them even rarer. As a result, organizations typically need to rely heavily on "lead" measures.[59]

FINDINGS

Organizations invest in continuous and incremental improvement of their biorisk management practices. Some organizations do so in an ad hoc and/or informal manner (Case: ASM, CBB, MIT-BF, RIVM, and *Science*) while others maintain more formal data collection, review, and/or improvement practices (Case: CSU, iGEM, and JGI). iGEM and CSU review and implement improvements to their biorisk management practices on a regular basis, and JGI and iGEM collect statistics about the projects they review and report overall trends publicly or upon request (see Section 3.3.2).

Regularly scheduled written reports enable organizations to update their practices consistently and maintain internal support for biorisk management. For example, iGEM tracks safety and security data in an end-of-year report, including data such as the number of teams flagged for biorisk concerns, reasons for in-depth reviews, and trends in areas of concern.[38] iGEM employees draft recommended policy changes, which then are reviewed by a safety and security committee alongside edge cases that arose in the previous competition cycle. In the future, iGEM intends to make these reports more quantitative and categorical, for example, by implementing risk severity ratings and designating categories of hazards. JGI also provides regular reports on its biorisk management activities to its scientific advisory committee, which enables it to sustain improvements over time.

Barriers to documentation and sharing may increase reliance on tacit knowledge, which can make it more difficult for organizations to maintain knowledge over time

Access to documentation of biorisk management reviews and outcomes enables organizations to learn from past experiences, improve their biorisk management systems, and onboard new staff. While some organizations allow researchers and/or reviewers access to project records to facilitate learning (Case: CBB, iGEM), others limit access for reasons of privacy and/or security (Case: JGI, *Science*). Organizations also vary in the extent to which they document their previous biorisk management decisions, which affects the ease with which project records can be shared. Barriers to documentation and sharing may increase reliance on tacit knowledge, which can make it more difficult for organizations to maintain knowledge over time (Case: *Science*). Among organizations that document biorisk management reviews, those that process a higher volume of projects have more examples from which to learn and may therefore be better able to make systematic improvements to their biorisk management practices over time (Case: iGEM).

Organizations adopt metrics for the aspects of biorisk management performance that are most important to them. For example, iGEM identifies recurring issues and modifies its policies to streamline its review; iGEM also keeps track of emerging or novel concerns and modifies its policies to better capture them. These practices enable iGEM to reduce its high burden of project review (hundreds of projects per year) and to catch potentially high-profile issues that could otherwise negatively affect the organization. By contrast, CSU places a strong emphasis on establishing and maintaining good relationships with researchers, and therefore focuses on streamlining and simplifying their practices to minimize the burden of biorisk management for researchers. In addition, RIVM is piloting a questionnaire and follow-up interviews with life scientists who use its Dual-Use Quickscan tool to determine whether and how the tool is used.

Organizations may invest more readily in performance improvement practices if biorisk management failures are perceived to pose a major threat to the organization. The value of preventing this harm can offset the costs of improvement, or if harm actually occurs, it can force improvement. For example, one non-attributed interview participant described how their institution restructured its biosafety and biosecurity practices after laboratory–acquired infections led to audits. iGEM also noted that its funding and international standing could be jeopardized if students caused or suffered harm as a result of a research project.

3.3 | MANAGING RESEARCH-RELATED BIORISKS ACROSS ORGANIZATIONS

3.3.1 | Distributing responsibilities across the research life cycle

BACKGROUND

Organizations involved in life science research vary in their ability to manage risks at different stages of research. For example, funders tend to have more control over research in early stages, and publishers at later stages.[1,34,63,65,94,95] By the time a research project manuscript reaches a publisher, the physical work of the research itself likely already has been performed and most of the associated biosafety and biosecurity risks may have been realized, although dual use risks associated with information sharing—commonly known as "information hazards"—may still exist.[1,57,67,96]

There is ambiguity about where responsibilities should lie for managing biorisks across the research life cycle. While WHO has elaborated responsibilities for different stakeholder groups in its *Global Guidance Framework for Responsible Use of the Life Sciences,*[7] acceptance and adoption of these responsibilities is ongoing. As a result, organizations that lack clarity about their responsibilities may defer to one another and collectively neglect some risks.[2,63,97]

Organizations may have a limited ability to manage risks that fall outside their mandates. For example, some IBCs may only receive funding, staffing, and a mandate to manage biosafety and biosecurity risks, but not dual use risks.[40] Similarly, several US government oversight policies only apply to organizations that receive funding from the government, which limits its authority to manage biorisks that arise within non-federally funded organizations.[43,44,60]

Unevenness in the adoption of biorisk management practices within stakeholder groups undermines the efficacy of individual organizations' efforts. For example, researchers can avoid publishers that are more sensitive to dual use risks by choosing to work with other publishers that have looser restrictions.[63] Service providers may be subject to a similar problem; for example, individuals seeking to order DNA sequences that raise potential biorisk concerns can choose to order from DNA synthesis companies that have less stringent review practices.[98]

Unevenness in the adoption of biorisk management practices within stakeholder groups undermines the efficacy of individual organizations' efforts.

FINDINGS

In general, research-performing organizations frequently take responsibility for biosafety risks. For example, IBCs have a clear responsibility for biosafety oversight at research institutions. Because they have power over the day-to-day practice of research, other organizations like funders and publishers tend to rely on them to ensure that research is performed safely in the lab. Even when a project may be separately subject to IBC review, some organizations choose to proactively consider and manage biosafety concerns in ways that further supplement the responsibilities afforded to an IBC (Case: iGEM, JGI, MIT-BF).

The locus of responsibility for managing dual use and related biosecurity risks is less clear. Several case study organizations with influence over laboratory practices choose to proactively consider biosafety and/or biosecurity risks (Case: CSU, iGEM, JGI, MIT-BF). However, IBCs at research institutions may not always attend to dual use risks, specifically, when they fall outside their mandate.[43] Some IBCs may be further disincentivized to manage biosecurity risks when their meeting minutes can be made public, which risks revealing sensitive biosecurity-related information.[77]

Case study organizations and interviewees concur that funders play a vital role in managing dual use risks at the start of research, with one interviewee stating, "funders decide what research should be done." However, of the funders we reached for interviews, only one reviews proposals for dual use risks and the other two do not. This indicates that funders may not always take on responsibility for managing dual use risks, even when others expect them to.

Publishers differ in their orientation to dual use risk management. Both ASM and *Science* have processes in place to review manuscripts for potential dual use risks. ASM retains the option to reject or redact manuscripts if necessary, but has not yet done either. *Science* chooses to play a more neutral role, focusing its efforts primarily on ensuring authors accurately report the dual use risk management methods that have already been applied to their work. A representative from *Science* expressed concern that researchers could evade the biorisk management efforts of any single publisher by seeking out less-restrictive publishers, which could include some preprint servers. While some preprint servers may not have dual use risk management practices in place, others do take steps to manage them and other biorisks (Interviews).

Some organizations can intervene into and manage risks at various points in the life cycle of a given research project. For example, CBB has a legal mandate to manage TMP, which grants it authority to intervene on research at any stage of development. iGEM and MIT-BF evaluate projects for dual use potential throughout their development and can intervene at any time, and JGI evaluates dual use concerns with project proposals at the start of development and sometimes requires researchers to provide updates if the risk profile of their project changes.

3.3.2 | Sharing information externally

BACKGROUND

While there is broad support for transparency in biorisk management, there is a lack of consensus about how to implement it in practice. In recent years there has been increasing attention to the need for transparency in biorisk management processes but disagreement about what should and should not be shared and with whom.[15,25,26]

Some organizations are (or can be) mandated to share information about whether and how they assess specific projects. Sometimes organizations are required to share information with regulatory authorities about specific projects as part of a mandated process of in-depth review and risk mitigation.[41,43,44,60,85,99] When centrally and systematically collected, data gathered via such requirements can be analyzed to better understand how and why biorisks emerge, improve biorisk assessment, and inform policy changes.[57]

Organizations may also consider voluntarily sharing information about specific project risks with other organizations or with the public. There are signs of demand for risk information, and the need for transparency features in guidance documents, but what can and should be shared continues to be a focal point of policy debates.[26] For example, scholars have called for increased transparency over the processes US government review bodies used to judge the risks and benefits of DURC and ePPP research, including H5N1 GoF research in 2011 and research at the Wuhan Institute of Virology in the mid-to-late 2010s.[87,88,100]

A variety of mechanisms exist for organizations to share information and receive feedback to improve their biorisk management practices. The recent WHO Framework outlines several types of groups with which organizations can engage, including research organizations, funders, technical experts, professional societies, data managers, editors, publishers, ethics committees, data repositories, regulators, and civil society.[7] There are also many different venues where organizations can seek feedback, including conferences, newsletters, websites, academic articles, and community meetings.[55,59] Several guidance documents note that organizations can benefit from exchanging information at different geographic scales from regional to global.[7,55,73,74,101] Guidance documents also have called for the establishment of specific communities of biorisk management practice, especially among biosafety/biosecurity officers and among journal editors.[7,25] Examples of existing communities of practice are the Global Health Security Agenda Action Package Prevent-3 (GHSA APP-3)[22] working group on biosafety and biosecurity, the International Working Group on Strengthening the Culture of Biosafety and Biosecurity and Responsible Conduct in the Life Sciences (IWG),[77] and the International Experts Groups of Biosafety and Biosecurity Regulators (IEGBBR).[54,102]

Table 6 | Reasons organizations share or do not share information about their biorisk management practices

REASONS TO SHARE	REASONS NOT TO SHARE
• Collecting external feedback to improve their own practices (see also Section 3.2.4); • Contributing to collective knowledge about more effective biorisk management practices; • Boosting their organization's prestige and/or access to resources; • Protecting themselves against liability or reputational risk by assuring outside stakeholders they have acceptable biorisk management practices in place; • Promoting social norms of biorisk management; • Because they are legally mandated to share certain information through formal reporting requirements.	• Concerns about liability, reputational risk, or demands for costly improvement if they make their practices public, particularly if an organization believes that others could see their practices as inadequate; • Concerns about creating the potential for harm by revealing information about specific dual use risks; • Concerns about giving outsiders the ability to "game" or evade their risk assessment practice.

In general, organizations involved with life science research tend to be cautious about sharing the details of their biorisk management practices. As noted in Section 1, Introduction and Section 5, Methodology, many organizations did not respond to our outreach, several made contact but went no further, and other organizations chose to participate under the condition that their responses would be not-for-attribution. In general, the default posture is not to share, and many organizations withhold information even when it is legally and organizationally permissible to do so. However, the eight case studies and 12 non-attributed interviews developed and conducted through VIRS are an indication that some organizations will share information if they are invited to do so and if they are aided with the process of documentation (see Table 6 above).

Organizations may be more reluctant to share information about specific project risks than general biorisk management practices. Some organizations specifically named concerns about the confidentiality of intellectual property (Case: CBB, JGI). Others mentioned concern about spreading dangerous information by disclosing the dual use risks associated with specific projects or by disclosing details of their biorisk management practice that could potentially enable researchers to circumvent it (Case: MIT-BF; Interviews). *Science* also expressed that it was reluctant to share risk assessment information about specific manuscripts as part of standard editorial practices around the confidentiality of peer review. Unless incentivized and enabled to do so within a trusted network, we should not expect most organizations to share details of specific cases.

Some organizations, including those with sophisticated biorisk management practices, expressed uncertainty about the quality of those practices, which may have affected their willingness to share. Because many organizations lack outside examples of the current state of biorisk management practice, some may inaccurately judge their own practices as sub-par, in a kind of "organizational imposter syndrome." Such organizations may be hesitant to share information about their biorisk management practices due to concerns about liability, reputational risk, or demands for costly improvement. Intermediaries that have more visibility across organizations may be able to provide assurance and support to overcome this barrier.

Funders were particularly reluctant to share information about their biorisk management practices. Overall government funder response rates to our requests to assist with information sharing were low despite extensive outreach and engagements in international fora, including with the Global Biosecurity Dialogue (GBD) and Global Health Security Agenda Action Package Prevent-3 (GHSA APP-3), and involvement with WHO consultative process to develop a *Global Guidance Framework for the Responsible Use of the Life Sciences.* We had promising early conversations with large and well-known government funders in two countries, but they expressed considerable hesitation about sharing information of their practices beyond what was already publicly available. They also expressed uncertainty about who within their organizations had the authority to approve of sharing. Many of the biorisk management experts with whom we consulted found it

likely that concerns about reputational and/or liability risk, particularly involving political sensitivities related to the COVID-19 pandemic, may have played a role in their reluctance to share. Several philanthropic organizations, including the Gates Foundation, Howard Hughes Medical Institute (HHMI), the Sloan Foundation, and Open Philanthropy were willing to share details of their practices, albeit only in not-for-attribution interviews.

Some organizations already share information publicly or semi-publicly about their biorisk management practices. Many of the organizations that chose to co-develop case studies via VIRS already publicly share information about their biorisk management practices. It is possible that these organizations may be positive outliers insofar as they are confident enough in their practices to be willing to share them. *Science* and ASM outline general information about their DURC review practices in their editorial policies on their websites. In the past, they also both have elected to publish controversial articles with accompanying editorials describing their rationale and inviting commentary. ASM, JGI, RIVM, and iGEM also have written academic publications describing their practices in more detail, which contribute to collective knowledge on how to practice biorisk management.[13,37,38,45,103–106] JGI, iGEM, RIVM, and MIT-BF give presentations on their practices at conferences and other professional events, and RIVM regularly sends a newsletter about their practices to biosafety officers and researchers in the Netherlands. Out of all the case study organizations, iGEM shares the most information publicly about its biorisk management practices. It provides detailed public information about its safety and security policies, and it maintains an online, public repository of previously completed safety forms for all years of the competition.

Some organizations share information about their practices to demonstrate their values and motivate others to adopt biorisk management practices (Case: iGEM, JGI, MIT-BF). For example, the JGI states that the process of documenting and presenting on its broader-aspects review process has been helpful in communicating to the public and other outside stakeholders that it is managing risks responsibly. MIT-BF also shares information about its biorisk management practices to encourage wider adoption. In addition to demonstrating their values, publicly sharing information about biorisk management practices may help organizations attract additional resources. For example, iGEM's maturing safety and security practices have enabled it to attract resources for project review and to expand its model into a convening forum for discussions related to responsibility and safety among a wider set of stakeholders.

Unless incentivized and enabled to do so within a trusted network, we should not expect most organizations to share details of specific cases.

Other organizations share information about their biorisk management practices privately or semi-privately and collect feedback to improve performance management. CSU describes the use of third-party consultants who endorse changes to institutional processes or structure. Other organizations make use of professional networks to solicit feedback more broadly at fora including meetings or conferences (Case: ASM, iGEM, JGI, MIT-BF, *Science*).

Organizations may be more willing to share detailed information within relevant communities and existing professional networks rather than in more public venues. For example, CSU shares information with other research institutions one-on-one and via its involvement in national and regional groups of research institutions (e.g., National Biocontainment Laboratories and Regional Biocontainment Laboratories, Research Alliance for Veterinary Science and Biodefense). MIT-BF similarly shares information about its practices with academic colleagues, iGEM shares yearly lessons learned upon request, and CBB, which is a national regulatory authority, shares information about its practices with organizations it oversees to facilitate its work. The editorial staff of *Science*, ASM, and several other journals also have convened to discuss the efficacy of their biorisk management practices during the rapid increase in SARS-CoV-2-related manuscript submissions. Intermediary groups appear to play a helpful role in facilitating sharing among trusted networks. For example, *Science,* RIVM, and iGEM mentioned that forums like WHO, Biological Weapons Convention (BWC), international working groups, and professional societies like the Association for Biosafety and Biosecurity (ABSA) and European Biosafety Association (EBSA) were useful for gathering feedback from their peers and other stakeholders.

4. Suggested Initiatives

We suggest three complementary initiatives that could be pursued to improve and promote knowledge sharing about biorisk management and to strengthen an ecosystem-wide norm of attention to biorisks. While the VIRS efforts advanced via this project and casebook report focused on how individual organizations understand and enact their responsibilities for biorisk management, these initiatives encourage supporting efforts across the ecosystem and among organizations. Where possible, they try to leverage the materials and insights from VIRS as well as those of complementary efforts. Each initiative addresses one or more challenges related to biorisk management, as noted in Section 2, Key Challenges and Opportunities, that could be tackled separately or in conjunction. The initiatives would:

- Strengthen project-level risk assessment transparency through the adoption of a structured reporting framework.
- Enhance visibility of organization-level practices by developing mechanisms to support knowledge sharing in trusted networks.
- Increase the availability of expertise through professional activities and formal resources that facilitate network development.

For each initiative we outline (i) a summary of goals and strategy, (ii) motivation for the initiative, (iii) design considerations, and (iv) the implementation strategy including potential implementers.

Implementing these initiatives will require resources and support. NTI's BIRRI efforts, including those launched through the IBBIS, are actively soliciting suggestions for, and seeking to direct resources toward, improving biosafety and biosecurity practices and would be well-positioned to support implementation of the initiatives suggested here. We also suggest other potential partners or lead organizations as implementers, noting that these suggestions are meant to be illustrative and not exhaustive.

Each initiative addresses one or more challenges related to biorisk management, as noted in Section 2, Key Challenges and Opportunities, that could be tackled separately or in conjunction.

4.1 | PILOT A STRUCTURED FRAMEWORK FOR DOCUMENTING PROJECT-LEVEL BIORISK MANAGEMENT

To accelerate the development, normalization, and standardization of biorisk management best practices, a structured documentation framework should be designed to facilitate collection, compilation, and comparison of project-level biorisk management decisions and actions. The framework could help organizations improve their internal decision-making strategies and enable diverse stakeholders to communicate concerns about a given project as it progresses through the research life cycle. Coordination among biorisk management practitioners, organizations piloting similar frameworks, and normative entities will be required to pilot and promulgate a documentation framework.

Motivation

Organizations rarely document their biorisk management practices formally (Section 2.4), and when they do, they may lack a framework for keeping track of project-level assessment and mitigation steps. This affects an organization's ability to learn from its own biorisk management practice history (Section 2.5), requiring future assessment and mitigation decisions, even those related to similar projects, to be made on a case-by-case basis. In short, inadequate documentation may negatively impact an organization's ability to systematically improve decision-making and evaluate and improve the performance of their internal biorisk management practices.

Moreover, the lack of a structured framework for project-level biorisk reporting presents a challenge for cross-organizational communication about biorisk management concerns and outcomes, for example, as a project moves among funders, research institutions, and publishers. Such a framework could improve visibility into efforts that stakeholder groups make in governing biorisks throughout the research ecosystem. Implementing a structured reporting framework that is relevant to, applicable for, and interoperable among stakeholder groups in the life science research ecosystem could thus increase transparency into systemwide biorisk management and, importantly, enhance communications among stakeholder groups to foster greater accountability (Section 2.1).

Implementing a structured reporting framework that is relevant to, applicable for, and interoperable among stakeholder groups in the life science research ecosystem could thus increase transparency into systemwide biorisk management and, importantly, enhance communications among stakeholder groups to foster greater accountability.

Previous initiatives have attempted to address these challenges. Notably, the MDAR framework, which was developed and piloted among a group of journals in 2017–2019, required authors of life science manuscripts to describe in a free-text response box whether their project had been subject to DURC oversight (Case: *Science*). The MDAR pilot marked a significant first step toward systematically collecting data about dual use review. However, it lacked sufficient structure to capture information about how project-level biorisks had been assessed and managed and it placed the onus of responsibility for reporting onto authors at the publication stage without much guidance as to what should be included. As a result, the pilot may have been premature in its assessment of the value of reporting and may have had limited relevance for other stakeholder groups that have important roles to play in biorisk governance (i.e., funders) and whose decision-making processes may likewise benefit from a structured biorisk reporting framework. When adopted pre-publication in the research life cycle, an improved reporting framework could enable potential biorisks to be addressed and mitigated much earlier as well as to be tracked and monitored as a project progresses and evolves from conception to conduct to publication.

Ultimately, systematic documentation of organizational biorisk management practices across the life science research ecosystem would facilitate large-scale data collection, the results of which could be compiled into an aggregated evidence base for evaluating when and how biorisks are recognized and managed in practice. Improved documentation of and increased visibility into system-wide biorisk management practices could accelerate the development, normalization, and standardization of empirically grounded biorisk management best practices.

Design Considerations

A framework for documenting project-level biorisk management outcomes should be designed to facilitate collection, compilation, and comparison of project-level biorisk management decisions and actions. At a minimum, a documentation framework should:

- Be **easily integrated** into an organization's existing workflow and designed to avoid time, resource, and cost burdens;
- Be **sufficiently general** to enable use by and interoperability among stakeholders at different stages of the research life cycle, including funders, research institutions, oversight bodies, service providers, and publishers;
- Leverage **existing tools** that go beyond agent- and experiment-based lists. For example, rather than using a single free-text response box as in the MDAR pilot, a more structured framework could draw inspiration from the RIVM Dual-Use Quickscan (Case: RIVM), MIT-Broad Foundry assessment matrix (Case: MIT-BF), PHAC Decision Tree for the Identification of Dual-Use Potential in Life Sciences Research,[46] and iGEM Safety Forms (Case: iGEM).

Specific framework content and form decisions could be derived via a consultative process with stakeholders (see Implementation Strategy below). For example, the framework could be operationalized as a series of questions enabling organizations to document the types of biorisks posed by a given project, the processes or mechanisms used to assess biorisks, mitigations recommended or implemented, and who was responsible for biorisk management for the project. Individuals responsible for biorisk management within those organizations, such as program managers, biosafety officers, biosafety committee members, or application reviewers and editors, would be well-positioned to implement the framework in collaboration with researchers.

At the organizational level, a structured framework could be used routinely to document project-level biorisk assessments and mitigation measures, keep track of internal decision-making and management strategies, guide decision making for similar projects and concerns, and evaluate the performance of biorisk management systems overall.

Improved documentation of and increased visibility into system-wide biorisk management practices could accelerate the development, normalization, and standardization of empirically grounded biorisk management best practices.

At the research ecosystem level, a structured framework could be used by stakeholders across the research life cycle to affirm their participation in biorisk management (e.g., demonstrate due diligence), increase transparency into decision making processes (which can contribute to greater accountability), and track and communicate concerns about a given project as it develops, from conception to publication. Note that, for project-level information to be shared among organizations, barriers such as privacy, liability, and information hazard concerns will need to be addressed. Sharing within trusted networks or coordinated by a trusted intermediary, as proposed in Section 4.2, may help mitigate some of these concerns.

Implementation Strategy

To develop the framework for utility and applicability across the life science research ecosystem, a consultative meeting should be convened involving a broad range of stakeholder groups including funders, publishers, research performers, and organizations responsible for oversight. The working groups organized by WHO in developing the Global Guidance Framework for Responsible Use of the Life Sciences and the NTI BIRRI groups used to conceive of VIRS are two examples that could be expanded and leveraged to develop this work.[27,32] These consultations should specifically determine the framework's goals, content, and form, options for operationalization and mechanisms both to pilot and incentivize broader adoption of the framework.

Current coalitions among funders and publishers committed to transparency initiatives via MDAR and the TOP Guidelines may be good candidates for co-designing this suggested initiative, along with other organizations from different stakeholder groups that have made commitments to managing biorisks (see Appendix 5, Tables 5.9 and 5.10). Connecting with funders of life science research will be critical to accelerate progress on systemwide accountability; participants in the NTI BIRRI-supported Biotechnology Funders' Compact may be particularly valuable partners in the co-design of this suggested initiative.[94]

Several organizations are motivated and/or well-positioned to assemble a coalition of stakeholders to develop and pilot this framework. The EBRC already has begun developing a pre-publication security evaluation that would enable piloting a standardized framework across several life science journals.[95] Additionally, the COS is actively developing infrastructure to support similar initiatives via the Open Science Framework (OSF) and has expressed interest in piloting a dual use review. By partnering with organizations such as WHO and IBBIS that are developing normative initiatives, COS may be well-positioned to rapidly promulgate, test, and update such a framework.

4.2 | DEVELOP MECHANISMS TO SUPPORT THE SHARING OF ORGANIZATIONAL PRACTICES IN TRUSTED NETWORKS

Formalized mechanisms for knowledge sharing, such as case studies, can facilitate cross-organizational learning when implemented in trusted networks. Efforts focused on supporting best practices between different stakeholders at the regional and international levels, including IBBIS, may be well-positioned to serve as trusted intermediaries that can facilitate coordination among existing communities and support the piloting of more formalized knowledge sharing mechanisms therein.

Motivation

Increased visibility into biorisk management practices could accelerate the development of best practices. However, organizations are reluctant to share information about their own practices, particularly publicly, even when they find value in learning about those of others (Section 2.6). Reported impediments to sharing include: concerns about liability and privacy, lack of time, resources, or support from top management, and what one reviewer called "organizational imposter syndrome" (Sections 1.4, 2.6, 3.3.2), that is, an organization's belief that their biorisk management practices are inadequate or inferior to those of others, even when this is not the case. These constraints indicate that a high level of trust as well as practical support are needed to incentivize organizations to document and share their biorisk management practices. One option for meeting these conditions would be for a trusted intermediary to devote time and resources to coordinate knowledge sharing among organizations (see Implementation Strategy).

Currently, there are several initiatives focused on developing standards or communities of practice among organizations that share similar roles and responsibilities in the life science research ecosystem. For example, the International Gene Synthesis Consortium brings together commercial DNA synthesis providers to develop and implement biosecurity protocols.[107,108] Similarly, the Biotechnology Funders' Compact, currently under development, will assemble funders committed to improving biosecurity in life science research funding.[94] Associations of biosafety and biosecurity professionals, such as ABSA,[47] EBSA,[48] and the International Federation of Biosafety Associations (IFBA)[50] serve as networks that connect organizations that perform life science research. By contrast, there are few initiatives that engage or host discussions among diverse stakeholder groups across the research life cycle. As a result, coordination and knowledge sharing across stakeholder divides remains rare.

That said, a few broad multi-stakeholder networks that engage with biosafety- and biosecurity-related issues already have been established, such as the Global Health Security Agenda (GHSA), Global Biosecurity Dialogue (GBD), the Biosafety Level 4 Zoonotic Laboratory Network (BLZ4),[109] and International Experts Group of Biosafety and Biosecurity Regulators (IEGBBR).[28,110,111] Although these groups primarily engage in high-level discussions about policy implementation rather than sharing specific details of biorisk management practice that may be more useful to organizations directly involved in life science research, they demonstrate that knowledge sharing related to biosafety and biosecurity is feasible in private or semi-public networks. With additional support to assist with facilitation and documentation, they could accelerate best practices and standards development.

Knowledge sharing related to biosafety and biosecurity is feasible in private or semi-public networks. With additional support to assist with facilitation and documentation, they could accelerate best practices and standards development.

Design Considerations

This suggested initiative should prioritize connecting existing communities of organizations that practice biorisk management with one another to facilitate knowledge sharing across stages of the life science research life cycle. It should also leverage these communities to co-design and test formalized mechanisms for knowledge sharing.

By co-developing case studies and convening an international set of organizations in a two-part workshop, VIRS demonstrated the feasibility and utility of **case studies** as a formal mechanism for knowledge sharing among stakeholders from across the life science research life cycle. The case studies developed via VIRS produced valuable insights, but the initial set was limited to eight organizations and required significant time and resources to refine and implement an initial case study format. By coordinating with existing networks, and with support from an intermediary that could devote additional resources to case study development, full or abridged case studies could be piloted among a broader cohort of organizations to better understand their utility as knowledge-sharing mechanisms at scale.

Beyond case studies, alternative knowledge-sharing mechanisms that could be piloted within existing networks include:

- **Stories of practice** that describe evolutions in organizations' biorisk management through short vignettes, potentially including specific biorisk-related incidents and how they were managed. Similarly, Global Health Security Agenda Action Package Prevent 3 (GHSA APP3) recently has proposed collating a set of "stories of impact" that highlight examples of progress toward global health security goals.[112] While short vignettes may be less resource-intensive to develop than case studies, they may lack the level of detail that would be most useful to organizations. Stories of practice could be compared with the VIRS case study for their utility and costs;
- **Shadowing programs** that enable representatives from organizations to sit in on each other's biorisk deliberations as a mechanism for sharing tacit knowledge. However, concerns about intellectual property and privacy may need to be addressed for these to be implemented effectively. While documentation may not be a primary focus of shadowing programs, it may be possible to couple case study co-development with these efforts;
- **Twinning programs** that pair organizations seeking biorisk management advice with organizations that have well-developed practices. For example, Sandia National Laboratories organizes capacity-building engagements that provide direct assistance to research institutions in need of biorisk management expertise, particularly in lower-income countries.[113] However, these one-on-one interactions may be less easily scaled than those involving multiple organizations. As above, there may be opportunities to integrate case study co-development to enable broader sharing of practices over time.

Note that each of these programs has advantages and disadvantages that would need to be weighed, in consultation with relevant stakeholders, when deciding which to implement.

Initially, organizations that are most comfortable with or able to devote resources to knowledge sharing may be more willing to share information about their biorisk management practices. With time, the number of organizations should increase as knowledge sharing becomes normalized and its value demonstrated. Support from top management will be critical for organizations to participate in piloting knowledge sharing mechanisms. Additional research into factors that disincentivize sharing could also inform efforts to reach organizations that currently may be reluctant to share information about their biorisk management practices.

Implementation Strategy

As described above, multiple communities exist in which organizations currently share or could share knowledge about biorisk management practices (see Motivation section), including the Biotechnology Funders' Compact, biosafety and biosecurity professional organizations (e.g., ABSA, EBSA, IFBA), and industry groups (e.g., IGSC, participants in the NTI "Seal of Approval" initiative for DNA synthesis biosecurity[114]). With support from an intermediary, these communities could be better integrated with one another and leveraged for broader pilots of knowledge sharing mechanisms. Given their goals of strengthening international biosecurity norms, both WHO (in their efforts to develop and promote the Global Guidance Framework for the Responsible Use of the Life Sciences) and IBBIS are potentially well-positioned to serve as intermediaries to coordinate these efforts. One immediate next step could be to convene users of the different knowledge sharing mechanisms (e.g., case studies, stories of practice, twinning programs, shadowing programs) to discuss their utility. By holding regular convenings (e.g., every year) different practices and formats for documentation could be shared, examined, and refined. These discussions could inform the selection or design of a set of formal knowledge-sharing mechanisms for future piloting.

4.3 | BUILD BIORISK MANAGEMENT EXPERTISE AND CONNECT EXPERTS TO ORGANIZATIONS

Comprehensive biorisk management training will be critical for cultivating and expanding the next generation of experts from within and beyond the life sciences. A searchable database of verified experts, when supported by an intermediary that can pair organizations with relevant experts, could expand access to expertise. The IBBIS is well-positioned to coordinate experiential learning opportunities and to develop, maintain, and support a database that could connect organizations to resources and expertise.

Motivation

Organizations report challenges to identifying experts to participate in their biorisk review processes (Section 2.3). This may be due to (i) a paucity of relevant experts, (ii) misperceptions regarding which experts are needed, or (iii) limited access to qualified experts who are amenable to participating in biorisk review.

Some initiatives address aspects of these concerns, for example, by expanding the cadre of qualified biosafety and biosecurity experts vis-a-vis training and education programs.[49] Biosafety professional organizations, such as ABSA and EBSA,[48] are among the principal providers of biosafety and biosecurity training and education through courses and other programs. In addition to formal training and educational opportunities, there are also many programs that provide simulated and practical hands-on experiences managing biorisks. For example, the iGEM competition[115] (Case: iGEM) requires participants to consider safety and security issues throughout the design and implementation of their synthetic biology projects. iGEM also convenes experts in biosafety and biosecurity through their project review processes and through convenings that focus on social responsibility and related issues. In addition, the Malice Analysis program,[116] hosted by the EBRC with support from the US Department of Homeland Security, used facilitated workshop sessions to help trainees recognize potential ways in which their research could be misused. Continued investments in education and experience-based comprehensive biorisk management training will be critical to cultivate and expand the next generation of experts.

Organizations might benefit from access to a regularly maintained database of biorisk experts. For example, Biosafety Clearing-House (BCH)[19] is a public resource provided by the Convention on Biological Diversity that includes biographical and contact information for biosafety experts, with a focus on those who have expertise in living modified organisms (LMOs). In some cases, databases are integrated with certification and credentialing programs. The IFBA[50] maintains a list of regional biosafety associations and a directory of more than 1,000 IFBA professionals who have completed IFBA certification programs.[117] ABSA International[47] also offers credentialing programs for biosafety and hosts a private membership directory of biosafety professionals, available only to ABSA members. While useful in their intended contexts, each of these databases was designed to serve a specific purpose and set of end users, which may limit their accessibility or utility to some life science research stakeholders.

Continued investments in education and experience-based comprehensive biorisk management training will be critical to cultivate and expand the next generation of experts.

Design Considerations

Two mechanisms for expanding the pool of experts include: (i) cultivating the next generation of experts to support biorisk management practices going forward and (ii) integrating more professionals with relevant expertise and experiences into extant biorisk management communities. Investing in comprehensive biorisk management training and education programs for professionals and students of life science is essential. To supplement these critical, ongoing activities, this suggested initiative should prioritize activities that (i) enable individuals within and outside the life sciences to develop biosafety and biosecurity expertise through practical and interactive experiences and (ii) simultaneously build relationships among individuals across disciplinary and sectoral divides. Such activities could include table-top exercises, competitions or games, and opportunities to interact with national security communities. It is particularly important that these activities be made accessible to individuals in regions where capacity-building efforts are most needed to bolster local pools of expertise.

Participation in training and education programs together with experiential learning and networking opportunities could subsequently serve as the basis for accreditation and inclusion in a searchable database of verified experts. A curated database would serve as a formal resource to expand accessibility to individuals who are not yet included in formal networks of expertise. Features of the database should include the contact information for verified experts along with a description of their expertise and relevant experiences. This description should be sufficiently specific such that database users can readily ascertain whether a given individual has the expertise they seek. The database could be further expanded to include organizations with experience managing biorisks and international fora that can be joined or leveraged for future network development. Such a database would need to be hosted and maintained by a reputable organization, advertised within the life science research, biosafety, and biosecurity communities, and updated regularly.

The proposed database could be made available publicly, semi-publicly, or privately or upon request by specific organizations seeking expertise. However, for a database to be most effective, the organization hosting it ideally would serve an intermediary function, acting as a single point of contact that connects organizations in need of specific expertise with relevant, validated experts. This intermediary function may be particularly important when organizations have uncertainties about the expertise that they require, and it could help to limit the number of requests experts receive by pre-screening for legitimate and relevant inquiries. Issues related to liability, including how information is distributed among an intermediary organization and individual experts, will need to be addressed prior to implementation.

Implementation Strategy

IBBIS, WHO, or the United Nations BWC Implementation Support Unit (UN BWC ISU) may be well-positioned to support and promote informal experiential learning activities, such as table-top exercises, competitions or games, and workshops, in which individuals can develop biosafety and biosecurity expertise. These activities should be conducted in coordination with organizations that have experience engaging life science researchers in formal or informal training, such as ABSA International, EBSA, iGEM, or EBRC. Consultations with these stakeholders and with other biorisk management experts will be helpful to determine the types of programs that can most effectively supplement other ongoing initiatives. While standards for verification and/or accreditation of expertise will also need to be developed, in the near-term, self-attestation of credentials may be sufficient to pilot the value of this effort.

IBBIS is also well-positioned to maintain a database of experts and to act as an intermediary that can connect organizations to the expertise they require. Such an initiative can build on existing databases (as described in Motivation), including an initial list of experts, organizations, and fora that we developed by VIRS (see Contributors and Appendix 5 in this document). Coordination with ABSA International and IFBA will be particularly valuable to avoid duplication of efforts given that they already have developed databases. IBBIS additionally could capitalize on organizations' requests for assistance to develop a community of organizations invested in performing and improving biorisk management and potentially interested in engaging in future initiatives (see Section 4.2).

5. Methodology

5.1 | SUMMARY

Our work included several stages to understand the key challenges and opportunities present in biorisk management, identify organizations whose practices we might highlight, and refine and validate our approach to information collection and insight generation. In brief, our process was as follows:

Background research and expert consultations

- Reviewed 171 background publications including academic journals, conference proceedings, government and academies reports, public hearings and testimonies, books, media publications, and policy documents;
- Conducted 61 expert consultations;
- Participated and presented in several ongoing international biorisk management discussions (e.g., NTI's Global Biosecurity Dialogue);
- Highlighted VIRS in three publications [95,118,119] as well as WHO's *Global Guidance Framework for the Responsible Development of the Life Science;*[7]
    - Pannu, J., Sandbrink, J.B., Watson, M., Palmer, M.J. & Relman, D.A. Protocols and risks: when less is more. *Nature Protocols* 17, 1–2 (2022);
    - Musunuri, S., Sandbrink, J.B., Monrad, J.T., Palmer, M.J., Koblentz, G.D. Rapid proliferation of pandemic research: implications for dual-use risks. *mBio* 12, e01864-21 (2021);
    - Mackelprang, R., Adamala, K., Aurand, E., Diggans, J., Ellington, A., Evans, S.W., Fortman, J.L., Hillson, N., Hinman, A., Isaacs, F., Medford, J., Mamaghani, S., Moon, T.S., Palmer, M.J., Peccoud, J., Vitalis, E., Hook-Barnard, I., Friedman, D. Making security viral: shifting engineering biology culture and publishing. *ACS Synthetic Biology* 11, 522–527 (2022).

Case study identification and selection

- Identified 380 organizations mentioned in our background research and consultations;
- Of these, 36 were universities located in the US Initially, we deprioritized these because the implementation of US DURC policy among universities in the US already had been documented through other means;[25]
- Identified 52 candidate case study organizations with some evidence of having a biorisk management practice;
- Selected 33 organizations to contact, prioritizing sample diversity;
- Made contact with 22 organizations;
- Developed complete case studies with eight organizations;
- Identified 21 candidate organizations for additional non-attributed interviews;
- Conducted non-attributed interviews with 12 organizations.

Case study refinement and validation

- Conducted a two-part workshop with case study organizations and other stakeholders to discuss and refine case study templates and identify insights.

Synthesis of cross-cutting insights and validation

- Case studies and interviews were compared to identify common themes, challenges, bright spots, and opportunities;
- Solicited feedback on a draft report from participants and an additional 18 experts. In total, 29 reviewers shared feedback which was incorporated wherever possible and appropriate.

5.2 | EXPERT CONSULTATIONS

We began *The Biorisk Management Casebook* project by reaching out to a set of international life science research biosafety and biosecurity experts to engage in open-ended conversations about the state of biorisk management. Conversations lasted 30–90 minutes and covered topics such as the design of biorisk management systems, incentives, and motivations to practice biorisk management, sharing biorisk management information, the resources and expertise required to effectively manage risks, options for risk mitigation, and the scope of risks organizations consider. A primary goal of these consultations was also to identify organizations that have biorisk management practices that we might highlight and learn from along with recommended contacts. We first contacted experts in our professional networks and then used snowball sampling to identify further contacts and potential case study organizations. In total, we communicated with 61 experts from academia, government, and industry across all continents except Antarctica. (See Contributors section for a full list.)

5.3 | CASE STUDY DEVELOPMENT

Having conducted initial outreach through expert consultations, we then began reaching out to potential partner organizations to co-develop case studies of their biorisk management practices. As opposed to a survey or other data collection methods, we chose to conduct case studies because they:

1. Can provide enough detail to be useful on their own as guides for practice;
2. Are developed through collaborative and trusting relationships, which are important for ensuring that organizations are comfortable sharing information about their practices;
3. Provide a flexible format and can be iteratively adapted. (In the process of developing case studies, we significantly revised our template five times);
4. Exemplify how a standardized mechanism can be used to share information about biorisk management practices among diverse stakeholder groups.

It was neither feasible nor our goal to develop a representative sample of different organizations practicing biorisk management across the globe. Instead, we sought to identify a diverse set of case studies that highlight potential bright spots of excellence and/or innovation in different contexts. We pursued case studies from different regions and organizational types (e.g., funders; research performers; publishers; service-providers; regulatory, oversight, and advisory bodies). To participate in a case study, organizations had to have a describable practice for assessing and mitigating biological risks with life science research projects, to be willing to work with us to document this practice, and to be provisionally willing to share it with at least the other organizations participating in the project.

In addition to our expert consultations, we searched for potential case study organizations by reviewing 171 academic and "grey literature" publications, including workshop reports, studies, and policy documents that addressed biosafety, biosecurity, and dual use-related issues. We also engaged in outreach within international fora, including the Global Biosecurity Dialogue Emerging Risks Workstream and Global Health Security Agenda Action Package Prevent-3 (GHSA APP-3) on Biosafety and Biosecurity.

We identified 380 organizations through our literature review and expert consultations. Of these, 36 were universities located in the US, which we initially deprioritized because some aspects of the implementation of US DURC oversight policy had already been documented at US universities through other means.[25] We identified 52 candidates with some evidence of a biorisk management practice and reached out to 33 of these, which were selected with the goal of creating a diverse set of case studies. We heard back from 22 organizations and were able to develop complete case studies with nine, of which eight are included in this report. One organization declined to proceed to public dissemination, and two additional organizations declined to co-develop their case studies to completion. We also identified and contacted several organizations which did not have a biorisk management practice in place at the time but were interested in learning from others' experiences as they developed their own approaches.

We worked with organizations to develop case studies through a combination of interviews, background research, and providing a copy of our case study template (Appendix 2) for organizations to fill in their own responses. This case-study template evolved through the development of several early case studies and through feedback sessions during workshops (see below). Organizations were first invited to share their case studies with a small group during workshops before they were asked if case studies could be shared more publicly.

5.4 | WORKSHOP

The Case Study Feedback & Future Engagements Workshop gathered representatives from organizations who participated in the development of VIRS case studies, along with representatives from related initiatives. The workshop took place virtually over two two-hour meetings on November 16 and December 10, 2021. Both meetings operated under Chatham House Rule to enable free and frank discussion among participants. Workshop participants were provided with background information and draft case studies.

Workshop Goals

- To share insights among participants from VIRS engagements so far;
- To learn from case study organizations about what they found useful in developing case studies and to discuss opportunities and limitations for sharing case studies more widely;
- To learn from organizations seeking to develop biorisk management standards about what might be most useful to learn from case studies;
- To refine the case study approach and identify opportunities to expand participation in VIRS, including priorities and partners for future work.

Invited Workshop Participants

Representatives from organizations participating in case studies:

- Addgene; Eric Perkins
- ASM Journals; Melissa Junior
- CBB; Line Gylling, Katja Nyholm Olsen
- CSU Biosafety Office; Rebecca Moritz
- iGEM Foundation; Piers Millett, Tessa Alexanian
- MIT-Broad Foundry
- RIVM; Rik Bleijs
- *Science*; Stella Hurtley
- JGI; Nathan Hillson

Organizations developing international standards, guidelines, and initiatives:

- Jaime Yassif, Jacob Eckles, Hayley Severance (NTI | bio)
- Soatiana Rajatonirina, Emanuelle Tuerlings (World Health Organization)
- Talkmore Maruta (Africa CDC, GHSA APP-3)

Organizing and research team:

- Megan Palmer, Daniel Greene, Kathryn Brink, Melissa Salm, Connor Hoffmann, Geetha Jeyapragasan (Stanford University)
- Sam Weiss Evans (Harvard University)

5.5 | NON-ATTRIBUTED INTERVIEWS

One major finding of our case study outreach effort was that many organizations—particularly government and private funding organizations—were reluctant to participate in a fully identified case study. Based on our interactions with organizations that initially expressed interest and then withdrew, we believe that fears about liability and/or reputational risk related to sharing details of their risk management practices may have been key deterrents more so than the additional burdens of co-developing a full written case study.

As a result, once we reached eight confirmed case studies, we changed our outreach messages to emphasize a new option for participation—one-time semi-structured interviews that were not-for-attribution by default, meaning that organizations would be listed as contributors and the information they provided incorporated into our findings, but their specific responses would be neither linked to their names or their organizations. Participants could also choose to participate anonymously or to have their comments attributed to them.

Drawing from the same pool of candidate organizations as in the case studies, we reached out to 21 additional organizations with our new outreach message and were able to conduct interviews with 12 of them. All participants provided explicit verbal consent to participate and stated their preferences for attribution in accordance with our protocol, which was approved by the Stanford University Institutional Review Board (IRB).

To conduct the non-attributed interviews, we used the interview protocol in Appendix 4, which was adapted from the sections of the case study template (see Appendix 2). We provided this protocol to participants in advance of each interview and modified some of the questions in real-time and as needed based on interviewees' responses. Interviews were recorded for internal note-taking purposes, ranged from 30–60 minutes, and always included both an interviewer and a note-taker. After each interview, our team reviewed the notes and discussed key points. We then analyzed the interview data for emerging themes.

5.6 | EXPERT REVIEW

In September 2022, we solicited feedback on a draft of this report from participants in our case studies, non-attributed interviews, and workshops, and a selection of our expert consultations from early in the development of the VIRS project. Reviewers who participated in case studies, non-attributed interviews, and workshops were offered the opportunity to provide feedback including any corrections. An additional set of 18 experts was recruited and offered honoraria of $500 USD in gratitude for providing a detailed review focused on the clarity of the report and the strength of its findings. In total, 29 reviewers shared feedback on this report. Feedback was incorporated wherever possible and appropriate; feedback that could not be addressed prior to the publication was added to Section 1.4, Limitations.

References

Note that, due to space constraints, this reference list represents a subset of all documents consulted throughout the development of VIRS.

1. National Academies of Sciences, Engineering, and Medicine. *Dual Use Research of Concern in the Life Sciences: Current Issues and Controversies.* (2017) doi:10.17226/24761.
2. Bezuidenhout, L. Research infrastructures, policies and the 'web of prevention': the ethical implications of inadequate research environments. *Med. Confl. Surviv.* 28, 19–30 (2012).
3. Harris, E. D., Acton, J. M. & Lin, H. *Governance of Dual-Use Technologies: Theory and Practice.* (American Academy of Arts & Sciences, 2016).
4. *A Web of Prevention: Biological Weapons, Life Sciences and the Governance of Research.* (Routledge, 2007). doi:10.4324/9781849770354.
5. Working Group on International Collaboration. Summary of Roundtable Meeting. (National Science Advisory Board for Biosecurity (US), 2007).
6. United States Government & World Health Organization. Sustaining Progress in the Life Sciences: Strategies for Managing Dual Use Research of Concern. (National Science Advisory Board for Biosecurity).
7. World Health Organization. *Global Guidance Framework for the Responsible Use of the Life Sciences: Mitigating Biorisks and Governing Dual-Use Research.* (World Health Organization, 2022).
8. National Research Council. *Biotechnology Research in an Age of Terrorism.* (National Academies Press, 2004). doi:10.17226/10827.
9. Kirkpatrick, J. et al. *Editing Biosecurity: Needs and Strategies for Governing Genome Editing.* (George Mason University, 2018).
10. Lewis, G., Millett, P., Sandberg, A., Snyder-Beattie, A. & Gronvall, G. Information Hazards in Biotechnology. *Risk Anal.* 39, 975–981 (2019).
11. Palmer, M. J., Fukuyama, F. & Relman, D. A. A more systematic approach to biological risk. *Science* 350, 1471–1473 (2015).
12. Patrone, D., Resnik, D. & Chin, L. Biosecurity and the Review and Publication of Dual-Use Research of Concern. *Biosecurity Bioterrorism Biodefense Strategy Pract. Sci.* 10, 290–298 (2012).
13. Casadevall, A., Dermody, T. S., Imperiale, M. J., Sandri-Goldin, R. M. & Shenk, T. Dual-use research of concern (DURC) review at American Society for Microbiology Journals. *mBio* 6, (2015).
14. Sankar, P. L. & Cho, M. K. Engineering Values into genetic engineering: a proposed analytic framework for scientific social responsibility. *Am. J. Bioeth. AJOB* 15, 18–24 (2015).
15. Schreider, J. et al. Enhancing the credibility of decisions based on scientific conclusions: transparency is imperative. *Toxicol. Sci. Off. J. Soc. Toxicol.* 116, 5–7 (2010).
16. Selgelid, M. J. Dual-use research codes of conduct: lessons from the life sciences. *NanoEthics* 3, 175 (2009).
17. Working Group Activities of the National Science Advisory Board for Biosecurity (NSABB). *Office of Science Policy* https://osp.od.nih.gov/biotechnology/national-science-advisory-board-for-biosecurity-nsabb/.
18. North Atlantic Treaty Organization. Security and Resilience for Emerging Synthetic Biology and Biotechnology Threats. *North Atlantic Treaty Organization* http://www.nato.int/cps/en/natohq/news_161451.htm.
19. Convention on Biological Diversity. Registries. *Biosafety Clearing-House* https://bch.cbd.int/en/registries.
20. Laboratory of Clinical Microbiology, Virology and Bioemergencies. CBRN CoE Project 18. *Laboratory of Clinical Microbiology, Virology and Bioemergencies* https://climvib.eu/cbrn-coe-project-18/.
21. National Academies of Sciences, Engineering, and Medicine. *Enhancing Scientific Reproducibility in Biomedical Research Through Transparent Reporting: Proceedings of a Workshop.* (The National Academies Press). doi:10.17226/25627.
22. Global Health Security Agenda (GHSA) Action Package on Biosafety and Biosecurity (GHSA-APP3). https://ghsagenda.org/2020/07/30/app3-statement-on-biosecurity-and-biosafety-during-the-covid-19-pandemic/.

23. International Experts Group of Biosafety and Biosecurity Regulators. Mobile Application of Biosafety, Biosecurity and Dual-Use Oversight.

24. Macleod, M. et al. MDAR (Materials Design Analysis Reporting) Framework for transparent reporting in the life sciences. *Proc. Natl. Acad. Sci.* 118, e2103238118 (2021).

25. United States Government National Institutes of Health. *Stakeholder Engagement Workshop on the Implementation of the United States Government Policy for Institutional Oversight of Life Sciences DURC, September 25-26, 2017.* https://osp.od.nih.gov/events/stakeholder-engagement-workshop-on-implementation-of-the-usg-policy-for-institutional-oversight-of-life-sciences-durc/.

26. NSABB. *National Science Advisory Board for Biosecurity (NSABB) Meeting Agenda, January 23–24, 2020,* Bethesda, MA. https://osp.od.nih.gov/wp-content/uploads/NSABB_Meeting_Agenda_Jan23-24_2020.pdf.

27. Biosecurity Innovation and Risk Reduction Initiative. *The Nuclear Threat Initiative* https://www.nti.org/about/programs-projects/project/fostering-biosecurity-innovation-and-risk-reduction/.

28. Global Biosecurity Dialogue. *The Nuclear Threat Initiative.* https://www.nti.org/about/programs-projects/project/global-biosecurity-dialogue/.

29. Open Scholarship Knowledge Base. OER Commons https://www.oercommons.org/hubs/OSKB.

30. Principles and Guidelines for Reporting Preclinical Research. National Institutes of Health (NIH). https://www.nih.gov/research-training/rigor-reproducibility/principles-guidelines-reporting-preclinical-research (2015).

31. Center for Open Science. TOP Guidelines. https://www.cos.io/initiatives/top-guidelines.

32. World Health Organization. Ensuring responsible use of life sciences research. *World Health Organization.* https://www.who.int/activities/ensuring-responsible-use-of-life-sciences-research.

33. International Biosecurity and Biosafety Initiative for Science (IBBIS). *The Nuclear Threat Initiative.* https://www.nti.org/about/programs-projects/project/international-biosafety-and-biosecurity-initiative-for-science-ibbis/.

34. Dual use life science research (DUR/C): dialogue with science editors and publishers (Meeting Report, July 28, 2020). (World Health Organization, 2020).

35. Dual use life science research (DUR/C): perspective from donors of life sciences research (Meeting Report, December 1, 2020). (World Health Organization, 2020).

36. Dual use life science research (DUR/C): dialogue with academies and councils (Meeting Report, July 7, 2020). (World Health Organization, 2020).

37. Millett, P., Isaac, C. R., Rais, I. & Rutten, P. The synthetic-biology challenges for biosecurity: examples from iGEM. *Nonproliferation* Rev. 27, 443–458 (2021).

38. Millett, P. et al. Developing a Comprehensive, Adaptive, and International Biosafety and Biosecurity Program for Advanced Biotechnology: The iGEM Experience. *Appl. Biosaf.* 24, 64–71 (2019).

39. Vinke, S., Rais, I. & Millett, P. The dual-use education gap: awareness and education of life science researchers on nonpathogen-related dual-use research. *Health Secur.* 20, 35–42 (2022).

40. The Australia Group—Common Control Lists. https://www.dfat.gov.au/publications/minisite/theaustraliagroupnet/site/en/controllists.html.

41. Federal Select Agent Program. HHS and USDA Select Agents and Toxins. *Federal Select Agent Program.* https://www.selectagents.gov/sat/list.htm (2022).

42. Meechen, P. & Potts J. *Biosafety in microbiological and biomedical laboratories, 6th Edition (BMBL).* US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institutes of Health (2020).

43. United States National Institutes of Health Office of Science Policy. *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules.* https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.pdf (2019).

44. US Department of Health and Human Services. "United States government policy for institutional oversight of life sciences dual use research of concern." (2014): 09-24.

45. Vennis, I. M. et al. Dual-Use Quickscan: A Web-Based Tool to Assess the Dual-Use Potential of Life Science Research. *Front. Bioeng. Biotechnol.* 9, (2021).

46. Plan for Administrative Oversight for Pathogens and Toxins in a Research Setting-Required Elements and Guidance. Public Health Agency of Canada. (2015).

47. ABSA International. ABSA International: The Association for Biosafety and Biosecurity. https://absa.org/ (2021).

48. European Biosafety Association. Welcome to EBSA. *European Biosafety Association.* https://www.ebsaweb.eu/.

49. Moritz, R. L., Berger, K. M., Owen, B. R. & Gillum, D. R. Promoting biosecurity by professionalizing biosecurity. *Science* 367, 856–858 (2020).

50. IFBA. Home. *IFBA—International Federation of Biosafety Associations.* https://internationalbiosafety.org/.

51. Publications. *Haut Conseil des Biotechnologies.* http://www.hautconseildesbiotechnologies.fr/en/article/publications.

52. Federal Reserve Board—Beige Book. *Board of Governors of the Federal Reserve System.* https://www.federalreserve.gov/monetarypolicy/beige-book-default.htm.

53. UAS Safety Reporting. *Aviation Safety Reporting System.*

54. International Experts Groups of Biosafety and Biosecurity Regulators—IEGBBR. https://iegbbr.org/.

55. Centre for Biosecurity and Biopreparedness. *An efficient and practical approach to Biosecurity.* (2015).

56. World Health Organization. Biorisk management: Laboratory biosecurity guidance. (2006).

57. National Science Advisory Board for Biosecurity. *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research.* (2016).

58. Gronvall, G. K. *H5N1: A Case Study for Dual-Use Research.* (2013).

59. Salerno, R. M. & Gaudioso, J. *Laboratory Biorisk Management.* (CRC Press, 2015). doi:10.1201/b18446.

60. US Department of Health and Human Services. *Framework for guiding funding decisions about proposed research involving enhanced potential pandemic pathogens.* https://www.phe.gov/s3/dualuse/Documents/P3CO.pdf (2017).

61. Public Health Agency of Canada. *Canadian Biosafety Guideline: Dual-Use in Life Science Research.* (2018).

62. Reed, M. S. & Curzon, R. Stakeholder mapping for the governance of biosecurity: a literature review. *J. Integr. Environ. Sci.* 12, 15–38 (2015).

63. Suk, J. E., Bartels, C., Broberg, E., Struelens, M. J. & Ozin, A. J. Dual-use research debates and public health: better integration would do no harm. *Front. Public Health* 2, 114 (2014).

64. Hamilton, R. A. *et al.* Opportunities, Challenges, and Future Considerations for Top-Down Governance for Biosecurity and Synthetic Biology. In *Emerging Threats of Synthetic Biology and Biotechnology* (eds. Trump, B. D., Florin, M.-V., Perkins, E. & Linkov, I.) 37–58 (Springer Netherlands, 2021). doi:10.1007/978-94-024-2086-9_3.

65. Inglesby, T. V. & Lipsitch, M. Proposed changes to US policy on potential pandemic pathogen oversight and implementation. *mSphere* 5, e00990-19 (2020).

66. Duprex, W. P., Fouchier, R. A. M., Imperiale, M. J., Lipsitch, M. & Relman, D. A. Gain-of-function experiments: time for a real debate. *Nat. Rev. Microbiol.* 13, 58–64 (2015).

67. White Paper on Publication Ethics. *Council of Science Editors.* https://www.councilscienceeditors.org/resource-library/editorial-policies/publication-ethics/.

68. Bork, K. H., Halkjaer-Knudsen, V., Stig Hansen, J.-E. & Heegaard, E. D. Biosecurity in Scandinavia. Biosecurity *Bioterrorism Biodefense Strategy Pract. Sci.* 5, 62–71 (2007).

69. United Nations Security Council. *Non-proliferation of weapons of mass destruction. Resolution 1540* (2004). http://unscr.com/en/resolutions/1540.

70. Herfst, S. *et al.* Airborne Transmission of Influenza A/H5N1 Virus Between Ferrets. Science 336, 1534–1541 (2012).

71. Russell, C. A. et al. The Potential for Respiratory Droplet–Transmissible A/H5N1 Influenza Virus to Evolve in a Mammalian Host. *Science* 336, 1541–1547 (2012).

72. International Organization for Standardization. ISO 35001—Biorisk management for laboratories and other related organisations. (2019). https://www.iso.org/standard/71293.html/.

73. World Health Organization. *Responsible life sciences research for global health security: a guidance document.* (2010). https://www.who.int/publications/i/item/WHO-HSE-GAR-BDP-2010.2.

74. Israel Academy of Sciences and Humanities & Israel National Security Council. *Biotechnological research in an age of terrorism.* (2008).

75. Clinical Biosafety Services. https://clinicalbiosafety.com/.

76. Advarra: Enabling Safer, Smarter, Faster Clinical Research. *Advarra* https://www.advarra.com/.

77. Evans, S., Greene, D., Hoffmann, C. & Lunte, S. Stakeholder engagement workshop on the implementation of the United States government policy for institutional oversight of life sciences dual use research of concern: workshop report. *SSRN Electron. J.* (2021) doi:10.2139/ssrn.3955051.

78. National Institutes of Health. Tools for the Identification, assessment, management, and responsible communication of dual use research of concern: A companion guide to the United States Government policies for oversight of life sciences dual use research of concern. (2014).

79. World Health Organization. *Towards a global guidance framework for the responsible use of life sciences: summary report of consultations on the principles, gaps and challenges of biorisk.* (2022).

80. Engel-Glatter, S. & Ienca, M. Life scientists' views and perspectives on the regulation of dual-use research of concern. *Sci. Public Policy* 45, 92–102 (2018).

81. Schröder, I., Czornyj, E., Blayney, M. B., Wayne, N. L. & Merlic, C. A. Proceedings of the 2018 laboratory safety workshop: hazard and risk management in the laboratory. *ACS Chem. Health Saf.* 27, 96–104 (2020).

82. Schuurbiers, D., Osseweijer, P. & Kinderlerer, J. Implementing the Netherlands code of conduct for scientific practice—a case study. *Sci. Eng. Ethics* 15, 213–231 (2009).

83. Greene, M. & Master, Z. Ethical issues of using CRISPR technologies for research on military enhancement. J. *Bioethical Inq. 15*, 327–335 (2018).

84. Moritz, R. Assessing dual use research of concern (DURC)—lessons from the United States government institutional DURC policy. *Can. J. Microbiol.* (2022) doi:10.1139/cjm-2021-0344.

85. Ministry of Health and Prevention (Denmark). *Executive Order on securing specific biological substances, delivery systems and related materials.* (2009).

86. Australian Government Department of Health and Aging. Security Sensitive Biological Agent (SSBA) Standards. (2013).

87. Casadevall, A. & Imperiale, M. J. Risks and benefits of gain-of-function experiments with pathogens of pandemic potential, such as influenza virus: a call for a science-based discussion. *mBio* 5, e01730-14 (2014).

88. Selgelid, M. J. Gain-of-function research: ethical analysis. *Sci. Eng. Ethics* 22, 923–964 (2016).

89. Evans, N. G., Lipsitch, M. & Levinson, M. The ethics of biosafety considerations in gain-of-function research resulting in the creation of potential pandemic pathogens. *J. Med. Ethics* 41, 901–908 (2015).

90. Tucker, J. *Innovation, Dual Use, and Security: Managing the Risks of Emerging Biological and Chemical Technologies.* (The MIT Press, 2012).

91. National Research Council. Biodefense in the Age of Synthetic Biology. *Biodefense in the Age of Synthetic Biology.* (2018) doi:10.17226/24890.

92. Ritterson, R. & Casagrande, R. Basic scholarship in biosafety Is critically needed to reduce risk of laboratory accidents. *mSphere* 2, (2017).

93. Association of Public Health Laboratories. *A Biosafety Checklist: Developing A Culture of Biosafety Background.* (2015).

94. NTI | bio. Biotechnology Funders' Compact for Better Biosecurity: A mechanism to improve biosecurity across the life sciences. (Nuclear Threat Initiative, 2019). https://media.nti.org/documents/Paper_4_Biotechnology_Funders_Compact.pdf.

95. Mackelprang, R. et al. Making security viral: shifting engineering biology culture and publishing. *ACS Synth. Biol.* 11, 522–527 (2022).

96. Atlas, R. et al. Statement on scientific publication and security. *Science* 299, 1149 (2003).

97. Atlas, R. M. & Dando, M. The dual-use dilemma for the life sciences: perspectives, conundrums, and global solutions. *Biosecurity Bioterrorism Biodefense Strategy Pract. Sci.* 4, 276–286 (2006).

98. DiEuliis, D., Carter, S. R. & Gronvall, G. K. Options for synthetic DNA order screening, revisited. *mSphere* 2, e00319-17 (2017).

99. Rager-Zisman, Bracha. Ethical and regulatory challenges posed by synthetic biology. P*erspectives in biology and medicine* 55,4 (2012): 590-607.

100. Relman, D. A. Opinion: To stop the next pandemic, we need to unravel the origins of COVID-19. *Proc. Natl. Acad. Sci.* 117, 29246–29248 (2020).

101. NSABB, US. “National Science Advisory Board for Biosecurity, Proposed Framework for the Oversight of Dual Use Life Sciences Research: Strategies for Minimizing the Potential Misuse of Research Information, June 2007.” oba.od.nih.gov/biosecurity/biosecurity_documents. html.

102. Establishing a global culture of biosafety, biosecurity, and responsible conduct in the life sciences. *Assistance Support Initiative* https://1540assistance.stimson.org/project/biological-threat-reduction-program-btrp/international-working-group-on-strengthening-the-culture-of-biosafety-biosecurity-and-responsible-conduct-in-the-life-sciences/.

103. Simirenko, L., Harmon-Smith, M., Visel, A., Rubin, E. M. & Hillson, N. J. The Joint Genome Institute’s synthetic biology internal review process. *J. Responsible Innov.* 2, 133–136 (2015).

104. Mcnamara, J., Lightfoot, S. B., Drinkwater, K., Appleton, E. & Oye, K. Designing safety policies to meet evolving needs: iGEM as a testbed for proactive and adaptive risk management. *ACS Synth. Biol.* 2013–2015 (2014).

105. Millett, P. & Alexanian, T. Implementing adaptive risk management for synthetic biology: Lessons from iGEM’s safety and security programme. *Eng. Biol.* 5, 64–71 (2021).

106. Millett, P. et al. iGEM and gene drives: a case study for governance. *Health Secur.* 20, 26–34 (2022).

107. Carter, S. & Friedman, R. *DNA Synthesis and Biosecurity: Lessons Learned and Options for the Future.* (2015).

108. International Gene Synthesis Consortium. https://genesynthesisconsortium.org/ (2020).

109. Biosafety Level 4 Zoonotic Laboratory Network. *Canadian Food Inspection Agency.* https://inspection.canada.ca/science-and-research/science-collaborations/biosafety-level-4-zoonotic-laboratory-network/eng/1597148065020/1597148065380.

110. Centers for Disease Control and Prevention. What is the Global Health Security Agenda? *Global Health—CDC and the Global Health Security Agenda.* https://www.cdc.gov/globalhealth/security/what-is-ghsa.htm (2022).

111. International Experts Group of Biosafety and Biosecurity Regulators. *International Experts Group of Biosafety and Biosecurity Regulators.* International Experts Group of Biosafety and Biosecurity Regulators. https://iegbbr.org/.

112. Global Health Security Agenda. “Stories of Impact.” https://globalhealthsecurityagenda.org/wp-content/uploads/2022/09/7fba2-stories-of-impacts-combined.pdf

113. Sandia National Laboratories. Global Chemical and Biological Security. *Global Chemical and Biological Security.* https://gcbs.sandia.gov/ (2022).

114. Establishing a Seal of Approval to Incentivize the Adoption of Biosecurity Norms. *NTI* https://www.nti.org/analysis/articles/establishing-seal-approval-incentivize-adoption-biosecurity-norms/ (2019).

115. International Genetically Engineered Machine Foundation. iGEM. https://igem.org.

116. Engineering Biology Research Consortium. Malice Analysis: Assessing Biotechnology Research for Security Concerns. https://ebrc.org/malice-analysis/ (2022).

117. International Federation of Biosafety Associations. “Directory of Certified Professionals.” https://internationalbiosafety.org/certification/directory-of-certified-professionals/

118. Musunuri, S., Sandbrink, J. B., Monrad, J. T., Palmer, M. J. & Koblentz, G. D. Rapid Proliferation of Pandemic Research: Implications for Dual-Use Risks. *mBio* 12, e01864-21 (2021).

119. Pannu, J., Sandbrink, J. B., Watson, M., Palmer, M. J. & Relman, D. A. Protocols and risks: when less is more. *Nat. Protoc.* 17, 1–2 (2022).

About the Authors

STANFORD UNIVERSITY

Bio.Polis is a strategic initiative of Stanford University's Department of Bioengineering (part of the School of Engineering and the School of Medicine), in partnership with the Center for International Security and Cooperation (part of the Freeman Spogli Institute for International Studies). Bio.Polis also receives support from the Stanford Ethics, Society, & Technology Hub, part of the Stanford Presidential Initiative on Ethics & Technology. Bio.Polis fosters strategic thinking on how biological innovations could shape societies, equips leaders to co-design technologies and policies to serve public interests, and enables diverse citizens to meaningfully engage with biological innovation.

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Daniel Greene is a Postdoctoral Fellow with the Biosecurity Program at the Center for International Security and Cooperation (CISAC). His research focuses on characterizing and promoting cultures of risk awareness and responsibility among life scientists. Previously, Dr. Greene received his Ph.D. in Education from Stanford University and was a research scientist at the Project for Education Research That Scales.

Kathryn Brink is a Postdoctoral Fellow with the Biosecurity Program at the Center for International Security and Cooperation (CISAC). Dr. Brink received her Ph.D. in Systems, Synthetic, and Physical Biology from Rice University, where she worked in the laboratory of Dr. Jeffrey Tabor developing approaches to discover and characterize bacterial signal transduction pathways. Prior to this, Dr. Brink received her S.B. in biological engineering from M.I.T. Dr. Brink is an active member of the EBRC Student and Postdoc Association where she has held several leadership roles.

Melissa Salm is a Postdoctoral Fellow with the Biosecurity Program at the Center for International Security and Cooperation (CISAC). Dr. Salm received her Ph.D. in Sociocultural Anthropology with a Designated Emphasis in Science & Technology Studies (STS) from the University of California, Davis. Her research focuses on the integration of 'One Health' principles into global health governance tools, epidemiological field investigations of zoonoses, and experimental laboratory research with pandemic potential pathogens. She previously conducted global health research sponsored by the National Institutes of Health (NIH) Fogarty International Center (FIC) and is currently an active member of the Consortium of Universities for Global Health (CUGH).

Connor Hoffmann is the Research & Programs Assistant to Dr. Megan Palmer appointed at the Center for International Security and Cooperation (CISAC). Before joining Stanford, he was a Connected and Autonomous Vehicle Policy Intern with the American Council for an Energy Efficient Economy (ACEEE). Mr. Hoffman was awarded an honors baccalaureate, as well as bachelor's in chemical engineering (B.S.), biological engineering (B.S.), and interdisciplinary studies integrating coursework in biological engineering, economics, and political science (B.S.) from Montana State University (MSU). During his time at MSU he was a student research assistant in the laboratory of Dr. Blake Wiedenheft studying the structural biology and evolution of CRISPR systems.

Megan J. Palmer is the Executive Director of Bio Policy & Leadership Initiatives and Adjunct Professor of Bioengineering at Stanford University. She leads integrated research, teaching, and engagement programs to explore how biological science and engineering is shaping our societies, and to guide innovation to serve public interests. She currently co-chairs the World Economic Forum Global Future Council on Synthetic Biology and is a member of the Council of the EBRC. She has led safety, security, and social responsibility programs for the international Genetically Engineered Machine (iGEM) competition and founded and served as Executive Director of the Synthetic Biology Leadership Excellence Accelerator Program (LEAP). Dr. Palmer also serves on the board of directors of Revive & Restore. Previously, Dr. Palmer was a Senior Research Scholar and William J. Perry Fellow in International Security at the Center for International Security and Cooperation (CISAC), part of the Freeman Spogli Institute for International Studies (FSI), where she is now an affiliated researcher. She also spent five years as Deputy Director of Policy and Practices for the multi-university NSF Synthetic Biology Engineering Research Center (Synberc). She previously has held positions as a project scientist at the California Center for Quantitative Bioscience at the University of California Berkeley (where she was an affiliate of Lawrence Berkeley National Labs), and a postdoctoral scholar in the Bioengineering Department at Stanford University. Dr. Palmer received her Ph.D. in Biological Engineering from M.I.T. and a B.Sc.E. in Engineering Chemistry from Queen's University, Canada.

HARVARD UNIVERSITY

Sam Weiss Evans is a Senior Research Fellow in Harvard's Program on Science, Technology, and Society at the John F. Kennedy School of Government, jointly appointed as a Research Associate at the John A. Paulson School of Engineering and Applied Sciences. He is Co-Director of the Trust in Science Project at Harvard, which analyzes the breakdowns in public trust in science, and to ask what steps could be taken to promote better mutual understanding. Dr. Evans sits on the Councils of the Engineering Biology Research Consortium and the Science and Democracy Network, and was a member of the Legal, Ethical, Environmental, Dual use, and Responsible (LEEDR) innovation advisory group to DARPA's Safe Genes program. He is a special advisor to the international Genetically Engineered Machine (iGEM) competition, where he has co-chaired the Human Practices Committee and also serves on the Safety and Security Committee. Dr. Evans has taught, conducted research, and helped build Science and Technology Studies (STS) programs at Oxford, Harvard, University of California, and Tufts. He completed his doctorate at Oxford University on the processes used to define and govern dual use research and technology within the international export control system.

About the Sponsors

NUCLEAR THREAT INITIATIVE (NTI)

The Nuclear Threat Initiative works to protect our lives, livelihoods, environment, and quality of life now and for future generations from the growing risk of catastrophic attacks with weapons of mass destruction and disruption (WMDD)—nuclear, biological, radiological, chemical, and cyber. Founded in 2001 by former US Senator Sam Nunn and philanthropist Ted Turner, NTI is guided by a prestigious, international board of directors. Ernest J. Moniz serves as the Chief Executive Officer; Des Browne is the vice chair; Joan Rohlfing serves as the president; and Jaime Yassif serves as VP for the NTI | bio program.

NTI GLOBAL BIOLOGICAL POLICY & PROGRAMS (NTI | BIO)

Biological threats—whether natural, accidental, or deliberate—can kill millions, cost billions, and create political and economic instability in individual countries and around the world. The risks and consequences of a global catastrophic biological event can be magnified by weak global health security, increasing urbanization and travel, growing terrorist interest in weapons of mass destruction, and rapid advances in technology that enable newly developed or manipulated pathogens with pandemic potential.

To reduce these risks and strengthen biosecurity, NTI | bio works with governments, industry, academia, international organizations, and NGOs to foster multilateral dialogue, identify weaknesses, and promote systemic change to improve biotechnology governance and national health security capacities.

NTI offers solutions through a range of projects. Among them:

- Global Health Security Index: Launched in 2019, the GHS Index is the first comprehensive assessment of the health security capacities of 195 countries. The second edition was released in December 2021.
- Global Biological Catastrophic Risks: NTI | bio's multi-faceted work in this area includes building a stronger case for decision-makers to prioritize action to counter catastrophic biological risks; establishing new forums focused on preventing the development and use of biological weapons by powerful actors; strengthening the BWC; and developing innovative solutions for early detection and rapid response.
- Global Biosecurity Dialogue: To identify ways to advance international biosecurity—and measure those advances—NTI | bio brings together senior officials from ministries of foreign affairs, health, defense, agriculture and other relevant sectors to build cross-border collaboration; increase the number of countries providing national, regional, or global financial and technical support to strengthen biosecurity; and promote new actions and investments among senior officials to mitigate emerging biological risks.
- Biosecurity Innovation and Risk Reduction Initiative (BIRRI): NTI | bio is working with stakeholders around the world to mitigate the misuse of tools and technologies to carry out biological attacks and reduce the risk of a laboratory accident that could result in a high-consequence or catastrophic biological event. In 2019, NTI and its BIRRI partners launched five working groups to engage new stakeholders, identify urgent actions, and catalyze the adoption of new approaches to reduce biological risks associated with advances in technology.

Appendices

APPENDIX 1: ORIGINAL VIRS CONCEPT PAPER

VISIBILITY INITIATIVE FOR RESPONSIBLE SCIENCE

Megan J. Palmer, Stanford University, Stella M. Hurtley, Science, *and Sam Weiss Evans,* Tufts University

NTI BIOSECURITY INNOVATION AND RISK REDUCTION INITIATIVE MEETING, OCTOBER 15, 2019

In April 2019 NTI | bio convened a working group meeting of the Biosecurity Innovation and Risk Reduction Initiative. At this meeting a group[1] conceived and created a pilot project concept aimed to improve the performance and recording of risk-benefit assessments before, during and at publication of biological research. This paper describes and builds upon the concept created by this group with specific recommendations to demonstrate proof of principle over a 12–16-month period.

PROBLEM

There is a lack of transparency and information sharing about the presence and process of risk assessment and management throughout the research lifecycle.

At this time, biosecurity risk assessment and management is not consistently conducted for research projects at the funding stage, within research institutions, or by journals. Even in cases where risk assessment and management is conducted, it is not necessarily documented or shared with other stakeholders in the research lifecycle. Moreover, such assessments and management plans are often made without standard or specific methods for comparison, and they typically rely on narrowly defined categories of risk rather than considering new forms of risk beyond traditionally recognized areas of concern.

The lack of transparency and sharing leaves stakeholders and decision makers in research (e.g., practitioners, research institutions, funders, publishers) both reinventing the wheel in conducting independent assessments and management plans and in the dark about whether and how they have been done at other stages in the research lifecycle. A dearth of public information about risk assessment and management processes is an impediment to the normalization of practice and to others learning about and improving existing practices.

The ability to learn about and adapt risk assessment and management is especially important in an era of rapidly emerging tools and technologies. Traditional approaches may no longer prove useful to forecast potential unintended consequences and hazards for cross-disciplinary or nascent scientific areas. Furthermore, growth in global research capacity and capability enables life science research by individuals trained in new disciplines and at institutions where life science research may not have been conducted previously. To standardize assessment and management processes and publicize them would be a tremendous benefit for both groups who may not otherwise have access to a local expert.

GOALS

(1) To promote the widespread performance of risk analysis through the promotion of the sharing of the presence and process of analyses across the research lifecycle—from funding, through study design, research performance, peer review, and eventual publication. Documentation should travel with the research from the proposal stage through peer review and into publication.

(2) To enable learning and adaptation in risk assessment and management processes.

BENEFITS

It is anticipated, though not assumed, that more transparent and regular risk assessment and management processes, and standardized ways by which this can be reported, will support researchers and their institutions. Similarly, such processes will benefit the entire decisionmaking process—from research proposal to manuscript submission

1 Working group participants: *Megan J. Palmer, Stanford University; *Sam Weiss Evans, University of Cambridge & Tufts University; *Stella M. Hurtley, *Science;* Ritu Dhand, *Nature;* Katherine Bowman, The US National Academies; Mark Perkins, World Health Organization; Nahoko Shindo, World Health Organization; Nusblat Leonora, UOCCB-ANLIS; Christopher Wallace, Australian Reinsurance Pool Corporation; Deborah Rosenblum, NTI; Jaime Yassif, NTI.

for publication e.g., by enabling a more informed, robust review process. Furthermore, such an approach should promote informed management of research (e.g., by encouraging risk management plans to be developed early in the research lifecycle when it is most cost-effective). Over time, sharing should enable collective learning about how and when risks emerge, which risks should be prioritized, and how they might be managed. This visibility initiative will also support a growing field in the science and practice of risk analysis, and encourage reflection by researchers and research stakeholders on the ways that risk is related to research design, conduct, and dissemination. Taken together, this initiative should then create a basis for learning, accountability, and shared responsibility. It should require a clear and standardized biosecurity framework through which biotechnology funders can commit to reducing biological risks, coordinate their risk reduction activities, and facilitate horizon scanning activities to identify emerging risks.

EXISTING INITIATIVES

There are a number of initiatives aimed at developing processes for risk assessment and management and ways in which to share these processes, and in some cases, their outcomes (see Appendix for detailed listing). These initiatives include research organizations conducting risk assessments above and beyond what is required as a result of anticipated risks outside of traditional areas of concern (e.g., involving pathogens). We also describe efforts aimed at promoting reproducibility, transparency and accountability in research. These initiatives may provide templates and models that can be expanded or combined. One notable initiative is a publisher-led effort to develop minimum reporting standards related to methods and study design (see MDAR framework in the Appendix). Their framework for sharing core information about research materials, study design, experimental design, data and analysis builds on many complementary efforts in the life sciences, including EQUATOR Network, MIBBI, STAR, and ARRIVE.

The most recent September 22, 2019, version of recommendations for use of the MDAR framework includes a reporting requirement on disclosing whether work is subject to dual use research of concern (DURC) risk management. However, there is relatively little general understanding of what information would be most useful and important to include in this reporting, compared to other aspects of minimal reporting framework (e.g., experimental design for statistical analysis). Moreover, these frameworks are not designed to promote detailed reporting of risk assessment and management strategies nor go beyond the confines of existing DURC implementation. A pilot study, however, could explore the value of leveraging and informing these reporting systems.

PILOT/FEASIBILITY STUDY

One pilot approach would be for groups involved in research management from ~3 universities to conduct a feasibility study for creating and implementing a simple and regular risk assessment and reporting process. This pilot could involve a small but diverse portfolio of life sciences research at each institution (e.g., in areas such as genomics, synthetic biology, and microbiology). The pilot would focus initially on the design and performance stages of research, where principal investigators have the most authority to implement changes. Ideally these university groups would work with another researcher, likely in the social sciences, who would co-design the pilot to generate robust and generalizable insights. The purpose of this pilot should be to:

(1) Develop a risk assessment and management reporting process based on input and involvement from institutional biosafety and biosecurity officials, principal investigators, risk analysis experts, funders, and publishers. This process would specify the role of different groups, and what information would be recorded and shared with the goals of holding the research to account and enabling communication and learning.

(2) Evaluate the ease, utility, and benefit of implementing the process over the course of a 12–16-month period.

(3) Develop a report with recommendations and lessons learned to improve upon the process and inform funders, publishers, and other researchers of important considerations to facilitate global use.

A second pilot approach, that could be conducted independently or in conjunction with the above pilot, would involve a major funder (or consortia of funders) that would provide incentives for conducting and sharing risk analysis and management processes. For example, the funder-led pilot would require that new proposals in an emerging technology area or applying a newly developed biotechnology tool include a statement summarizing the initial risk assessment performed prior to proposal submission. The funder(s) would further require that the researcher(s) conduct reviews of the analysis throughout the project, and include a statement of the process of the risk assessment and mitigation strategies in any final publications. Ideally the funder would provide additional resources, on top of normal research funding, to support these additional risk assessment and management

tasks (and potentially also the research on risk management described above). Conducted over a 12–16-month period, this pilot project would inform the funder(s) of potential unforeseen risks in research as well as best practices to recommend for all awardees working in a certain technology area.

Like the first pilot approach described, a key output from this small-scale proof of concept would be lessons learned regarding the benefits and burdens created by instituting this requirement. Additionally, it will be important to confirm that the requirements do not disadvantage any type of research proposed based on size, geography, or other criteria.

These two pilot approaches could leverage the MDAR framework reporting requirements as a starting point. A separate study could look at the value of information conveyed through this broadly collected but lower resolution reporting as compared to the more detailed reporting that might be generated by the two pilots described above.

QUESTIONS THE PILOT(S) SHOULD SEEK TO ANSWER

- What are the current practices, if any, for risk assessment and management at different stages of research?
- What are possible organizational structures and formats for reporting? How could reports travel with the research?
- What information is used in designing and conducting risk assessment and management (i.e., what parts of the reporting are useful for others in informing their processes)?

INCENTIVES

Funders (and other stakeholders) want to protect the research enterprise from reputational risk. Journals would benefit from access to information about previous decisions regarding risk assessment as part of their commitment to assess security concerns in research. If required by funders or publishers, researchers and research institutions will be incentivized to participate. If also resourced by a funder on top of normal funding, then institutions will be much more likely to be engaged.

Research institutions want to develop more effective, scalable and streamlined approaches for safety and security management and the scale and scope of life science research increases. Institutional biosafety and biosecurity officers may benefit from learning about approaches at other institutions. Members of institutional biosafety (and biosecurity) committees (ICBBCs) may have an easier job if their researchers they are overseeing are engaged in risk management and greater visibility of their role in the research process. IBBC members and biosafety professionals could be incentivized further by thanking them in the acknowledgment section of the publication, or even adding them as co-authors if the risk assessments ended up significantly adapting the research design.

For *biological investigators*, this initiative could provide support for conducting risk management by putting them in contact with groups with expertise, especially if these tasks are funded or otherwise rewarded. By revising the reporting process based on early pilots, a more streamlined and useful structure could emerge that would be less burdensome and more informative for all communities.

Investigators in the social sciences may be compelled to be involved in a rich study of what processes are effective in risk assessment, and in promoting increased attention to and mitigation of risk in research. For both the social and biological researchers, this may also spur new lines of applied biosafety and biosecurity research.

POTENTIAL FOR GLOBAL ADOPTION AND SCALE

Commitment to this idea by a major research funder and/or group of major publishers would significantly advance global reach of the concept. Assuming the inclusion of requirements for risk analysis was well received, government funding agencies would be likely to follow suit.

This model could help to provide a framework that could be expanded for use in research settings globally. This could iteratively go on to improve the system itself by, for example, sharing templates for risk assessments and by providing models of the types of questions asked between different stakeholders. By highlighting the need for risk assessments, and providing visibility and credit for conducting those assessments, it would help make a case for more funding in applied biosafety and biosecurity research.

APPENDIX 2: CASE STUDY TEMPLATE

BIORISK MANAGEMENT CASE STUDY: ORGANIZATION NAME

Last Updated: August 22, 2022

SUMMARY

A high-level summary of the case study findings, including:

- A brief description of the organization, its mission, and the context in which it operates.
- Why this organization is unique and why its practices are relevant.
- Key features and unique aspects of the biorisk management strategy of the organization.
- Key insights and reflections about the biorisk management approach and its generalizability.

DISCLAIMER

Biosafety and biosecurity risk management practices can change over time. This case study represents one point in time and is a sample of an evolving set of risk management practices. For additional information on current practices please contact the organization directly.

CONTRIBUTORS

A list of case study contributors, including both representatives from the organization and members of the VIRS research team.

THE VISIBILITY INITIATIVE FOR RESPONSIBLE SCIENCE (VIRS)

VIRS was conceived by a multi-stakeholder group during an April 2019 working group meeting of the Biosecurity Innovation and Risk Reduction Initiative (BIRRI) program of NTI Global Biological Policy & Programs. With support from NTI, Stanford University Bio Policy & Leadership in Society VIRS produced a set of Case Studies in biorisk management, and The Biorisk Management Casebook that provides cross-cutting insights into contemporary practices.

THE BIORISK MANAGEMENT CASE STUDIES

The Biorisk Management Case Studies describes biorisk management processes for a diverse set of life science research stakeholders. The collection serves to evaluate the feasibility and value of knowledge sharing among both organizations that have similar roles and those that have different roles in managing research. Case studies were developed in consultation with organizations through a combination of research based on public sources, interviews, and providing a template with guiding questions for organizations to complete directly. Additional analysis can be found in The Biorisk Management Casebook: Insights into Contemporary Practices[1] in this collection. Project Directors: Megan Palmer, Stanford University; Sam Weiss Evans, Harvard University.

ORGANIZATION BACKGROUND

A brief introduction to the organization and its risk management practice.

- How would you introduce your organization to provide context for your risk management practice?
- Is there an "origin story" for your risk management practice? Where did the inspiration or design come from?
- The purpose of your risk management practice. Why is it necessary and what are the benefits for your organization?

PROCESS

Scope of risks considered

The risks the organization considers in its biorisk management process.

- What types of risks do you consider in your risk management process? What types of risks do you not consider?
- Do you rely on any frameworks, guidance, templates, or other tools produced by other organizations for identifying, assessing, and mitigating risks? Do you develop your own?

Overall sequence of steps

The sequence of steps and decision points in the biorisk management process for a given research project or program. These steps might include collecting information about a given project, performing a risk assessment (or assigning it to others), taking steps to mitigate risk based on assessment results, and/or following up later to confirm the success of mitigation and/or to revise the risk management process.

- In what order and on what timescale do the steps unfold?
- Are risk assessments and mitigation steps performed once or are they revisited multiple times?
- Who provides and who reviews project information? Who manages the process of obtaining and reviewing information?
- Is there any other contextual information that would help a reader understand the process?

RISK ASSESSMENT

How the organization assesses the risks of a life science research project or program. If aspects of this process are delegated to others, how that delegation happens and how these individuals assess risks.

- How are assessments structured—what is their format?
- If you are able to provide them, what specific questions are asked? How would someone else administer this assessment?
- What assessment outcomes are possible, and how are these assessment outcomes encoded? A numerical score, a binary answer, or something else?
- How much time does the assessment process require for answering questions and for reviewing the answers?
- Can you provide any examples of completed assessments?
- How is information exchanged between applicants and reviewers before, during, and after the assessment process? With what frequency do these interactions occur?

RISK MITIGATION

A description of decisions made or actions taken based on the organization's risk assessment.

- What methods of risk mitigation are considered? Examples could include changing the project, requiring certain research environments, or requiring changes to the disclosure of project-related information.
- How is it decided which mitigation methods to use?
- Can you provide any examples of mitigation actions that have been taken?
- Has any project ever been rejected or blocked based on a risk assessment?
- Do people completing a risk assessment get the opportunity to make changes and complete it again?
- When and how do you stay involved with projects after initial assessment and mitigation steps?

EXPERTISE REQUIRED

The role that specialized expert knowledge plays in the organization's risk management process, including how that knowledge is found and used.

- Who reviews information considered in the risk management process? What is their expertise?
- How do you source expertise for reviews, internally and/or externally?
- If you source expertise externally, do you compensate reviewers for their time? How?
- Do you train your reviewers? If so, how?
- Do you train your applicants? If so, how?
- How do reviewers get a sense for commonly held views about risk management, either within your organization or more broadly in society?
- Do reviewers have access to previous applications and reviews?

FEEDBACK

Feedback mechanisms that the organization uses to improve their risk management process over time.

- How often do you modify your risk management process? When does this happen? Is it on a regular schedule? Is there any other trigger for making modifications?
- What information do you use to modify your process? How do you know that it is "working" or not?
- Where do you source this feedback? For example, do you ask for feedback from the individuals who provide information or perform assessments in the risk management process? Do you source feedback from outside your organization in professional groups or other settings?
- Do you track data on the quantity, process, and outcomes of your reviews (e.g., number of reviews, number of reviewers, percent approved, etc.)?

IMPACT

Reflections about the impact of the organization's risk management process on its own work.

- What effect has your process had on the quality and quantity of projects your organization engages with?
- What are the costs and benefits of your process? How are they felt in the organization? Are the benefits seen as outweighing the costs? What salient evidence can you demonstrate of costs and benefits?
- How easy or difficult has it been to sustain the process over time?
- What do different stakeholders and collaborators think of the process?

SHARING

Reflections on elements of the organization's risk management process or results that are shared outside the organization.

- Do you ever share your risk management process with other organizations or collaborators? Why or why not? If so, how do you share it?
- Do you ever share your risk assessments and/or approaches to risk mitigation for any specific projects? Why or why not? If so, how do you share them?
- Do you share any metrics on the quantity, process, and outcomes of your reviews (e.g., number of reviews, number of reviewers, percent approved, etc.)? Why or why not? If so, how?
- Does your organization participate in any professional groups related to biorisk management?

REFLECTIONS

Insights that could be useful to a reader of the case study seeking to implement their own biorisk management process.

- Is there any remaining information, advice, or impressions that you would like to share with this reader about why or how to implement such a process?
- How would your advice differ for organizations that are different from your own (e.g., different size, different mission, different resources)? How much does your advice generalize?

REFERENCES

List of key references for the case study document, including:

- Web page(s) for the organization
- Relevant legal documents
- Frameworks, guidance, or tools used by the organization in their risk management process

APPENDIX 3: CASE STUDIES

Table A3.1 | Biorisk management case studies

All case studies developed through VIRS are publicly available via Stanford Libraries using the digital object identifiers (DOIs) listed below.

ORGANIZATION	PERSISTENT UNIFORM RESOURCE LOCATOR (PURL)	DIGITAL OBJECT IDENTIFIER (DOI)
American Society for Microbiology (ASM) Journals	https://purl.stanford.edu/wb258gg9708	https://doi.org/10.25740/wb258gg9708
Centre for Biosecurity and Biopreparedness (CBB)	https://purl.stanford.edu/bz140yy7585	https://doi.org/10.25740/bz140yy7585
Colorado State University (CSU) Biosafety Office	https://purl.stanford.edu/ck629kc3503	https://doi.org/10.25740/ck629kc3503
International Genetically Engineered Machine (iGEM) Foundation	https://purl.stanford.edu/cc191wv3999	https://doi.org/10.25740/cc191wv3999
Massachusetts Institute of Technology (MIT)-Broad Foundry	https://purl.stanford.edu/mq491gw2822	https://doi.org/10.25740/mq491gw2822
National Institute for Public Health and the Environment (RIVM)	https://purl.stanford.edu/bq389xk1015	https://doi.org/10.25740/bq389xk1015
Science	https://purl.stanford.edu/qr280xp6531	https://doi.org/10.25740/qr280xp6531
United States Department of Energy Joint Genome Institute (JGI)	https://purl.stanford.edu/rr427mq4842	https://doi.org/10.25740/rr427mq4842

APPENDIX 4: INTERVIEW QUESTIONS FOR NON-ATTRIBUTED INTERVIEWS

Note: These questions were developed with the goal of understanding how diverse organizations approach biosafety and biosecurity risks coupled to life science research. We expect some questions below may not be applicable in your specific context; through the interview, we hope to understand which aspects of risk management, if any, are relevant (or not relevant) to you or your organization.

1. Tell us about yourself and your position at your organization. What is unique about your organization relative to others with similar roles in the life science research ecosystem?
2. Do questions of biosafety and biosecurity factor into your work? If so, how?
3. What steps do you or your colleagues take to review projects, programs, or publications for safety or security concerns? How do you decide whether modifications or mitigations might be needed? These steps could be part of a formal, standardized process or could occur through more informal, customized means.
4. Do you use any specific frameworks or tools to guide these decisions? Do you consult others within or outside of your organization?
5. How did these risk management practices develop or emerge and what reactions have there been to their implementation?
6. Risk management practices may not always work perfectly. What are some challenges you or your colleagues faced when trying to manage biosafety or biosecurity risks? What are some strategies you have used to address these challenges?
7. What aspects of your risk management practices do you think would be useful (or not useful) to other organizations?
8. What do you like or are you most proud of regarding the way you or your organization manage potential risks?
9. What tools or frameworks for risk management would you like to see developed that do not currently exist?

APPENDIX 5: ADDITIONAL RESOURCES

Table A5.1 | Examples of biorisk management guidance documents

DOCUMENT	DESCRIPTION
Biorisk management Laboratory biosecurity guidance	A World Health Organization biosafety guidance document for national regulatory authorities, laboratory directors, and laboratory workers that introduces the "biorisk management" approach
Biosafety in Microbiological and Biomedical Laboratories Advisory Document, 6th Edition	An advisory document by the National Institutes of Health & United States Centers for Disease Control & Prevention recommending best practices for protocol-driven risk assessment and mitigation steps in biomedical and clinical laboratories
Biotechnology in Age of Terrorism Recommendations	An advisory report approved by the Council of the Israel Academy of Sciences and Humanities and the Israel National Security Council recommending legislation for the Israeli government in the oversight of dual use biological research
Canada Biosafety Guidelines: Dual-Use in Life Sciences Research	A Canadian government guidance document for the identification and mitigation of dual use potential in research involving pathogens, toxins, or other infectious materials.
An Efficient and Practical Approach to Biosecurity	Centre for Biosecurity and Biopreparedness handbook guiding United Nations Member States to establish efficient and practical biosecurity systems to address modern-day threats and issues
Global guidance framework for the responsible use of the life sciences: mitigating biorisks and governing dual-use research	A global, technical, and normative framework for informing the development of national frameworks and approaches for mitigating biorisks and governing dual use research
A Guide to Training and Information Resources on the Culture of Biosafety, Biosecurity, and Responsible Conduct in the Life Sciences	An International Working Group on Strengthening the Culture of Biosafety, Biosecurity, and Responsible Conduct in the Life Sciences framework for assessing the biosafety-biosecurity interface in organizational culture
Laboratory Biorisk Management: Biosafety and Biosecurity	A guidance manual from researchers at Sandia National Laboratories in the United States that provides a framework for considering biorisk assessment, mitigation, and performance monitoring.
Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research	National Science Advisory Board for Biosecurity advisory report recommending policy for the United States government in the evaluation and oversight of proposed GOF studies
Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO)	A United States government policy guidance document for the enhanced oversight of federally funded research involving enhanced pathogens with pandemic potential
Responsible Life Sciences Research for Global Health Security	A World Health Organization guidance document providing Member States with a conceptual framework for biorisk reduction, namely, the biorisk management framework for responsible life sciences research
Tools for the Identification, Assessment, Management, and Responsible Communication of Dual Use Research of Concern	A Companion Guide to the United States Government Policies for Oversight of Life Sciences Dual Use Research of Concern prepared by the National Institutes of Health on behalf of the United States Government for the oversight of life sciences DURC funded by the US Government (USG) or taking place at institutions receiving funding from the USG for life sciences research

Table A5.2 | Examples of biorisk assessment & management models

MODEL	DESCRIPTION
The AMP model (World Health Organization)	A simple method for supporting the implementation of biorisk management. It is composed of three basic components: assessment (A), mitigation (M), and performance (P)
ISO 35001 PDCA model	An iterative process used by organizations to achieve continual improvement of biorisk management processes and products. The PDCA principle is: Plan- Do- Check- Act
NRC 4-step paradigm	Designates four steps as integral to any risk assessment: (1) hazard identification, (2) dose-response assessment, (3) exposure assessment, and (4) risk characterization

Table A5.3 | Examples of biorisk identification & assessment tools

TOOL	DESCRIPTION
BIORAM 2.0 (Sandia National Laboratories)	A software tool designed to complement the Laboratory Biosecurity Risk Handbook defining biosecurity risk assessment methodologies
Bureau Biosecurity, "Toolkit" (RIVM)	The Biosecurity Self-scan Toolkit and the Vulnerability Scan is a suite of online tools to analyze organizational biosecurity vulnerabilities. The Dual-Use Quickscan is a tool to identify potential dual-use aspects in research
Centre for Biosecurity, "Analytical Approach" (PHAC)	A tool for identifying biosafety and biosecurity systemic needs, improving biorisk management capabilities, and achieving compliance with BWC and UN Security Council Resolution 1540
Companion Guide to USG Policies for Oversight of Life Sciences DURC (NIH)	A set of tools designed for institutions, principal investigators, and institutional review entities implementing the Policy for Institutional DURC Oversight, namely, the identification of DURC, risk-benefit assessments, and risk mitigation strategy development
CWA 15793 2011 Planning and Implementation Tool	A software tool to assist organizations in the implementation of a biorisk management system compliant with requirements of guidance document CWA 15793 including gap analysis and performance monitoring support
iGEM Safety & Security Forms (iGEM)	A tool for self-assessing and managing risks to iGEM teams and for promoting transparency about possible risk and management strategies
Institutional Biosafety Committee (IBC) Self-Assessment Tool (NIH)	A tool that institutions may use to evaluate their IBCs and programs of oversight for research involving recombinant or synthetic nucleic acid molecules for compliance with NIH requirements
Joint External Evaluations (JEE) Tool (WHO)	A processual tool for evaluating a country's baseline health security capabilities
Safety Laboratory Mapping Tool (Food and Agriculture Organization (FAO))	A tool for assessing laboratory functionality and improving laboratory standards by establishing a baseline for laboratory status prior to and after an intervention

Table A5.4 | Examples of national biorisk policies

**This table depicts countries that have enacted hard law for governing risks related to research and has been adapted from Appendix E of National Academies of Sciences, Engineering, and Medicine. 2018. Governance of Dual Use Research in the Life Sciences: Advancing Global Consensus on Research Oversight: Proceedings of a Workshop. Washington, DC: The National Academies Press.*

COUNTRY	NAME(S) OF POLICY
Australia	Weapons of Mass Destruction (Prevention of Proliferation) Act 1995 National Health Security Act (2007) National Health Security Regulations (2008) Security Sensitive Biological Agent Standards
Brazil	Law 11.105 Biosafety Law
Bulgaria	Bulgarian Criminal Code, Chapter 11, Section 1 Bulgarian Defence Related Products and Dual-Use Items and Technologies Expert Control Act Ministry of Labor and Social Policy and the Ministry of Health on the protection of workers from risks related to exposure to biological agents at work Instruction No. 5 from 19.11.2003 of the Ministry of Health on the work with causative agents of bacterial, fungal, and viral infections with a high medical and epidemic risk
Canada	Human Pathogens and Toxins Act (2009) Human Pathogens and Toxins Regulation (2015) Tri-Agency Framework: Responsible Conduct of Research (2011) Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans (2010)
China	Regulation on the Biosafety Management of Pathogenic Microbiology Laboratories Regulations on Transportation Management of Highly Pathogenic Microbial Strains or Samples of Microorganisms Contagious to Humans
Croatia	Law on GMOs established in 2018, Law on Homeland Security System in 2017, and National Security Strategy in 2017
Denmark	Act on securing biological substances, delivery systems, and related materials. Act no. 474 of June 2008. Executive Order on securing specific biological substances, delivery systems, and related materials. EO no. 981 of 15 October 2009 with Updated Annex 1 to EO 2017 (under Related Materials Section J)
Egypt	(1) created the Ministry of Higher Education and Scientific Research (HCST) to design research policies; (2) restructured the Academy of Scientific Research and Technology (ASRT) as an advisory board for assessment and evaluation of research and policy only, no longer a funding body; (3) created the Science and Technology Development Fund (STDF) as a new funding agency; and (4) created the Egyptian Network of Research Ethics Committees (ENREC), focusing on the protection of research subjects.
France	Code de la recherché (authorizes high council for evaluation of research and higher education) Code de la santé (imposes regulations on genetic and biomedical research for the protection of human subjects) Code de l'environnement (regulation on GMOs)

Table A5.4 | Examples of national biorisk policies (continued)

COUNTRY	NAME(S) OF POLICY
Germany	"Biosecurity from an occupational safety and health perspective" (Decision 36/2011 of the ABAS)
India	Rules for the Manufacture/Use/Import/Export and Storage of Hazardous Microorganisms, Genetically Engineered Organisms or Cells Biotechnology Regulatory Authority of India Act
Israel	Regulation of Research into Biological Disease Agents Act (2008)
Japan	Infectious Diseases Control Law (2007) Domestic Animal Infectious Disease Control Law Jordan Biorisk Management Guidelines (Ministry of Health, 2016)
Jordan	Jordan Biorisk Management Guidelines (2016)
Kenya	Regulations and Guidelines for Biosafety in Biotechnology, 1998 National Biosafety Act of 2009
Malaysia	Malaysia Laboratory Biosafety and Biosecurity Policy and Guideline (2015, Ministry of Health) National Biosafety Act (2007)
Netherlands	Ministry of Economic Affairs, Manual on Strategic Goods (2011) Ministerial Regulation on GMOs; Environmental Management Act; Establishment and Permits Decree
Pakistan	Pakistan Biosafety Rules (2005)
Singapore	Biological Agents and Toxins Act (2006) Research Involving Human Subjects: Guidelines for IRBs (2004, Bioethics Advisory Committee report)
South Africa	Non-Proliferation of Weapons of Mass Destruction Act (1993) Health Act (2003): various regulations updating the act (2012) Animal Diseases Act (1984) Hazardous Substances Act (1973)
Switzerland	Ordinance on Handling Organisms in Contained Systems (2012) Ordinance on Protection against Major Accidents (2013) Federal Act on Non-Human Gene Technology (2003) Federal Act on War Material (1996)
United Kingdom	Anti-Terrorism, Crime and Security Act (2001/2007) Biological Security Strategy (2018)
United States	United States Government Policy for Institutional Oversight of Life Sciences DURC (2014) United States Government Policy for Oversight of Life Sciences DURC (2012) National Biodefense Strategy (2018) Federal Select Agent Program HHS Screening Framework Guidance for Providers of Synthetic Double- Stranded DNA (2010) Gain-of-function policies

Table A5.5 | International biosecurity organizations

**This list provides an illustrative snapshot of fora comprising the current risk governance landscape and is not intended to provide a complete accounting.*

- Africa Centers for Disease Control (Africa CDC)
- Association for Biosafety and Biosecurity (ABSA)
- Association of Southeast Asian Nations (ASEAN)
- Australia Group
- Biological Weapons Convention (BWC)
- Biorisk Association of Singapore (BAS)
- Biosafety and Biosecurity International Consortium (BBIC)
- Caribbean Public Health Agency (CARPHA)
- Center for Biosecurity and Biopreparedness (CBB), Denmark
- Council on Strategic Risks (CSR)
- Convention on Biological Diversity
- Croatian Society for Biosafety and Biosecurity
- EU CBRN Risk Mitigation Centres of Excellence
- EU Internal Compliance Programme (ICP)
- European Academies Science Advisory Council (EASAC)
- European Biosecurity Regulators Forum (EBRF)
- European Commission
- Food and Agriculture Organization (FAO)
- Federation of American Scientists (FAS)
- Global Biosecurity Forum
- Global Health Security Agenda: APP3
- G8 Global Partnership Against the Spread of Weapons and Materials of Mass Destruction
- Global Research Council
- iGEM
- InterAcademy Partnership
- International Center for Genetic Engineering and Technology (ICGEB)
- International Council for Science (ICSU)
- International Experts Group of Biosafety and Biosecurity Regulators (IEGBBR)
- International Federation of Biosafety Associations (IFBA)
- International Science Council
- International Union of Biochemistry and Molecular Biology (IUBMB)
- Interpol Bioterrorism Prevention Unit
- Malaysia Academy of Sciences
- Moroccan Biosafety Association (MOBSA)
- National Institute of Public Health (RIVM), The Netherlands
- Next Generation Biosecurity
- National Science Advisory Board for Biosecurity (NSABB), USA
- Nuclear Threat Initiative (NTI) Global Biosecurity Dialogue
- Nuclear Threat Initiative (NTI) Biosecurity Innovation and Risk Reduction Initiative (BIRRI)
- UN Interregional Crime and Justice Research Institute (UNICRI)
- United Nations Educational, Scientific and Cultural Organization (UNESCO)
- United Nations Security Council (UNSCR) 1540 Committee
- Verification Research, Training and Information Centre (VERTIC)
- World Health Organization (WHO)
- World Organization for Animal Health (OIE)
- World Conferences on Research Integrity
- World Science Forum

Table A5.6 | Expert statements advocating for funding agencies to play key role in biorisk management

ORGANIZATION/INDIVIDUAL	DATE	STATEMENTS
Hamilton, R. et al. "Opportunities, Challenges, and Future Considerations for Top-Down Governance for Biosecurity and Synthetic Biology"	2021	"Generally speaking, biosecurity can't be taken for granted—it comes with costs that have to be built in, regardless of the provider. Funders or investors of synthesis technologies must support this and it is often not in today's world."
Sandbrink, J.B. and Koblentz, G.D. "Biosecurity Risks Associated with Vaccine Platform Technologies"	2021	"Research-funding bodies need to prioritise the evaluation and reduction of biosecurity risks across a broader swathe of the life sciences research enterprise."
Inglesby, T. and Lipsitch, M. "Proposed Changes to US Policy on Potential Pandemic Pathogen Oversight and Implementation"	2020	"Funders should establish a set of criteria for flagging research of potential concern for enhanced PPP work, ideally following the USG criteria." "Funders should establish policies and procedures for high-level review of research meeting such criteria, again mirroring to the extent possible the USG policies and procedures. This is consistent with OSTP guidance on this issue which called for consideration of extending P3CO policy guidance in ways that "would enable oversight of all relevant research activities, regardless of funding source."
National Academies of Sciences, Engineering and Medicine. "Governance of Dual Use Research in the Life Sciences: Advancing Global Consensus on Research Oversight: Proceedings of a Workshop."	2018	"Garfinkel also discussed the importance of intellectual property and funders, with the latter particularly important in the funding review process and in encouraging investigators to provide reassurance by supporting training in responsible research." "The funders of life sciences research have considerable leverage to request that scientists applying for support consider dual use issues, to require the adoption of procedures to mitigate concerns, or to require that adjustments to research plans be made as conditions of funding. Thus, the funding stage has become an important opportunity to support governance and oversight."
DiEuliis D., Carter S.R., and Gronvall G.K. "Options for Synthetic DNA Order Screening, Revisited"	2017	"...options include direct financial support to companies for screening. The US Government could award an infrastructure grant to the IGSC to support screening or to fund activities of the IGSC to make it less burdensome to join or participate."
National Academies of Sciences, Engineering and Medicine. "Dual Use Research of Concern in the Life Sciences: Current Issues and Controversies"	2017	"[Imperiale] suggested that we "change the status quo and encourage [funding agency] responsibility by identifying potential DURC projects upfront and com[ing] up with a proactive plan."
NSABB. "Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research"	2016	"Institutions and agencies that fund research establish the framework for decisions about the research considered eligible for funding and provide oversight to ensure responsible stewardship of funds. In order to avoid endangering public health, agriculture, plants, animals, the environment, or materiel, they are responsible for ensuring that projects that could be considered dual use research of concern are identified prior to funding. When a project meets the criteria for this type of research, the funders should ensure that a process is in place to manage risks through a thoughtful and informed consideration of options that could mitigate or manage them."
Academy of Science in South Africa. "The State of Biosafety and Biosecurity in South Africa"	2015	"It is also recommended that the funding agencies (such as NRF, MRC) take ownership of addressing the more general research guidelines for all life science research."

Table A5.6 | Expert statements advocating for funding agencies to play key role in biorisk management (continued)

ORGANIZATION/INDIVIDUAL	DATE	STATEMENTS
Duprex, P. et al. "Gain-of-Function Experiments: Time for a Real Debate"	2015	"Universities have developed policies and established DURC committees that can work with scientists who have conceived studies that are flagged during institutional review. Funders could request that applications with a DURC component be presented for review to a standing committee of scientific experts. In both cases, the responsibility would be on institutions and funders to ensure expeditious review, and the scientists who conceived the study should be intimately involved."
Kilianski, A. and Murch, R. "When Gain-of-Function Research Is not 'Gain-of-Function' Research"	2015	"The review process should be initiated earlier, at the proposal step at the funding agency. In addition, it may require regular monitoring after the initial review to avoid 'surprises,' as occurred with Kawaoka's and Fouchier's original papers. As the NIH and NSABB determine a course forward on how 'gain-of-function' research should be evaluated in the USA in the future, it needs to flesh out guidelines that list which pathogens and experiments require review and that standardize the review process itself. We suggest that the review and reporting should encompass the most critical phases of research from the proposal to the publications stage."
Pakistan Academy of Sciences. "Dual-Use Education Concerns in Biotechnology: Pakistani Perspective"	2015	"Funding organizations should provide funds and support to research institutes for the progress of education and training workshops on conduct of responsible science. The funding agencies should evade rules and strategies that might overemphasize quantity over quality in the incentive systems for scholars...Funding agencies should ensure the implementation of rules and regulations when supporting international research collaborations."
Trevan, T. "Biological Research: Rethink Biosafety"	2015	"Provide leadership, funds, time and commitment. The process starts with senior management laying out what safety means for their particular organization. All layers of the organization are then involved in identifying what facilities, equipment and practices need to be changed. Lastly, a master plan is drawn up to realize the vision."
Evans, S. "What's the Matter with Biosecurity?"	2014	"funding bodies have a key role to play reshaping our understanding of what it means to engage in biosecurity governance."
Gronvall, G.K. "H5N1: A Case Study for Dual-Use Research"	2013	"While the controversial studies received federal funding, the leadership of NIH was unaware of the research and its potential implications until the manuscripts were submitted for publication; the new policy was intended to address this problem."
Royal Netherlands Academy of Arts and Sciences, Biosecurity Committee. "Improving Biosecurity: Assessment of Dual Use Research"	2013	"The Code of Conduct for Biosecurity should be an ongoing topic of interest in education and researcher training and for research team heads and funding bodies. Drawing attention to the Code will raise awareness of possible dilemmas in dual-use research and may encourage stakeholders to be more active and vigilant."
Epstein, G. "Preventing Biological Weapon Development Through the Governance of Life Science Research"	2012	"One shortcoming of the proposed NSABB oversight framework is that it makes no specific reference to obligations that funders of life science research should assume for addressing the dual-use implications of the research they are asked to fund. Funders, of course, cannot necessarily anticipate surprises that arise during the conduct of research. Yet some of the most significant dual-use concerns described above, such as the reconstruction of the 1918 influenza virus or the creation of a more transmissible version of H5N1 avian influenza, resulted from the intended outcome of research, not from unanticipated surprises. These issues should have been apparent, and should have been assessed, before funding was approved."

Table A5.6 | Expert statements advocating for funding agencies to play key role in biorisk management (continued)

ORGANIZATION/INDIVIDUAL	DATE	STATEMENTS
InterAcademy Council." Responsible Conduct in the Global Research Enterprise"	2012	"The leaders of research institutions, laboratory and department heads, research funding agencies, journal editors, and others need to act as role models for the management and governance of research."
Malakoff, D. "Proposed H5N1 Research Reviews Raise Concerns"	2012	"The controversy prompted H5N1 influenza researchers to impose a voluntary moratorium on such potentially risky 'gain-of-function' studies, and it renewed calls from biosecurity experts for funding agencies to do more to identify problematic experiments before they begin."
National Research Council and American Association for the Advancement of Science. "A Survey of Attitudes and Actions on Dual Use Research in the Life Sciences"	2009	"Of the life scientists researchers surveyed (n = 1633), 11% strongly agreed and 48% agreed, "funding agencies should require grantees to attest they have considered dual use implications of their proposed research on grant applications."
National Research Council. "Responsible Research with Biological Select Agents and Toxins"	2009	"The committee urges federal agencies that fund BSAT (biological select agents and toxins) research to establish dedicated funding for ongoing security and compliance responsibilities associated with this type of research. This is an essential obligation, and no facility should operate without appropriate security measures in place."
Israel Academy of Science and Humanities and the Israel National Security Council. "Biological Research in an Age of Terrorism"	2008	"The Committee recommends that the Israel Science Foundation (ISF) and government research foundations (national and binational research funds under the auspices of various government ministries) require, as part of their approval process, biosecurity approval from the institution in which the research will be conducted." "Dual-use research issue can be addressed at two junctures: during the initial evaluation for funding (the submitting institute already checks grant proposals for adherence to safety regulations, etc.) and upon completion before its results are published (or disseminated via conferences, the internet, etc.). As a general rule, the Committee recommends focusing on the initial evaluation stage."
European Commission. "Green Paper on Bio-Preparedness"	2007	"Organisations such as not-for-profit organisations, foundations and trusts which provide funding for scientific biological research could play an important role. Research grants should not only be conditioned upon the quality of a proposal, but also upon the ability of the given applicant to comply with bio-standards as well as possible future security guidelines."
van Aken, J. "When Risk Outweighs Benefit: Dual-Use Research Needs a Scientifically Sound Risk -Benefit Analysis and Legally Binding Biosecurity Measures"	2006	"In fact, the whole debate on dual-use research pays scant attention to the possibility of regulating or stopping experiments of concern before they are started. Indeed, for experiments that touch on matters of security, and where the potential harm is likely to outweigh any potential benefits, the preferred option is not to prevent publication but to stop the research immediately."

Table A5.7 | Expert statements advocating for publishers to play a key role in biorisk management

ORGANIZATION/INDIVIDUAL	DATE	STATEMENTS
Volk, K. and Gering, T. "Predicting Biosecurity Threats: Deployment and Detection of Biological Weapons"	2021	"Biological journals also need to take responsibility for screening papers so that information that could be easily used by nefarious actors to create biological weapons doesn't become readily available."
Inglesby, T. and Lipsitch, M. "Proposed Changes to US Policy on Potential Pandemic Pathogen Oversight and Implementation"	2020	"Any journal submission of enhanced PPP work, as defined by the P3CO guidance, regardless of funding source, should be considered for publication only upon submission of the transparent reporting of the funding source, USG or otherwise, of the reviews described above and in the P3CO guidance, including the identity of reviewers, their qualifications, the risk and benefit calculations, and dissenting views if present." "Journals should make exceptions to policies on reproducibility and resource sharing that normally apply to all published articles in the event that such sharing would create a concern of biosafety or biosecurity."
Lipsitch, M. "Responsible Communication: Balancing Security and Transparency"	2020	"Publishers: Similar to human subjects protection requirements, publishers should publish only if the funder or equivalent has provided documentation of this review, including the risks and benefits and weighing thereof. Exactly how to implement this needs further discussion. Preprint publishers: Policy development needed. Extensive review is antithetical to their purpose, but biosecurity risks are real."
Council for Science Editors. "White Paper on Publication Ethics"	2019	"Identification and consideration of DURC throughout the research continuum before submission of manuscripts for publication is an important early step. However, while journal editors do not have sole responsibility for the management of DURC, inevitably, editors will be faced with submissions that could be considered DURC and the challenges that come with handling them. Considering the risks and benefits of publishing DURC is a task in which many editors have no experience. Identifying DURC is subjective, and it is difficult for even the most knowledgeable editors and scientists to manage submissions that provide legitimate scientific contributions without censoring their communication because of potential harmful use."
National Academies of Sciences, Engineering and Medicine. "Governance of Dual Use Research in the Life Sciences: Advancing Global Consensus on Research Oversight: Proceedings of a Workshop"	2018	"Charo noted that the principle of free movement of ideas was crucial to journalism and science; yet at the same time there was some awareness that there could be occasions where the publication of information can be more harmful than helpful. She provided examples of past initiatives in this area, highlighting how these extend beyond formal classification processes. The first example was the 2003 statement by leading journals endorsing review of manuscripts for dual use material (Journal Editors and Authors Group, 2003), and the second was the white paper prepared by the Council of Science Editors, which made a similar call (Council of Science Editors, 2018)."
National Academies of Sciences, Engineering and Medicine. "Dual Use Research of Concern in the Life Sciences: Current Issues and Controversies"	2017	"A key issue identified during the committee's public meetings and private discussions was how to provide researchers—and particularly journal editors—with guidance about potentially problematic research findings or manuscripts."

Table A5.7 | Expert statements advocating for funding agencies to play a key role in biorisk management (continued)

ORGANIZATION/INDIVIDUAL	DATE	STATEMENTS
National Academies of Sciences, Engineering and Medicine. "Dual Use Research of Concern in the Life Sciences: Current Issues and Controversies"	2017	"In all, the NSABB has reviewed six manuscripts of dual use concern between 2005 and 2012. While, to some, this suggests that there is not a significant problem, to others this suggests that problematic research is not being identified. It is difficult to make an assessment either way as data on the number of papers rejected for publication (or modified prior to publication) on the basis of dual use concerns are not collected across journals. Moreover, given the vital role that publishing plays in defining the success of a research career, there is a strong disincentive to impose restrictions at the time of publication. As such, leaving such decisions to the final stages of a research project is not ideal."
NSABB. "Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research"	2016	"Those who play decision-making roles in the process of communicating scientific information have an ethical responsibility to consider whether the information being considered for publication could be used to endanger public health, agriculture, plants, animals, the environment, or materiel. Depending on their analysis of the risks and benefits of communications regarding information or technology that meet criteria for dual use research of concern, they may choose to proceed in a way that mitigates or manages the risks associated with communication—for example, by adding contextual information not found in the original article, or delaying communication until a time at which the risks would be reduced."
Patrone, D. et al. "Biosecurity and the Review and Publication of Dual-Use Research of Concern"	2012	"One important finding of this study was that most respondents [researchers] agreed that life science journal editors have a responsibility to consider potential biosecurity threats during the review process."
Salsbury, D. "Editors Must be Aware of Dual-Use Research"	2011	"The need to follow up with authors to help them understand dual-use concerns is a task that should not be overlooked. If you are going to publish DURC, contextualizing the research with editorials or commentaries or issuing a press release to put the research in the proper context is recommended. As an ethical editor, you must have procedures in place for identifying, reviewing, and publishing DURC."
National Research Council and American Association for the Advancement of Science. "A Survey of Attitudes and Actions on Dual Use Research in the Life Sciences"	2009	"In response to the question of whether journals should have policies on publication of dual use research, a majority (57 percent) of the 1755 respondents who answered the question thought that they should." "The PNAS review considered both the above criteria [threat of botulinum toxin to the milk supply] and a more general sense that our publication of an article must not constitute a "roadmap for terrorists" by providing anyone who intends to do harm with key information that is otherwise difficult to obtain."
World Health Organization. "Sustaining Progress in the Life Sciences: Strategies for Managing Dual Use Research of Concern"	2008	"There is a need to ensure 'upstream' review of research as well as review at the time of submission for publication. It is also important that there be a consistent approach for the identification of DURC across various scientific publications. Editors should work to define an appropriate review process and provide instructions to authors and manuscript reviewers for the identification and management of risks. In order to facilitate the review of scientific publications it would be valuable to establish core systems by which journals can share experience and best practices, advise smaller journals in the review of manuscripts, and develop a registry of experts for this review."

Table A5.7 | Expert statements advocating for funding agencies to play a key role in biorisk management (continued)

ORGANIZATION/INDIVIDUAL	DATE	STATEMENTS
NSABB. "Proposed Framework for the Oversight of Dual Use Life Science Research: Strategies for Minimizing the Potential Misuse of Research Information"	2007	"Those who play decision making roles in the process of communicating scientific information have an ethical responsibility to consider whether the information being considered for publication could be used to endanger public health, agriculture, plants, animals, the environment, or materiel. Depending on their analysis of the risks and benefits of communications regarding information or technology that meet criteria for dual use research of concern, they may choose to proceed in a way that mitigates or manages the risks associated with communication..."
National Research Council. "Biotechnology in an Age of Terrorism"	2004	"The Committee believes that continued discussion among those involved in publishing journals—and between editors and the national security community—will be essential to creating a system that is considered responsive to the risks but also credible with the research community."

Table A5.8 | Existing funder and oversight agency pledges to biorisk management

ORGANIZATION/INDIVIDUAL	DATE	STATEMENTS
World Health Organization. "Ensuring Responsible Use of Life Sciences Research"	2020	"Using its role as a leader in public health globally, WHO works with Member States and partners to limit the risks of DURC and establish mechanisms to adopt changes in practice to support responsible life sciences research. This includes creating research oversight mechanisms, framework and policies such as international regulations such as the Biological and Toxin Weapons Convention, professional codes of conduct, educational campaigns to raise awareness for a range of audiences and the International Health Regulations (2005)."
CIDRAP. "Feds Lift Gain-of-Function Research Pause, Offer Guidance"	2017	Francis Collins: "We have a responsibility to ensure that research with infectious agents is conducted responsibly, and that we consider the potential biosafety and biosecurity risks associated with such research." He added that he is confident the review process spelled out in the new framework "will help to facilitate the safe, secure, and responsible conduct of this type of research in a manner that maximizes the benefits to public health."
US DHHS. "Department of Health and Human Services for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens"	2017	"Overview of [Funder] Responsibilities under the HHS P3CO Framework: Conduct standard scientific merit review; Refer proposed research that is reasonably anticipated to create, transfer, or use enhanced PPPs for departmental-level review; Provide relevant information necessary for departmental-level review; Participate in departmental-level review process, as requested; Consider the recommendations resulting from the departmental-level review; Make a funding decision, stipulating terms and conditions of award including additional risk mitigation measures if appropriate; Report relevant information on funding decisions to HHS and OSTP; Ensure implementation of and adherence to required risk mitigation procedures and other terms/conditions of award, if funded."
BBSRC (Biotechnology and Biological Sciences Research Council), MRC (Medical Research Council), and WT (Wellcome Trust). "BBSRC, MRC and Wellcome Trust Position Statement on Dual Use Research of Concern and Research Misuse"	2015	"First and foremost, we recognise that we as research funders must take a proactive lead. We believe that the approach set out in this policy is proportionate, in balancing the need to address dual use risks, with the need to ensure that the benefits for society of responsibly conducted life sciences research are realised. We are committed to ensuring dual use research of concern is identified and assessed where possible both during the funding process and as research proceeds, and to raising awareness of these issues."
Leopoldina and DFG. "Scientific Freedom and Scientific Responsibility: Recommendations for Handling Security-Relevant Research"	2014	"The DFG and Leopoldina advocate greater awareness of the problem of potential misuse of research findings and minimising associated risks without disproportionately restricting freedom of research and its further development for peaceful purposes and the well-being of society."
US Government. "United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern"	2014	Require all institutions they fund that meet the applicability criteria in Section 6.1 to implement this policy. Respond to questions from institutions regarding the oversight of DURC and provide guidance to institutions regarding compliance with this policy. For USG agency-funded and proposed life sciences research that meets the criteria listed in Section 6.2.1, assess the applicability of the criteria listed in Section 6.2.2, and for such research that also meets the definition of DURC, complete a risk assessment prior to the funding decision and when progress reports are submitted by PIs.
US DHHS. "A Framework for Guiding US Department of Health and Human Services Funding Decisions about Research Proposals with the Potential for Generating Highly Pathogenic Avian Influenza H5N1 Viruses that are Transmissible among Mammals by Respiratory Droplets"	2013	"To address these concerns, the US Department of Health and Human Services (HHS), a major funder of influenza research, has developed this Framework for guiding HHS funding decisions on individual proposals involving HPAI H5N1 research with specific attributes. The Framework aims to ensure a robust review of research proposals—prior to making a funding decision—that considers the scientific and public health benefits of the proposal; the biosafety and biosecurity risks associated with the proposal; and the risk mitigation measures that are required."

Table A5.9 | Existing publisher pledges to biorisk management

ORGANIZATION/INDIVIDUAL	DATE	STATEMENTS
American Society for Microbiology Journals (ASM). "Dual-Use Research of Concern (DURC) Review at American Society for Microbiology Journals"	2015	"In 2007, the American Society for Microbiology (ASM) responded to the NSABB directives by introducing a questionnaire in the manuscript referee review form used by its journals that asked reviewers to provide an assessment about whether the work involved experiments of concern."
World Health Organization. "Sustaining Progress in the Life Sciences: Strategies for Managing Dual Use Research of Concern"	2008	"A joint journal statement, signed by many journals and publishers, came out of this meeting: All papers in peer-reviewed journals must contain enough information to adequately reproduce the results, and editors would not remove methods to make a paper more 'palatable' if it prevents verification and replication. Papers that have the potential for abuse would be identified before review and/or publication. Consistent internal procedures would be created to handle such papers. If a paper were deemed inappropriate for publication as initially written, it would either be modified without compromising its reproducibility or communicated to the scientific community through other avenues."
Journal Editors and Authors Group. "Statement on Scientific Publication and Security"	2003	"We recognize that the prospect of bioterrorism has raised legitimate concerns about the potential abuse of published information, but also recognize that research in the very same fields will be critical to society in meeting the challenges of defense. We are committed to dealing responsibly and effectively with safety and security issues that may be raised by papers submitted for publication, and to increasing our capacity to identify such issues as they arise."

ABOUT THE BIORISK MANAGEMENT CASEBOOK AND THE VISIBILITY INITIATIVE FOR RESPONSIBLE SCIENCE

The aim of the Visibility Initiative for Responsible Science (VIRS) is to share information about how life science stakeholder organizations approach biorisk management and the value of assessing and managing biorisks. By sharing this information, we aim to help organizations initiate biorisk management programs, learn from their peers, establish norms, and improve their practices over time. *The Biorisk Management Casebook* describes an initial effort by researchers and policy experts at Stanford University, Harvard University, and NTI | bio to serve the goal of VIRS by compiling and summarizing case studies and interviews with organizations with biorisk management practices.

"This wonderful report is so well researched, detailed, and filled with useful information. It's probably the best report on biorisk management I have seen."

—LANE WARMBROD, BIOLOGICAL AND CHEMICAL WEAPONS POLICY ANALYST AT PACIFIC NORTHWEST NATIONAL LABORATORY

"The Biorisk Management Casebook is very impressive. The problem it addresses is important and previously unaddressed; the methodology taken is well constructed and appropriate to the task, and the findings and initiatives are well-reasoned. This systematic study will be of considerable value to improving biorisk assessment and mitigation practices."

—GERALD EPSTEIN, FORMER ASSISTANT DIRECTOR FOR BIOSECURITY AND EMERGING TECHNOLOGIES AT THE WHITE HOUSE OFFICE OF SCIENCE AND TECHNOLOGY POLICY

"In terms of its relevance for life sciences researchers as well as the biosafety profession, The Biorisk Management Casebook *will have tremendous impact on the planning, designing, creating, and innovating of new research that can benefit the worldwide community."*

— LUIS ALBERTO OCHOA CARRERA, HIGH CONTAINMENT LAB/ PANDEMIC SAFETY MANAGER AT MICHIGAN STATE UNIVERSITY, AND FORMER BSL-3 LABORATORY COORDINATOR AT NATIONAL REFERENCE LABORATORY OF MEXICO

"This is an extremely impressive body of work and clearly the result of much careful, thorough, and time-consuming research. What a valuable service to put these practices together in one place and to start the difficult task of comparing strategies that different organizations have taken to try to implement biosecurity practices."

—GIGI GRONVALL, SENIOR SCHOLAR, JOHNS HOPKINS CENTER FOR HEALTH SECURITY

"A very consolidated and well written document, which will set the pace for future discussions to build upon!"

—AAMER IKRAM, CHIEF EXECUTIVE OFFICER OF THE NATIONAL INSTITUTES OF HEALTH OF PAKISTAN

"An excellent report that illuminates the challenges faced and successes achieved through the development of biorisk management programs. The selection of case study organizations helps to identify well-founded best practices and demonstrates that a common overall approach to biorisk management can be successfully adopted and adapted to meet the unique organizational characteristics of the disparate formal national and international biorisk management programs."

— JOE KANABROCKI, ASSOCIATE VICE PRESIDENT FOR RESEARCH SAFETY AT UNIVERSITY OF CHICAGO

"The Visibility Initiative for Responsible Science (VIRS) project has done excellent work by compiling and summarizing case studies and interviews with organizations, making visible the variety of practices that organizations currently employ to manage biorisks related to life science research and thereby showcasing what is and is not working on the ground. By sharing information about how and why organizations assess and manage biorisks, this work can serve as a foundation for future visibility initiatives in identifying emergent best practices and establishing norms."

—WEIWEN ZHANG, DISTINGUISHED PROFESSOR OF SYNTHETIC BIOLOGY & BIOCHEMICAL ENGINEERING AT TIANJIN UNIVERSITY OF CHINA

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