Global guidance framework for the responsible use of life sciences

Mitigating biorisks and governing dual-use research

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Contents

Foreword

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Acknowledgements

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Acronyms

BWC	Biological Weapons Convention
CNCB	National Consultative Council for Biosecurity
DFG	German Research Foundation
DIY	do it yourself
DNA	deoxyribonucleic acid
DURC	dual-use research of concern
FAO	Food and Agriculture Organization of the United Nations
GMO	genetically modified organism
HSE	Health and Safety Executive (United Kingdom)
IAP	InterAcademy Partnership
INSEN	International Nuclear Security Education Network
ISO	International Organization for Standardization
ISU	Implementation Support Unit
JEE	joint external evaluation
LMIC	low- and middle-income countries
NASEM	National Academies of Sciences, Engineering, and Medicine
NRC	National Research Council (USA)
NSABB	National Science Advisory Board for Biosecurity
OIE	World Organisation for Animal Health
PI	principal investigator
PPE	personal protective equipment
SDG	Sustainable Development Goal
SOPs	standard operating procedures
UN	United Nations
UNESCO	United Nations Educational, Scientific and Cultural Organization
UNICRI	United Nations Interregional Crime and Justice Research Institute
United Kingdom	United Kingdom of Great Britain and Northern Ireland
USA	United States of America
VIRS	Visibility Initiative for Responsible Science
WHO	World Health Organization
WMD	weapons of mass destruction

Glossary

Accident: An unintended occurrence that could result in harm, such as infection, illness or injury in humans and nonhuman animals, or contamination of the environment.

Awareness raising: Attempts to inform the scientific community and the broader global community of the importance of biosecurity as an essential part of responsible basic and applied life sciences.

Biological diversity (biodiversity): The variability among living organisms from all sources, including terrestrial, marine and other aquatic ecosystems, and the ecological complexes of which they are part; this includes diversity within species, between species and of ecosystems).

Biorisk: The risk that an event caused by health-related research and innovation in the life sciences – such as a naturally occurring disease, accidental infection, unexpected discovery, inappropriate use or misuse of life sciences, or unauthorized access to or loss, theft, misuse, diversion or intentional release of a biological agent or biological material – adversely affects the health of humans, nonhuman animals and the environment.

Biosafety: Containment principles, technologies, measures and practices that can be used to prevent inadvertent release or unintentional exposure to biological agents or biological material.

Biosecurity: Principles, technologies, measures and practices that can be used to prevent the unauthorized access to or loss, theft, misuse, diversion or intentional release of a biological agent or biological material.

Civil society networks: Groups or organizations working in the interest of citizens but operating outside of the governmental and for-profit sectors.

Codes of ethics: Nonlegislated guidelines intended to establish standards of practice.

Collaborative ambition: A situation in which people collaborate to achieve a common ambition; which can mean that people put more into and get more out of activities such as work and advocacy, where those activities benefit both themselves and others.

Converging technologies: The integration of insights, principles, approaches and actors from originally distinct fields.

Disinformation: The sharing of information that is known to be false, inaccurate or misleading with the intent to mislead, cause confusion, introduce doubt or incite violence for the purpose of causing harm.

Dual-use: Findings, techniques and knowledge generated by peaceful and legitimate life sciences that may be appropriated for non-peaceful or harmful purposes with no, or only minor, modification.

Dual-use research: Life sciences research conducted for peaceful and beneficial purposes that 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 and the environment.

Education: The systematic provision of knowledge, competencies, skills and tools on aspects of biosecurity.

Empowerment: Strengthening of the processes of engagement to increase active participation in activities such as agenda setting and priority setting.

Engagement: Efforts to involve scientists, the scientific community and other stakeholders in biorisk management, biosecurity and governance efforts.

Gain-of-function research: Gain-of-function research results in increasing the transmissibility and/or the virulence of pathogens. Gain-of function research can be conducted with the aim of improving the understanding of the diseases caused by pathogens in order to develop preventive and therapeutic approaches.

Global health security: The activities required, both proactive and reactive, to minimize the risk of public health events that endanger the health of humans, nonhuman animals and the environment across national boundaries, geographical regions and generations.

Governance: The systematic use of frameworks, tools and mechanisms to provide direction and oversight consistent with a chosen set of values, principles and objectives.

Infodemic: An overabundance of information (including misinformation and disinformation) that occurs during a health crisis, and that is spread via digital and physical information systems.

Intergenerational justice: A commitment to the fair distribution of (sometimes scarce) resources across different age groups, often with a focus on future generations.

Life sciences: All sciences that deal with living organisms, including humans, nonhuman animals and the environment, or products of living organisms or that incorporate components derived directly or synthetically from living organisms; and including but not limited to biology, biotechnology, genomics, proteomics, bioinformatics, and pharmaceutical and biomedical research and technologies.

Misinformation: The sharing of false, inaccurate or misleading information without malicious intent, which misleads, causes confusion, introduces doubt or incites violence, with or without knowledge of the falsehood or inaccuracy of the information.

Participatory governance: Governance focused on deepening democratic engagement.

Pathogen: A biological agent capable of causing disease in humans, nonhuman animals or plants.

Policies: Includes laws, regulations, standards, guidelines, best practices, codes of ethics, research review processes, training and education.

Publics: Groups of the population. Just as there is no monolithic "science" there is no unified "public". This term is used to emphasize the plurality and diversity of perspectives, locations and engagement of groups and collectives.

Risk: A probability of harm.

Risk assessment: A systematic process, quantitative or qualitative, of gathering information and evaluating the nature, probability and magnitude of potential harms and determining the appropriate control measures.

Risk management: The quantitative or qualitative forecasting and evaluation of potentially harmful consequences (risk assessment) together with the identification and implementation of technologies, measures or practices to avoid or minimize their impact (risk mitigation).

Scientific community: A network of interacting scientists and other actors (public or private) involved in research oragnizations, life sciences funding, standard-setting, project management, publication, dissemination, development and commercialization, education, training, regulation and governance, as well as academics and scholars, including social scientists and humanists.

Scientist: A person with expertise in natural or social sciences who systematically uses research and gathers information for knowledge production.

Social justice: A concern with equity and fair access to social goods such as rights, privileges and opportunities. It differs from distributive justice, which is about the fair distribution of quantifiable goods (e.g. vaccines, food and shelter). Social justice aims to ensure that political and social structures do not entrench systematic disadvantages in society.

Stakeholders: Includes scientists, the scientific community, ethics committee members, institutional and repository managers, biosafety officers, funding bodies, publishers, editors, security officials, regulators, institutional and other authorities, civil society networks, the private sector, other relevant organizations and publics.

Executive summary

1. Life sciences research and associated technologies play a critical role in improving global health, supporting healthier populations worldwide and promoting health equity for all to achieve the health-related United Nations Sustainable Development Goals (SDGs). Research and applications in the life sciences and converging technologies contribute to a better understanding of diseases, and to the development of new drugs, vaccines, innovative treatment and medical devices. The key objectives of the World Health Organization (WHO) for global health research are anticipating scientific, technological and epidemiological shifts; setting a global research agenda to address gaps, emerging areas and country priorities; and strengthening confidence in science. However, developments and advances in the life sciences raise ethical, legal, societal, safety and security risks. This document focuses on the role that responsible research can play in preventing and mitigating risks caused by accidents, inadvertent applications and deliberate misapplications with the intention to cause harm to humans, nonhuman animals and the environment.

2. Attending to the safety and security risks of life sciences research and converging technologies is a complex endeavour because the same scientific information and technologies that can generate potential benefits for health and society can also be misused to cause harm to humans, nonhuman animals and the environment. This raises the challenge of how to develop and implement governance tools and mechanisms that mitigate the risks posed by life sciences research, without hampering their development and use for global health and society.

3. The governance of biorisks is an issue that should engage all countries, although countries will have different starting points. In today's interconnected world, scientific collaboration is increasing and information is rapidly disseminated. Moreover, diseases and the risks associated with accidents, inadvertent applications and deliberate misuse can rapidly spread globally. Measures for the governance of biorisks have been developed by several Member States, academia and scientific bodies, funding bodies, publishers, editors and other stakeholders. However, governance and oversight frameworks to manage the risks posed by science and technologies lag behind developments and innovation in the life sciences. There are several reasons for this situation, including the rapid development and diffusion of biotechnology capabilities; the lack of biorisk governance structures in many countries and the increasing convergence of the life sciences with other scientific fields (e.g. chemistry, artificial intelligence, nanotechnology and neurosciences). In addition, there is an important lack of awareness of these biorisks and a lack of incentives among practising scientists,

technologists and other managers and funders of scientific research and technology development to identify and mitigate such risks.

4. Ensuring that scientific advances in the life sciences are used for the betterment of humans and the biodiversity of our planet requires collaboration among different stakeholders and disciplines. To support this aim, and to strengthen safe, secure and responsible practices in the life sciences, the *Global guidance framework for the responsible use of life sciences* (hereinafter the framework) intends to support Member States and other relevant stakeholders with different needs and starting points to address these risks. The framework does this by providing guidance on tools and mechanisms to effectively prevent and mitigate risks posed by the life sciences, while ensuring the beneficial use of the life sciences for global health and society.

5. The framework adopts an integrated approach of "biorisk management" as an overarching structure to address the full spectrum of risks associated with the life sciences research enterprise; that is, risks caused by accidents, by inadvertent applications and by deliberate misapplications. Robust biorisk management relies on three core pillars: biosafety, biosecurity and the oversight of dual-use research.

6. The framework is divided into six sections. **Section 1** introduces key considerations and gaps in the governance of biorisks, the purpose and audiences of the framework and the process leading to its development. **Section 2** highlights the evolving challenges and major gaps in the governance of biorisks. **Section 3** outlines the values and principles, and their associated commitments, that underpin the framework and should guide the development and implementation of effective biorisk management policies by Member States, and the actions of relevant stakeholders. This section also outlines key elements of good governance of biorisks. **Section 4** identifies practical tools and mechanisms for the governance of biorisks, arranged by different groups of stakeholders who have responsibilities in the oversight of biorisks. This section covers both formal and informal governance measures at individual, institutional, national, regional and international levels. It aims to reach different communities associated with the life sciences, from scientists, research institutions, funders and publishers, to those communities working with disciplines that intersect with the life sciences (e.g. chemistry, artificial intelligence and computer science). A series of case studies illustrate how values, principles, tools and mechanisms have been used in real situations. **Section 5** describes a step-by-step approach with checklists applicable to different stakeholders to start implementing the framework within their own contexts and settings. It pulls together the various elements of the framework, and outlines the steps in terms of stakeholders, tools and mechanisms, principles and values, and key questions for the governance of biorisks. **Section 6** makes conclusions and highlights critical elements for the responsible use of life sciences. **Annex 1** of this framework includes seven scenarios that have been designed to further assist in the implementation of the framework. **Annex 2** puts

forward three case studies that illustrate challenges and gaps in the governance of biorisks. Finally, **Annex 3** lists several examples of awareness raising, education, training and capacity building in the life sciences and related fields in different countries.

Section 1. Introduction

1.1 Context

7. Advances in life sciences research and converging technologies hold great promise for new and improved ways to address global health and support healthier populations worldwide. They contribute to the development of new drugs, vaccines, innovative treatment and medical devices, and are critical for realizing the United Nations (UN) Sustainable Development Goals (SDGs). Moreover, new scientific information and techniques are crucial for responding to public health emergencies. Life sciences research and innovation have accelerated the development of diagnostics, therapeutics and vaccines to address the coronavirus disease (COVID-19) pandemic *(1)*. During this pandemic, an immense and unprecedented global collaboration among scientists and other experts has been taking place across all key relevant research areas *(2)*.

8. Scientific and technology advances in the life sciences and converging technologies raise significant ethical, legal, societal, safety and security risks. This *Global guidance framework for the responsible use of life sciences* (hereinafter the framework) focuses on the safety and security risks of health-related research caused by accidents, by inadvertent applications and by deliberate misapplications with the intention to cause harm. The same scientific information and technologies that can generate potential benefits for health and society could also be misused to cause harm to humans, nonhuman animals and the environment. Irrespective of whether risks arise from the latest developments in the life sciences or from well-established practices, all life sciences research and applications must be used responsibly.

9. Risks can arise from unintentional actions; for example, from accidents that occur in the course of research and that result in harm (e.g. infection, illness or injury in humans and nonhuman animals) or contamination of the environment. Accidents can happen in laboratories; for example, through unintentional exposure to pathogenic biological agents, needle-stick injuries, the absence or improper use of laboratory safety equipment, inadequate risk assessments, errors in labelling, explosion or fire, the improper disposal of contaminated waste, insufficiently training personnel and lack of standard operating procedures (SOPs). Accidents can also occur outside of laboratory premises; for example, through the handling of biological substances.

10. Risks can stem from unanticipated research findings that could potentially cause harm. Researchers may discover unexpected results during their research and experiments; for example, scientists accidentally increased the virulence of mousepox as part of an experiment to control mice as pests *(3)*. Risks can also arise from the deliberate misuse

of life sciences research, knowledge, materials and skills. New scientific information and techniques developed for the public good could be misused to cause harm. For example, the sending of letters containing anthrax in the United States of America (USA) in 2001 is a case of deliberate misapplication of a biological agent with the intention to cause harm.

11. The risks caused by accidents, by inadvertent applications and by deliberate misapplications of science research and technologies can cause different types of harm. Although research on infectious diseases is critical for improving our responses to diseases (e.g. through prevention, diagnosis and treatment), accidents involving pathogens or the deliberate misuse of infectious biological agents could generate infections and diseases that could harm global health and societies. Neurosciences, which is a field of the life sciences, provides a greater understanding of the functions of the brain and can help to prevent and treat neurological disorders such as Parkinson's disease and Alzheimer's disease. However, research in this field could be misused to manipulate the way we think, move or behave. Advances in synthetic biology – which combines biology, chemistry and genetic engineering to enable the design and modification of biological organisms – can have beneficial applications in medicine, energy, and environmental remediation. However, these advances can also create safety and security concerns; for example, through the creation of new pathogens from DNA synthesis *(4)* or the reconstruction of extinct pathogens *(5)*.

12. The risks caused by accidents, by inadvertent applications and by deliberate misapplications of science research and technologies, can arise throughout the research life cycle. Hence, governance measures need to be taken throughout the research process, before and during the conception of a research project; during funding applications; during the conduct of research; and during the publication, translation and application of findings *(6)*. Risks can emerge from different settings, including the public health-related research sector (e.g. universities, research institutes and other publicly funded research), the private and commercial health-related research sector (e.g. pharmaceutical and biotechnology companies), defence laboratories developing medical countermeasures, do-it-yourself (DIY) research spaces, nonprofit entities and manufacturing facilities; they can also emerge through the collection of samplings during outbreaks and fieldwork. There is also a considerable risk in public health and medical microbiology laboratories that process and analyse samples taken from humans or nonhuman animals. This framework will be focused on the risks posed by health-related research. Therefore, various stakeholders need to be involved in the governance of safety and security risks, including scientists and their institutions, funding bodies, publishers, editors, governments, civil society, security communities, DIY laboratory communities and the private sector.

13. Over the past 2 decades, various measures for the governance of biorisks have been developed by several Member States, academia and scientific bodies, funding bodies, publishers, editors and other stakeholders (Section 2 and Section 4). Several international bodies and initiatives have also been addressing the governance of biorisks.[1] The misuse of the life sciences is banned by international treaties. The 1972 Biological Weapons Convention (BWC), which is the first treaty to ban an entire category of weapons, bans the development, production, acquisition, transfer, stockpiling and use of biological and toxin weapons. States Parties to the BWC have adopted national measures to implement their obligations under this treaty. The BWC is supported by the Implementation Support Unit (ISU), and plays a key role in discussing and reaching common understandings on issues associated with the governance of dual-use research. The BWC however lacks verification mechanisms for compliance. In addition, the remit of the 1993 Chemical Weapons Convention overlaps with the BWC as both conventions cover toxins and bioregulators. Moreover, the convergence of biology and chemistry increases the overlap between the CWC and BWC.[2]

14. Despite these various efforts and activities, governance and oversight frameworks to manage the risks posed by science and technologies and their applications lag behind developments and innovation in the life sciences. There are several reasons for this situation. The rapid development and diffusion of biotechnology capabilities makes it challenging for governance mechanisms to keep pace with these trends. Many countries and scientific institutions lack structures for biorisk governance, and even existing governance mechanisms are often not adequate to address current technologies, let alone future ones. Life sciences are also increasingly converging with other fields such as chemistry, artificial intelligence, nanotechnology and neurosciences *(9)*. Risks can emerge at these interfaces and are not necessarily covered under existing biorisk frameworks. There is also a paucity of international standards or norms for preventing and mitigating these emerging health security risks.

15. A chronic and fundamental challenge is that practising scientists, technologists, and other managers and funders of scientific research and technology development lack a basic awareness that their work – which is predominantly undertaken to advance knowledge and tools to improve health, economies and societies – could be conducted or misused in ways that result in health and security risks to the public. There is also a lack of incentives for these groups to identify and mitigate such risks.

16. WHO has been active in this area of work since the late 1960s, with the resolution WHA 22.58 from 1969, the publication of the report *Health aspects of chemical and biological weapons (10)* in 1970 and its second edition in 2004 *(11)*. More recently, WHO has

[1] For example, the Global Health Security Agenda *(7)* and the Global Partnership Against the Spread of Weapons and Materials of Mass Destruction *(8)*.

[2] Microsoft Word - TWG-End_of_Mandate-FINAL-v2.rtf (opcw.org)

published guidance on responsible life sciences research *(12)* and convened consultations on dual-use research *(13, 14)*. This framework has been developed by the WHO Science Division, in collaboration with the WHO Health Emergencies Programme. WHO's key objectives for global health research are anticipating scientific, technological and epidemiological shifts; setting a global research agenda to address gaps, emerging areas and country priorities; and strengthening confidence in science. While recognizing that the governance of biorisks cannot be under the sole responsibility of one international body, WHO, through its leadership, aims to harness the developments of life sciences to improve global health while anticipating and identifying risks posed by such developments. The risk landscape evolves alongside new science and applications; thus, governance strategies, including this framework, will need to be regularly updated and improved.

1.2 Purpose and scope

17. The framework aims to uphold the power of life sciences and innovation, and their potential positive impacts on health and societies, while guarding against the potential harms that could emerge from existing and new scientific information and technologies. Ensuring that current and scientific advances in the life sciences are used for the betterment of humanity and the biodiversity of our planet requires collaboration among different stakeholders and disciplines. To support such collaboration and strengthen the use of safe, secure and responsible practices in the life sciences, this framework provides guidance to help mitigate biorisks while leveraging the potential benefits of life sciences for global health. It provides tools and mechanisms to promote the responsible use of the life sciences and to protect against the risks caused by accidents, unanticipated findings and misuse.

18. The framework adopts "biorisk management" as an integrated overarching approach to address the risks associated with the life sciences research enterprise, from accidental and inadvertent risks to deliberate misuse. Robust biorisk management relies on three core pillars – biosafety, biosecurity and the oversight of dual-use research – and requires a range of tools and mechanisms to address both existing and unknown risks.

19. Governance of biorisks is relevant to all countries, although levels of governance vary among countries. Some countries may already have some systems to manage biorisks while others may decide to develop new or leverage existing systems. The use of foresight can help governance actors to proactively identify emerging technologies and issues in order to respond in a timely manner to advances in science and technology, and develop appropriate governance frameworks.

20. The risks arising in one location can rapidly affect distant communities, and the COVID-19 pandemic is showing us the importance of taking a One Health approach. The framework does not address the management of responses to disease outbreaks

affecting humans, nonhuman animals and plants; however, it does recognize the importance of preventing and mitigating these risks in collaboration with the relevant actors and sectors, including with the World Organisation for Animal Health (OIE) and the Food and Agriculture Organization of the United Nations (FAO).

1.3 Audiences

21. The framework is intended to serve those who have responsibilities in the governance of biorisks, such as policy-makers and regulators in charge of developing national policies to harness the potential benefits of the life sciences while constraining their risks. The safe, secure and responsible governance of the life sciences will require the involvement and cooperation of different government ministries, including health agencies.

22. The framework is intended for researchers and research institutions, funding bodies, publishers, editors, the private sector and all relevant stakeholders that are part of the research life cycle. It aims to support citizen groups, civil society, and nongovernmental, regional and international organizations that will (in coordination with other relevant stakeholders) be involved in the governance of biorisks.

23. Given the rapidly evolving challenges, managing biorisks requires a coordinated and multidisciplinary approach that fosters cross-disciplinary policies and actions, covering humans, nonhuman animals and the environment. It requires Member States and multiple stakeholders to develop and strengthen existing governance mechanisms, and to invest resources to build capacity in this area. Given that the responsibility to govern these risks will fall on various stakeholders, the framework underscores the importance of individual as well as collective efforts to address these risks, from the scientific community and its institutions, to Member States, funding bodies, publishers, editors, security actors and the private sector. The framework also highlights the need for collaboration at all levels: individual, institutional, national, regional and international.

1.4 Methodology

24. The framework builds on pre-existing work and initiatives aimed at managing the risks of accidents, inadvertent applications and the deliberate misuse of life sciences research and technologies. It identifies lessons learned and explores collaborative efforts. Development of the framework was informed by the insights and expertise of a broad range of multidisciplinary stakeholders; for example, in 2020, the WHO Science Division organized three dialogues with academies, science councils, publishers, editors and research donors to better understand the perspectives of different stakeholders and to identify areas for collaboration.

25. On 11 March 2021, a first consultative meeting was convened to consult on the scope, terminology and critical elements of the framework *(15)*. As a result of this meeting,

three working groups were established to provide inputs on three themes: the values and principles that should underpin the framework and guide policies in this area; the tools and mechanisms to promote the responsible use of the life sciences and minimize risks of accidents and misuse; and awareness raising, education, capacity-building and engagement. On 7 September 2021, a second consultative meeting was convened to share the findings and recommendations of the three working groups and to discuss next steps in the development of the framework. Two additional working groups were subsequently set up to carry out particular activities: one group to develop a glossary of terms, to link the values and principles with the recommendations of the working groups and produce a document integrating the work of the three original working groups; the other to develop scenarios to test the framework and help stakeholders to identify robust biorisk management strategies. The framework draws directly on the findings and recommendations of these five working groups and has been developed in collaboration with a broad range of stakeholders and experts from around the world.

26. In February 2022, the draft framework was posted on the project website for public consultation over a 3-week period. Feedback received through the public consultation informed the further development of the framework. The draft framework was subsequently circulated for peer review to an external review group.

27. The framework draws on several WHO publications that provide guidance on the governance of emerging technologies; for example, the framework for the governance of and recommendations on human genome editing *(16, 17)* provided critical elements in terms of approach and process; similarly, guidance on artificial intelligence *(18)* provided relevant insights. The framework builds upon the 2010 WHO publication *Responsible life sciences research for global health security (12)*, and on that publication's use of biorisk management, which was based on research excellence, ethics, biosafety and laboratory biosecurity. However, whereas the 2010 guidance focused on infectious biological agents and toxins, this framework extends its scope to encompass life sciences and converging fields, including biology. The framework also draws on the fourth edition of the WHO Laboratory biosafety manual (*46*).

28. The framework is not an end-point; instead, it aims to be an iterative and proactive process that regularly re-evaluates new ways in which life sciences research and technologies may create risks. It will be updated based on experience gained from implementation and emerging challenges, needs and priorities that will continue to arise in this rapidly changing area of work.

Section 2. Evolving challenges and gaps in the governance of biorisks

29. Preventing the misuse of the life sciences and biology is not a new issue. There is no single solution for addressing accidental, inadvertent and deliberate misuse risks; rather, a web of preventive, complementary and synergistic measures at all levels is needed *(19, 20)*. Likewise, governing biorisks cannot be done by a single group of stakeholders; instead, it needs to bring together multiple stakeholders with different roles and responsibilities, working together at different levels – individual, institutional, national, regional and international and from different geographical regions. For decades, the policy-making community and relevant stakeholders have recognized and wrestled with the misuse of the life sciences and biology. There are several challenges and gaps in governance that explain this situation, as outlined below.[1]

2.1 Increasing pace of advances in the life sciences

30. Advances in the life sciences are a fast-moving and global endeavour *(21)*. The advances are accompanied by a rapid decrease in the cost of technologies and an increase in the diffusion of knowledge and capabilities. These trends can contribute to the development of new therapeutics and vaccines, and can enhance our understanding of diseases and our ability to respond to them; however, they also have implications for governance of biorisks.

31. First, the rapid development of the life sciences and technologies and the diffusion of biotechnology capabilities pose challenges to policy-makers, who need to keep pace with advances and innovations. Governance systems need to be flexible and responsive to scientific and technological changes – this is a systemic issue associated with the governance of emerging technologies. Many countries and scientific institutions lack biorisk governance structures, and even existing governance mechanisms are often not adequate to address current technologies, let alone future ones. The various fields of the life sciences progress at different rates, have different levels of maturity and may pose different risks. Progress is fast but not all potential advances in science and technology become a reality *(22)*. Also, some areas of biotechnology and procedures are more subject to deskilling (and thus to potential misuse) than others *(23, 24)*.

32. Life sciences are increasingly converging with other fields such as chemistry, artificial intelligence, nanotechnology and neurosciences *(9)*, causing changes in the landscape of

[1] Section 2 directly draws on the reports developed by the WHO working groups on values and principles, on tools and mechanisms for biorisk management and on awareness raising, education, training and capacity-building (not published) and on Towards a global guidance framework on responsible use of life sciences: summary report of consultations on the principles, gaps and challenges of biorisk management. 2022 (Forthcoming).

risks. Risks that could emerge at these interfaces may not be covered by traditional biorisk frameworks, and could contribute to a diversification of risks and stakeholders. For example, synthetic biology, which combines biology with genetic engineering and chemistry, is a fast-evolving discipline of the life sciences that aims to design and assemble new biological functions with applications in several fields (e.g. health, agriculture and food). Amateur communities and DIY biotechnology communities have emerged over recent years as a result of open-source access, the sharing of materials and the low cost of tools; also, commercial companies have entered the field of synthetic biology and DNA sequencing. However, concerns were raised about the synthesis of new or existing pathogens that could potentially be deliberately misused to cause harm.

33. New risks extend beyond pathogens and biology. For example, new developments in neurosciences could potentially be misused (e.g. to enhance or diminish human performance) *(25)*. Advances in nanotechnology and its applications in the life sciences have led to the development of nanocarriers that can improve the efficacy of drugs, but there are concerns that nanoparticles could be misused (e.g. being delivered as aerosols that could traverse the blood–brain barrier) *(22)*. The scope of governance needs to be broadened to areas where life sciences intersect and overlap with other scientific disciplines.

34. The growing diversity of scientific fields and stakeholders requires cross-disciplinary dialogues and collaboration between different sectors (e.g. public, private and the laboratory community of DIY biotechnology), scientific disciplines and stakeholders. A broad range of stakeholders will need to develop their capacities to govern both the potential benefits and risks of life sciences research and its applications. Such stakeholders include researchers and their institutions (including research conducted by scientists other than life scientists who use biological knowledge, expertise, data, materials and technologies), funding bodies, publishers, editors, policy-makers and regulators, the private sector and security actors.

35. Risks are becoming more diverse; they exist beyond pathogens, beyond the life sciences and technologies, and beyond traditional laboratory settings. The rapid pace of advances in the life sciences, the convergence of the life sciences with other scientific disciplines, the diffusion of capacity and knowledge, and the multiplicity of actors and sectors require responsible governance mechanisms and systems to be anticipatory, flexible, responsive and collaborative.

2.2 Identifying and managing potential risks

36. Research and technologies that have the potential to benefit health and societies also have the potential to be exploited for harmful purposes – a situation referred to as the "dual-use dilemma" *(26)*. This dilemma raises the critical challenge of identifying dual-

use research, technologies and knowledge, and then effectively managing the associated risks without hindering their potential benefits for health and society.

37. Two prominent attempts to characterize the security risks stemming from life sciences research were made in two reports from the US National Research Council (NRC) – one in 2004, the other in 2006 *(26, 27)*. The 2004 report *(26)* identified seven types of experiments of concern involving microbial agents that would warrant review and discussion before their commencement. The seven types of experiment would demonstrate how to render a vaccine ineffective; confer resistance to therapeutically useful antibiotics or antiviral agents; enhance the virulence of a pathogen or render a nonpathogen virulent; increase transmissibility of a pathogen; alter the host range of a pathogen; enable the evasion of diagnostic or detection modalities; and enable the weaponization of a biological agent or toxins.

38. Whereas the 2004 NRC report focused on microbial threats and the oversight of research, the 2006 *(27)* report identified classes of advances that shared characteristics (i.e. common purposes, common conceptual underpinnings and common technical enabling platforms), and outlined a logical framework for assessing the potential for beneficial and destructive applications of new life sciences and technologies. The new technologies were classified into four groups of technologies that seek to acquire novel biological or molecular diversity; generate novel but pre-determined and specific biological or molecular entities through directed design; understand and manipulate biological systems in a more comprehensive and effective manner; and enhance production, delivery and "packaging" of biologically active materials. The report recommended adopting a broader perspective of threats beyond pathogenic organisms and toxins. Box 1 lists several reports and tools aimed at identifying or managing dual-use research.

39. A subsequent challenge concerns the difficulty of assessing the benefits and risks posed by dual-use life sciences and technologies, and managing the risks once they have been identified. Over the past decade, several quantitative and qualitative frameworks have been developed for assessing the security risks stemming from the life sciences (Box 1). These frameworks vary in terms of drivers, goals and the technologies considered, and in their considerations of intents, risks and benefits and time horizons and design *(28)*. Moreover, few frameworks balance the benefits and risks of dual-use biological research. Assessment of both the benefits and risks of emerging technologies will also be influenced by value judgements and uncertainties, and by societal factors that impact the acceptance of risks and values of benefits *(28)*. Inappropriate applications of life sciences can generate different types of harms, including harms to public health, safety and security; harms to privacy and human rights; harms to the economy and to the environment and biodiversity. This illustrates the difficulty of measuring risks and benefits. Answers to questions such as "who benefits?; how are benefits and risks

distributed?; how do we measure risks and benefits, over what time frames, and by what metric or indicator" will be influenced by value judgments, uncertainties and societal factors. A pilot exercise on two qualitative frameworks run by the InterAcademy Partnership (IAP) and the US National Academies of Sciences, Engineering, and Medicine (NASEM) concluded that qualitative frameworks are useful for fostering systematic discussions that enable the assessment of security risks; the IAP and NASEM highlighted the need for benefits frameworks *(29)*.

Box 1. Examples of reports and tools for identifying or managing dual-use research

- National Research Council. Biotechnology research in an age of terrorism. Washington, DC: The National Academies Press; 2004 (https://www.nap.edu/catalog/10827/biotechnology-research-in-an-age-of-terrorism) *(26)*.
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40. As the life sciences evolve and intersect with other scientific fields and technologies, the assessment of risks and benefits is becoming more complex and uncertain. Also, in identifying life sciences research and technologies that could cause harm through inadvertent use or deliberate misuse, we need to think beyond pathogens and biology. Assessment frameworks will need to be adapted to encompass evolving risks and benefits. Clearly, there is a need for a comprehensive and integrated framework approach. Moreover, foresight approaches offer tools that can inform assessment methodologies to deal with the evolving, dynamic and diversification of risks.

Altogether, these approaches provide guidance at the international level on addressing different risks, in a forward-facing posture, outline various tools and mechanisms, and serve different stakeholders (Box 2).

Box 2. Foresight and biorisk management: role and methods

Foresight offers the ability to monitor and plan for what will happen in the future. It gives the power to shape the futures by thinking ahead and be prepared to take advantage of all the new opportunities that rapid social and technological changes are creating.

Rapid technological changes and emerging technologies transform our societies, bringing potential tremendous benefits for societies and improving health but could also result in major economic and societal disruptions. Technological and scientific advancement and innovation are characterised by complex and dynamic interactions, serendipity, and inherent unpredictability.

In order to support the responsible use of the life sciences, foresight can be seen as a systemic approach to look at future science, technology and innovation developments and emerging issues in order to make better-informed decisions and policies. It is not a predictive or forecasting tool, but it involves a broad range of actors with diverse perspectives to inform and support strategic decision-making. Rather than trying to reduce the future to a single definitive prediction, the value of foresight is in having alternative perspectives illuminating a range of options and reduce blind spots in anticipating unintended consequences and emerging changes.

Foresight can be used to design anticipatory and responsive biorisk frameworks. This framework has developed multiple scenarios (Annex 1) to explore different potential futures and to identify practical and robust strategies to address a range of plausible futures and to test the framework against these alternative futures.

Innovation and risks associated with technological developments often emerge at the interface or convergence of various technological fields, as it is the case in the life sciences. Foresight involves a wide range of methods, including among others horizon scanning, scenarios, brainstorming, expert panel, SWOT analysis. For example, horizon scans are one of the foresight tools that has been used to monitor advances in science and technology to identify emerging opportunities and risks.[1] The results of a 2021 horizon scan performed by an international group of experts in identifying priority areas to monitor in dual-use research identified 15 priority issues that merit close attention.[2]

2.3 Persistent lack of awareness

41. A chronic and fundamental challenge in biorisk management is that many practising scientists, technologists, and other managers and funders of scientific research and

[1] Monitoring emerging technologies and building futures-thinking - WHO Foresight, https://www.who.int/activities/monitoring-emerging-technologies-and-building-futures-thinking-who-foresight

[2] World Health Organization. 2021. Emerging technologies and dual-use concerns: a horizon scan for global public health, https://www.who.int/publications/i/item/9789240036161

technology development are not aware that their work could be misused in ways that result in health and security risks to the public. The lack of awareness is unsurprising, given that biorisks are often overlooked or underemphasized in both educational curricula and on-the-job training.

42. The lack of awareness can be reinforced by a lack of institutional incentives to attend to safety and security concerns, coupled with ambiguities around the roles and responsibilities of different stakeholders. In addition, there are few opportunities for shared feedback and learning forums for exchange of information on such concerns.

43. Among stakeholders overall, there is a lack of awareness of biosecurity, biosafety and dual-use research. Globally, many scientists conducting life sciences research are not trained in biosecurity, not familiar with the BWC and not incentivized to devote time and resources to biorisk management. This lack of awareness is even be more acute in LMICs. A similar lack of education in biorisk management policies and practices is found among other stakeholders. Thus, high priorities for any biorisk management system must include education, awareness building, and creation of a culture of individual and institutional investment in biosafety, biosecurity and oversight of dual-use research.

44. The scale of the problem of the need for awareness raising and education should be understood. Globally, life scientists number in the millions and this number is likely to increase in the future. Only a small percentage of life scientists are aware of, and have the ability to manage biosafety, biosecurity and dual-use issues. Improving biorisks management will require resources. Collaborative ambition among stakeholders along with changes in awareness raising, education, training, professional development and cultural shifts will be critical to help meeting the challenge.

45. The lack of awareness is compounded by a lack of incentives promoting biorisk management at an individual and institutional level. Oversight of biosafety, biosecurity and dual-use research is critical for responsible research and depends on the behaviour of individuals and the culture of institutions. Creating an adequate biorisk management framework requires buy-in from all organizational levels and adequate incentives if all levels are to be able and willing to invest in the creation and maintenance of biorisk management systems.

2.4 Attending gaps in biorisk governance

46. The deliberate misuse of biological agents and toxins for harmful purposes is formally prohibited by international law, through the 1925 Geneva Protocol *(44)*, the 1972 BWC

(45) and the 1993 CWC.[1,2] The BWC, which was the first treaty to ban an entire category of weapons, prohibits the development, production, acquisition, transfer, stockpiling and use of biological and toxin weapons *(6)*.[3] States Parties to the BWC have developed national laws and regulations to implement these obligations, and some countries have put into place policies and measures to govern dual-use life sciences research.[4] The 1993 CWC, which prohibits the development, production, acquisition, stockpiling, retention, transfer or use of chemical weapons, also includes under its remit toxins.[5] Furthermore, in accordance with the UN Security Council Resolution 1540 (2004), all States are required to develop and enforce controls to prevent the spread of WMD to non-State actors.[6]

47. Other communities (e.g. academia and scientific bodies, organizations or councils, research institutions, funders, publishers, editors, the private sector and regional and international organizations) have been working towards the development of measures to reduce the risks of accidents, inadvertent applications and deliberate misuse of the life sciences (Section 4).

48. Despite these endeavours, all countries continue to have gaps in biorisk management. There are no international norms or international guidance for Member States and other stakeholders covering ways to identify, prevent and mitigate risks related to life sciences research and technologies. In general, countries have stronger mitigation measures for biosafety risk than that for biosecurity, and often lack oversight of advanced life sciences research to mitigate potential biorisk concerns. Biorisk oversight is even less common for research in fields adjacent to the life sciences, such as technology development that leverages biology, and science and technology development hubs that are not traditional laboratories (e.g. DIY laboratories, small start-up companies and other privately funded spaces). Critically, biotechnology is rapidly advancing and converging with other technologies, changing the potential risk landscape. Existing strategies may

[1] Moreover, States Parties to the 1977 Convention on the Prohibition of Military or Any Other Hostile Use of Environmental Modification Techniques (ENMOD) undertake "not to engage in military or any other hostile use of environmental modification techniques having widespread, long-lasting or severe effects as the means of destruction, damage or injury to any other State Party" and not to assist, encourage or induce any State, group of States or international organization to engage in activities contrary to the provisions of paragraph 1 of this article." UNODA Treaties

[2] Several countries have also adopted policies coordinating their national export controls of dual-use goods to prevent the proliferation of chemical and biological weapons. These include the Wassenaar Arrangement and the Australia Group. Home - The Wassenaar Arrangement and The Australia Group (dfat.gov.au).

[3] The BWC, supported by the ISU, is playing a critical role in preventing the misuse of the life sciences. Review conferences of the BWC are held every 5 years to evaluate the impact of science and technology advances on the Convention and to ensure that the Convention remains relevant and effective. Moreover, annual meetings of experts and States Parties are being held to share information on specific topics.

[4] See also Appendix E. Examples of activities across the governance landscape *(45)*.

[5] What is a Chemical Weapon? | OPCW

[6] UN Security Council Resolution 1540 (2004) – UNODA

not be adequate to address the risk posed by these technologies; hence, new proactive, innovative, holistic frameworks are needed.

49. Another core problem and overarching gap is the paucity of national legislation, regulations and guidance for governing biorisk management and their implementation. Increasing both awareness and incentives is hindered by a lack of top-down activities or formal national legislation, regulations and policies. While both top-down and bottom-up approaches are needed for a holistic system, development of bottom-up approaches requires creation of awareness or incentives from the top.

50. The governance of biorisks varies considerably across countries. It includes both formal mechanisms (e.g. international laws, national legislation and regulations, and mandated national and institutional oversight) and informal mechanisms (e.g. self-governance, awareness raising among scientists, codes of conducts, institutional oversight and international guidance). Some countries have chosen particular frameworks to implement biorisk management systems; in some cases, tools from several systems have been adapted to address different risks. Other countries have biosafety measures in place but do not have any national governance framework for oversight of biosecurity or dual-use research. Whether the components of biorisk management are assessed individually or collectively, biorisk management practices and governance structures are clearly inadequate at most levels – individual, institutional, national, regional and international. Agreed definitions and an integrated approach to biorisk management in the life sciences research enterprise will strengthen global health security.

2.5 Updating terminologies and framing

51. Biorisk management relies on three pillars: biosafety, biosecurity and dual-use research. In the context of this framework, the meanings of these terms are as outlined below:[1]

    a. Biosafety refers to the containment principles, technologies and practices that are implemented to prevent unintentional exposure to biological agents or their inadvertent release. The fourth edition of the WHO *Laboratory biosafety manual* takes a risk-based and evidence-based approach to biosafety. It emphasizes the importance of a safety culture to ensure a safe workplace where adequate measures are applied to minimize the likelihood and severity of any potential exposure to biological agents *(46)*.

    b. Biosecurity refers to the principles, technologies and practices that are implemented to prevent the unauthorized access, loss, theft, misuse, diversion or intentional release of a biological agent or biological material. Effective

[1] These definitions are consistent with how these terms are currently used in various publications from WHO *(12, 46)* and the ISO *(39)*.

biosafety practices are the foundation of laboratory biosecurity, and biosecurity risk control measures must be performed as an integral part of an institution's biosafety programme management. Risks are addressed through biosafety activities and measures that are intended to protect laboratory staff and others from risks associated with conducting research.

c. Dual-use research refers to life sciences research that is conducted for peaceful and legitimate purposes but has the potential to produce knowledge, information, methods, products or technologies that could be intentionally misused to endanger the health of humans, nonhuman animals and the environment.

52. There are no unique definitions of biosafety, biosecurity and dual-use life sciences. These terms have gained specific meanings within different disciplines, countries, languages and international treaties *(47)*. For example, in the context of environmental protection, biosafety is associated with the potential impact of genetically modified organisms (GMOs) on biodiversity. In the context of agriculture, biosecurity is associated with preventing pests, diseases, zoonoses, invasive alien species and GMOs from harming animal and plant health. Challenges arise when terms are interpreted differently by stakeholders. A further complication is that these terms translate differently in different languages; also, in some languages, a single word denotes both biosecurity and biosafety. Therefore, it is incumbent on individuals and institutions to clearly define these terms and to be aware that alternative definitions may be used by other stakeholders.

53. There is a growing recognition that the ways in which biosafety, biosecurity and dual-use research have traditionally been defined in the context of life sciences research needs to be updated. For example, biosafety is typically discussed in the context of laboratory operations – hence the WHO *Laboratory biosafety manual (46)* and the US *Biosafety in medical and microbiological laboratories (48)* – but that is too narrow a construction. WHO's supplemental monograph on biosafety during an outbreak focuses on the collection and handling of biomedical samples taken from patients *(46)*. Practices for safely collecting samples from wild and domesticated animals that may be infected with a zoonotic pathogen should also be considered within the biosafety realm, but are often overlooked and are therefore underdeveloped *(49)*, even though large-scale efforts to collect thousands of viral samples to identify novel zoonoses and potential pandemic pathogens have been associated with accidental exposure and release risks *(50)*.

54. The traditional focus of biosecurity was on preventing unauthorized personnel from gaining access to biological materials in a laboratory; however, biosecurity increasingly includes measures to address so-called insider threats and measures needed to reduce the risks of unauthorized access, theft or diversion of materials from places not

traditionally thought of as a laboratory (e.g. DIY research spaces, private or nonprofit entities or manufacturing facilities). In addition, there is a growing recognition of cyber threats to the life sciences enterprise, including hospitals, biomedical research institutions, genomic databases, biotechnology companies and facilities that manufacture medical countermeasures, which can cause physical disruption or damage, or can compromise confidential or proprietary information.

55. The term dual-use has different meanings. It can be understood as technologies that can be used for both civilian and military applications *(51)*, or can refer to the features (both tangible and intangible) of a technology that enable it to be applied to both hostile and peaceful ends with little or no modification *(52)*. In the life sciences, dual-use research raises the challenge of mitigating the risks while harnessing the power and promoting the diffusion of technologies for global health and society. In the context of this framework, dual-use research refers to life sciences research that is conducted for peaceful and legitimate 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 and the environment.

56. The term dual-use research can be limiting when policy implementation is scoped around a narrow set of concerns. First, in practice the term has often been focused primarily on mitigating the risk of intentional misuse of high consequence pathogens used in biological research. As such, it fails to adequately acknowledge risks presented by a broader set of fields of research involving the life sciences that do not focus on pathogens (e.g. neurosciences *(53)* and synthetic biology); risks presented by techniques, platforms and practices that facilitate research and development (e.g. genome editing and vaccine development platforms); and scientific fields adjacent to and converging with the biological sciences (e.g. artificial intelligence, automation, bioinformatics, chemistry and nanotechnology) *(54)*. Second, the term dual-use fails to reflect the fact that technologies can have different functions and multiple applications. Third, traditional concepts of dual-use research do not account for the possibility that multiple forms of misuse (e.g. accidental, reckless, negligent and deliberate) may stem from the same research.

57. Studies of the terms dual-use and dual-use dilemma have emphasized problems with and limits of these concepts *(55)*. Different understandings of the term dual-use can lead to the creation of different governance mechanisms *(56)*. Also, definitions of dual-use research typically focus on the potential consequences for humans, nonhuman animals and plants, but it is increasingly clear that advances in the life sciences and associated fields can have dramatic effects on areas such as privacy and human rights.

58. In terms of reducing biorisks associated with research and technology development, Member States and other stakeholders can understandably be confused about how to

define and govern “risky” practices. Hence, this framework adopts the umbrella term of “biorisk management” as an overarching framework for discussing the full spectrum of risks associated with the life sciences research enterprise, recognizing that risk mitigation measures may address multiple types of risk.

59. Beyond the problem of definitions, the way in which dual-use is framed and approached is critical. An emphasis on the responsible conduct and use of the life sciences could enable greater involvement from relevant communities and mitigate concerns about additional measures or limitations on research. This framework seeks to approach the governance of biorisks through the promotion of safe, secure and responsible life sciences research and technologies, while harnessing the power of science and innovation to achieve health for all.

60. The three case studies in Annex 2 illustrate several challenges and gaps in the governance of biorisks and put forward some elements of biorisk management for further consideration.

Section 3. Values and principles to guide governance of biorisks

61. This section and Section 4 provide key considerations for addressing the challenges and gaps identified in Section 2. Section 3 identifies the aspects of good governance of biorisks and outlines the values and principles, and their associated commitments. These values and principles underpin the framework and should guide the development and implementation of effective biorisk management policies by Member States, and the actions of relevant stakeholders.[1] Moreover, given that countries and stakeholders have different needs and starting points, common values and principles are critical to guide decision-making.

3.1 Governance for the responsible use of the life sciences

62. This framework understands governance as "... the norms, values and rules of the processes through which public affairs are managed so as to ensure transparency, participation, inclusivity and responsiveness. Governance also represents the structures and processes that are designed to ensure accountability, transparency, responsiveness, adherence to the rule of law, stability, equity and inclusiveness, empowerment, and broad-based participation".[2]

63. Governance includes both formal mechanisms (e.g. international laws, and national legislation and regulations) and informal mechanisms (e.g. ethical, social and professional norms, industrial norms, publishers' review processes, funding bodies' measures, practices associated with self-governance, education, training and codes of conducts). Moreover, governance "includes forces to shape the direction and conditions of research and practice, such as well-crafted public and private funding priorities and conditions" *(16)*.

64. Governance systems and mechanisms for biorisks will depend on context. Member States vary in terms of level of resources, regulatory environments and types of research conducted; thus, it is not possible or appropriate to have a one-size-fits-all approach to governance in this area. Also, Member States will start from different points (e.g. with or

[1] Section 3 directly draws on the report developed by the WHO working group on values and principles (not published) and on the WHO background paper Towards a Global Framework Guidance on Responsible Use of Life Sciences: Summary Report of Consultations on the Principles, Gaps and Challenges of Biorisk Management. 2021 (forthcoming).

[2] Section 3.1 draws upon the definition of governance put forward by the report *Human genome editing: a framework for governance (16)* and builds upon its key considerations associated with the good governance of new and emerging technologies.

without governance systems in place, and with or without resources) and their priorities will differ over time.

65. Governance of biorisks requires the involvement of all actors associated with the life sciences, including those in charge of its funding, development, publication and applications. Each actor and Member State will need to decide which measures are most appropriate and relevant according to their own national circumstances and contexts.

66. Good governance for the responsible use of the life sciences also entails the anticipation of risks and encourages the responsiveness of governance systems *(92)*. As the life sciences evolve and the landscape of risks changes, governance systems need to establish flexible, proactive and enduring frameworks that include iterative processes to regularly re-evaluate the new ways in which life sciences may create risks.

67. The 2021 WHO Human Genome Editing: a framework for governance (*16*) identifies several key elements for the good governance of new and emerging technologies, which can apply to the good governance of biorisks. These include:

    a. "promotes public confidence by ensuring that choices are made in ways that are transparent and inclusive; and it includes means to hold policy-makers accountable for those choices. As needed, good governance also has mechanisms to handle non-compliance with formal governance mechanisms.

    b. "requires access to adequate resources, capacity and technical knowledge to educate, engage and empower members of the scientific, medical and health care communities as well as the public.

    c. "is value-based and principle-driven. It promotes public trust by ensuring public values and viewpoints are carefully considered as part of the policy-making process." *(16)*

3.2 Values and principles to guide the governance of biorisks

68. The governance of biorisks involves specific tools and mechanisms to mitigate risks (Section 4); however, strategies to manage biorisks inevitably entail judgements about values and different levels of societal acceptance of risks and uncertainties (Section 2). Therefore, this framework identifies a common set of values and principles that are viewed as "touchstones" for considered ethical judgements to support the development and implementation of effective biorisk management mechanisms. In addition, because there is no single approach for the effective governance of biorisks (Section 2), the values and principles highlight why governance of biorisks is necessary and how it can be achieved through a set of commitments.

69. The values and principles serve as a reminder for decision-makers about the beliefs that are important to individuals and organizations, and that should guide decision-making, taking into consideration a wide range of contextual factors. They also underline the need for the scientific community and other stakeholders associated with the life sciences to adhere to high scientific and ethical standards, to ensure that life sciences research and developments are used for the betterment of humans, the planet's biodiversity, ecosystems and environments. The values and principles are intended to motivate and strengthen ethical and responsible practice, and to guide the policies and actions of Member States and other stakeholders.

70. The purpose of the values and principles is threefold:

    a. to delineate the ethical commitments that should guide scientists and the scientific community;
    b. to encourage the use of ethical commitments as an anchor for policy and a community of practice that is aligned with recognized (international) standards, best practices and good governance; and
    c. to serve as a common and unifying language among stakeholders when values, culture and customs diverge.

71. The framework draws on the values and principles and the commitments listed in Table 1. The values and principles listed are not discrete – they overlap where appropriate.

Table 1. Values and principles for safe, secure and responsible use of life sciences

Values and principles	Associated commitments
Health, safety and security	Use basic and applied life sciences knowledge, materials and skills for peaceful purposes and for the betterment of humans, the planet's biodiversity, ecosystems and environments. Use appropriate biosafety and biosecurity measures to prevent life sciences knowledge, materials and skills from causing harm so that we may live together peacefully. Preserve biodiversity where possible, both as a means to promote health, safety and security and as an intrinsic value.
Responsible stewardship of science	Pursue rigorous, evidence-based basic and applied life sciences aimed at generating ideas, knowledge, data, products or technologies for peaceful purposes and for the betterment of humans, the planet's biodiversity, ecosystems and environments.

	Exercise caution (e.g. appropriate use of safe practices, appropriate biosafety equipment and biosecurity measures) in the planning and pursuit of basic and applied life sciences, to minimize risks to health, safety and security. Identify, manage and mitigate reasonably foreseeable potentially harmful consequences of basic and applied life sciences as a result of accidental, inadvertent and intentional actions by assessing, through a multidisciplinary review process, whether: • the identified risks are proportionate to the potential benefits of the research; • less risky forms of research could be equally beneficial; and • modifying the research design or the dissemination and publication plans as the research proceeds or once the research has been completed. Develop and support policies (including laws, regulations, standards, guidelines, best practices, codes of ethics research review processes, training and education) at all levels of governance that are specific to basic and applied life sciences which could result in harm to health, safety or security. These policies should reflect the community's values, priorities and risk-taking strategies. Develop and support ethical practices (with particular attention to issues of intent, integrity and conflicts of interest) that align the processes and outcomes of basic and applied life sciences with societal values, needs and expectations. Stay informed of current policies and associated best practices for safe, secure and responsible basic and applied life sciences; educate stakeholders about these policies and associated best practices; and contribute time and expertise to efforts to improve relevant policies and practices. Align incentive structures and rewards with these guiding values and principles.
Integrity	Uphold the integrity of the scientific process by generating and responsibly communicating high-quality information (e.g. ideas, knowledge and data), in sufficient detail to permit reproducibility and careful peer review aimed at identifying and effectively dealing with biosafety and biosecurity risks. Counter the dissemination of information that misinterprets or mischaracterises ideas, knowledge and data with particular attention to issues of authorship as well as fabrication and falsification of data. Report possible illegal, unethical or unsafe basic and applied life sciences to relevant institutional, national and international authorities.
Fairness	Ensure fair dealings in pursuit of basic and applied life sciences, including benefit sharing (which includes sharing research benefits, research skills and research capacity). Develop and implement fair processes for the confidential reporting and investigation of possible illegal, unethical or unsafe basic and applied life sciences in pursuit of fair outcomes. These tools and mechanisms should provide appropriate support and protection for both those reporting concerns and those alleged to have engaged in illegal, unethical or unsafe activities.

Openness, transparency, honesty and accountability	Use open, transparent, honest and accountable processes to share relevant information about biosafety and biosecurity risks with: • the scientific community including project management, funders, editors and publishers; • biosafety officers, security officials, regulators, institutional and other authorities; and • civil society networks. Make scientific information (e.g. ideas, knowledge and data) accessible, except where assessments conclude that wide dissemination (including publication) poses a safety or security threat, in which case dissemination should be curtailed. This could mean that manuscripts are: • modified prior to publication (with this information duly noted in the publication consistent with a commitment not to intentionally mischaracterize or falsify ideas, knowledge and data) or • not published. Hold scientists and the scientific community accountable for the design, pursuit and consequences of basic and applied life sciences. Conduct regular audits to ensure compliance with relevant policies aimed at eliminating or minimising biosafety and biosecurity risks.
Inclusiveness and collaboration	Actively involve social science and humanities disciplines in the design and pursuit of basic and applied life sciences, consistent with the recognized value of interdisciplinary research. Carefully consider perspectives on basic and applied life sciences that are informed by different social, cultural and religious beliefs, ethical values, organizational sectors (e.g. academia, government and industry), experiential knowledge and skill sets. Adopt an international outlook, including consultation, sharing, negotiation, coordination and related forms of active engagement (e.g. programmes for awareness raising and education), with other countries and the wider international community. Practise basic and applied life sciences in a manner that invites collaborative ambition and work.
Social justice	Consider the needs (and aspirations) of all and ensure adequate access to the potentially beneficial outcomes of basic and applied life sciences. Provide scientists in LMIC with equitable access to relevant research training and capacity-building. Include and empower scientists in LMIC in both the pursuit and governance of basic and applied life sciences.
Intergenerational justice	Protect and promote the health, safety and security of humans, nonhuman animals and the environment out of respect for past generations and for the benefit of future generations. These responsibilities include: • accepting responsibility for the consequences of one's actions; • pursuing life sciences of potential benefit to future generations; • managing and mitigating harms that might accrue to future generations; and • ensuring that biodiversity, ecosystems and environments are preserved where possible.

Public education, engagement and empowerment	Educate civil society networks and publics about the potential benefits, potential harms, limitations and capabilities of basic and applied life sciences in ways that balance competing influences and demands. Engage civil society networks and publics in deliberations about possible future uses (and potential misuses – accidental, inadvertent and intentional) of basic and applied life sciences. Empower civil society networks and publics by enhancing participatory governance and promoting collaborative ambition to promote trust and strengthen global solidarity in support of health, safety and security.

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

Section 4. Tools and mechanisms for the governance of biorisks

72. Biorisk governance mechanisms for the responsible use of the life sciences should be guided by values and principles (Section 3) that are subsequently put into practice through tools and mechanisms for managing biorisks. This section outlines the elements of biorisk governance and considerations for creating a comprehensive and integrated governance framework. Examples of tools and mechanisms to manage biorisks are identified and arranged according to the stakeholders who have responsibilities for such governance.[1]

4.1 Elements of biorisk governance

73. Effective and robust biorisk governance systems involve a range of tools and mechanisms and should address all goals. Biorisk governance is multifaceted and includes multiple goals, multiple stakeholders and different governance tools and mechanisms, as outlined below:

    a. The *multiple goals* include reducing accidents, reducing security incidents, enabling early detection of safety and security incidents, reducing future opportunities for misuse of research, tools and knowledge, enabling rapid response to safety and security incidents and increasing information exchange and learning. Robust biorisk governance systems can also include features such as minimizing undue burdens and costs, have high feasibility and applying a validated or tested approach, managing liability and reputational risks.

    b. The *multiple stakeholders* are those that are best positioned to achieve various goals. These include researchers, academic institutions, public health and medical microbiology research institutions, commercial research companies, standard-setters, funders of research, editors, publishers, and scientific societies. Member States and governments are critical in reinforcing, resourcing and requiring biorisk management options among diverse stakeholders.

    c. *Different governance tools and mechanisms* are needed to achieve diverse goals and engage different stakeholders. They include laws and regulations, standards, guidelines, best practices, codes of ethics, research review processes, raising awareness activities, training and education. Tools and mechanisms will vary in their levels of formality, incentives and enforcement (self-governance versus mandatory requirements). Some tools and mechanisms can apply to a range of

[1] Section 4 directly draws on the report developed by the WHO working group on tools and mechanisms for biorisk management (unpublished) and Towards a global guidance framework on responsible use of life sciences: summary report of consultations on the principles, gaps and challenges of biorisk management. World Health Organization 2022 (Forthcoming).

goals and stakeholders (e.g. training and education can be developed by different stakeholders); others are can apply to one or two goals and stakeholders (e.g. laws are developed by governments but they can apply to different goals).

74. Table 2[1] illustrates examples of biorisk governance tools and mechanisms that can be development and implemented by various stakeholders and for reinforcing different goals.

[1] Chart adapted from the synthetic genomics options for governance report *(57)* and from the WHO working group on tools and mechanisms for biorisk management (unpublished).

Table 2. Examples of tools and mechanisms of biorisk governance

Stakeholders Goals	Scientists	Research institutions	Funding bodies	Publishers	National govern-ments	Standard-setting organizations	International organizations	Civil society networks and the publics	Educators	Private sector
Reducing accidents **Reducing security incidents** **Enabling early detection of incidents** **Enabling rapid response to incidents** **Reducing opportunities for malicious misuse of research tools and knowledge** **Increasing information exchange and learning** **Other goals, e.g. cost effectiveness, feasibility**	Raising awareness activities Training and education Codes of ethics Research on biorisk manage-ment Laboratory biosafety Laboratory biosecurity Reporting risks Research design	Raising awareness activities Training, education, and capacity building Laboratory biosafety Laboratory biosecurity Institutional oversight	Raising awareness activities Research design review Funding requirements Agenda setting Active accountability	Raising awareness activities Training, education, of reviewers and editors Review of manuscripts Guidelines on biorisk for editors and reviews Access to expertise on biorisk management Publication strategy	Raising awareness activities Legislation, regulation and guidelines on biorisk governance Resources for education and training Biorisk oversight frameworks Advisory bodies	Raising awareness activities Codes of ethics Laboratory biosafety and biosecurity training by biosafety associations Standard for biorisk management	Raising awareness activities Training and education Guidance and norms Sharing information and resources	Raising awareness activities Information and education Empowering activities	Raising awareness activities Training and education	Raising awareness activities Training and education Laboratory biosafety Laboratory biosecurity Biorisk oversight framework

4.2 A comprehensive governance approach to biorisk management

75. A comprehensive governance approach to biorisk management will be based on values, principles and will include a range of governance tools and mechanisms, as well as stakeholders at the individual, institutional, national, regional and international levels. Tools and mechanisms can be adopted to mitigate the risks of accidents, inadvertent applications and deliberate misuse; the tools and mechanisms chosen will depend on the particular stakeholders and goals but should be complementary and mutually reinforcing (Table 2). Simple frameworks can be helpful in assessing which combinations of approaches taken by different stakeholders might best achieve multiple goals and can be adapted across different organizational contexts (see Table 3 for an illustrative example).

Table 3. An illustrative framework for systematically evaluating tools and mechanisms towards a comprehensive governance approach for biorisk management.

GOALS	**Stakeholder A** (e.g. scientific societies)	**Stakeholder B** (e.g. national governments)	**Stakeholder C** (e.g. funding bodies)
	Tool (e.g. codes of conduct)	**Mechanism** (e.g. oversight and reporting requirements)	**Mechanism** (e.g. funding of applied safety and security research)
Reducing accidents	++	+++	+
Reducing security incidents	++	+++	+
Enabling early detection of safety and security incidents	+	++	++
Enabling rapid response to safety and security incidents	+	++	+++
Reducing opportunities for malicious misuse of research tools and knowledge	++	+++	+
Increasing information exchange and learning	+	++	+++
Other goals, e.g. cost effectiveness, feasibility, enabling of constructive applications			

Scoring key (qualitative and relative)
++++ most effective
+++ relatively effective

++ moderately effective
+ somewhat effective
— not effective

Notes on example framework and scoring
Systemically approaching biorisk management requires assessing how different goals might be most effectively realised via different stakeholders, tools and mechanisms. Mapping this out, as the limited table above illustrates, can help facilitate planning and assessments both within and across tools and mechanisms. By comparing across rows, each tool can be considered for its effectiveness across different goals. By comparing across columns, tools and mechanisms that are more or less effective for achieving a certain goal can be considered. A comprehensive approach should seek to fulfill all goals among a suite of approaches. It is only through a mutually reinforcing set of tools that can countries reach the most effective level.

Please note: Examples, including scoring, are illustrative only as the most effective tools and mechanisms and their combination will be context-dependent.

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

76. Risk management will depend on the active management of biorisks by institutions (including through sharing best practices and incentives) and the government initiatives that set out the responsibilities and obligations of individuals, institutions and other relevant stakeholders (e.g. guidance or legislation). One ultimate vision for success in the governance of biorisks is that life sciences knowledge, materials and skills are used for peaceful purposes and for the betterment of humans, and the planet's biodiversity, ecosystems and environments. These tools must cohere *(97)* and the governance approaches must be adaptable to enable innovations in both policies and practices *(93, 94)*.

77. Robust biorisk governance for the responsible use of the life sciences requires awareness of potential risks and threats that may arise to adapt to a dynamic and evolving science and technology landscape. Surveying the landscape and scanning the horizon for misuse potential and emerging challenges and risk, as well as generating different scenarios for policy options can critically enhance not only early detection but also offer more flexible and adaptable responses.

78. The three core pillars of biorisk governance are biosafety, biosecurity and oversight of dual-use research. Across the world, biosafety has gained more attention than biosecurity and dual-use research, but all three pillars need better governance. The domains of biosafety, biosecurity and oversight of dual-use research are closely related – in theory if not in practice. Approaching these domains collectively under an integrated and comprehensive biorisk management framework has the advantage of recognizing and capitalizing on how the domains are interconnected without sacrificing the specific demands, challenges and risks that each presents (Box 3).

Box 3. A comprehensive biorisk management framework

A global guidance framework for the safe, secure and responsible governance of biorisks should be comprehensive, anticipatory, flexible, enduring and responsive, as outlined below.

- **Comprehensive**: given the rapid advances in the life sciences and the convergence of the life sciences with other scientific fields and technologies, governance systems need to address the new risks that are emerging at these interfaces. A comprehensive framework therefore covers risks stemming from biological agents and toxins, but also extends beyond biology to cover risks arising in fields such as synthetic biology, neurosciences, gene drives, bioregulators, genome editing and bioinformatics. It also incorporates the full spectrum of risks arising from accidents and inadvertent and deliberate misuse that could cause harm to humans, nonhuman animals and the environment. A comprehensive framework includes values and principles that guide governance; tools and mechanisms that contribute to the application of values and principles and various stakeholders that develop and implement governance frameworks. A comprehensive framework relies on three core pillars of biorisk governance: laboratory biosafety, biosecurity and the oversight of dual-use life sciences research.

- **Anticipatory**: as life sciences rapidly evolves, the governance of biorisks needs to rely on information and develop tools to identify and anticipate risks, to best prepare current systems to react to unanticipated risks Foresight approaches offer multiple tools to consider different futures and make explicit assumptions about preferred, probable, and possible futures. By integrating diverse and varied perspectives, cognitive biases can be counteracted and blind spots reduced to formulate more robust governance options as well as a more nuanced assessment of risks.

- **Flexible, enduring and responsive**: the framework needs to be agile to address existing risks and to react to emerging risks posed by advances in science and technologies. A key element in the good governance of biorisks will be the development of management systems that combine formal mechanisms and top-down measures with informal mechanisms and bottom-up measures. As risks and social context evolve, it will also be important to develop the capacity to regularly assess how distinct goals can be best achieved through different combinations of governance tools and mechanisms and various stakeholders, adapt approaches and enable innovation in both policies and practices. Building effective biorisk management systems will require experimentation and regular revisiting tools and mechanisms and their implementation *(63, 93, 94, 98)*. It will also require building tools and mechanisms to exchange information among different stakeholders.

4.3 Biorisk governance tools and mechanisms for different stakeholders

79. This section outlines examples of biorisk governance tools and mechanisms organized by different stakeholders. Although various stakeholders can take distinct tools and mechanisms, these will often overlap. For example, research institutions can reduce biorisks with the support of national legislations, regulations and guidance. The work of scientists can be supported through raising awareness activities and training developed by academies, institutions, professional organizations and other standard-setting organizations.

a. *Scientists* conceive and implement their ideas (although those ideas are clearly shaped by the scientists' environments and communities), and they are the first line of control for assessing, preventing and mitigating risks. Scientists are incentivized to consider, articulate and defend the potential benefits of their work. They also have a duty to consider and mitigate the risks that the information, technologies or methods they develop and disseminate could pose if used for harmful purposes.

b. *Research institutions* are the employers of scientists and are responsible for their professional activities. Research institutions include all organisations pursuing basic and applied life sciences (e.g. universities, institutes, companies, government laboratories and community labs). They are the second line of control for biorisk assessment and mitigation.

c. *National governments* are responsible for enacting and enforcing policies (e.g. laws, regulations, standards, guidelines, best practices, codes of ethics and research review processes). They are ultimately responsible for defining the standards for biorisk management that all stakeholders are required to meet.

d. *Other important stakeholders* include *funding bodies, academies, professional societies and other standard-setting institutions, publishers and editors, educators, security actors, international organizations, the private sector, civil society networks, publics, and other venues and networks* where biorisks are being addressed. As research is increasingly conducted across different organizations and countries, the role of such stakeholders in promulgating and translating standards has increased.

4.3.1 Stakeholder: scientists

80. Scientists as designers and makers of research projects are critical in the governance of biorisks. However, many scientists are unaware of their individual responsibility for management of biorisks associated with their own work and its relationship to the responsibilities of other groups and institutions.

81. Examples of tools and mechanisms are given below:

    a. **Training.** Biorisk assessment and mitigation should be processes familiar to all life scientists. At a minimum, students, trainees and scientists at all levels must know how to assess and document biorisks in a way that is accessible to co-workers as well as internal and external auditors, and how to identify and implement technologies, measures or practices to avoid or minimise the impact of biorisks. Training in risk assessment and risk mitigation is essential to assist students, trainees and scientists in understanding what is expected for effective biorisk management, and how to achieve it. For example, the International Federation of Biosafety Associations facilitates

training in partnership with national biosafety organisations and provides certification for biosafety and biosecurity professionals *(58)*. Critically, training must go beyond competencies and also address commitments, especially where risks may require going "beyond compliance" to proactively monitoring for non-routine biorisks. If a biorisk is identified, scientists' reporting responsibilities come into play. Training should ensure that these responsibilities are well understood and that there is clarity regarding what to report, and to whom. Training should be interdisciplinary to highlight that researchers from different disciplines may be good resources to draw on in identifying a larger range of risks and especially in convergent areas, or they may be able to provide best practices for risk mitigation solutions.

b. **Codes of ethics**. Codes of ethics can be a useful tool to raise awareness of the need for biorisk management and to provide norm-setting standards. An early example of a national code of conduct for biorisk management is the Biosecurity Code of Conduct for the Netherlands developed by the Royal Netherlands Academy of Arts & Science (KNAW) *(95)*. There have also been efforts to outline high-level principles that can serve as references in developing or amending national- or institutional-level codes of conduct. The most recent effort is the Tianjin Biosecurity Guidelines for Codes of Conduct for Scientists *(96)*. Inspired by the Hague Ethical Guidelines that were developed by the Organisation for the Prohibition of Chemical Weapons, the Tianjin Biosecurity Guidelines emerged from foundational work by China and Pakistan, and were developed collaboratively by InterAcademy Partnership leaders, Tianjin University's Centre for Biosafety Research and Strategy, and Johns Hopkins University's Center for Health Security, with input from scientists from 20 countries.

c. **Aligned research agendas**. A strategic opportunity to create incentives for scientists to engage in proactive biorisk management is to support research programmes to develop new knowledge, tools and mechanisms that can help improve biorisk management. Applied biosafety and biosecurity research programmes can span technological solutions (e.g. new types of biological or physical containment or monitoring strategies) and/or social and behavioural solutions (e.g. innovations in training), and/or innovative policy approaches (e.g. revisions in regulatory frameworks and the supporting science). This work is often most effective when coupled directly with science and technology research programmes in their earliest stages of development. One example is the integrated policy and practices research thrust supported over a ten-year period by the multi-university US National Science Foundation Synthetic Biology Engineering Research Consortium (Synberc) and which involved both natural and social scientists as well as stakeholders in industry and policy *(61)*. Some of the scientists trained in these settings now have research labs dedicated to developing technologies to support biosafety and have become champions for proactive engagement with biorisk management. The international Genetically Engineered Machine Competition (iGEM)—a synthetic biology research competition that has engaged over 50,000 students in over 60 countries—rewards and recognises not only technological advances but also innovation in safety, security and social responsibility, and has become a testbed for policy implementation engaging groups responsible for biorisk management from many countries *(62, 63)*.

d. **National legislation, regulation and guidance**. These tools can be applied to scientists and/or institutions to ensure adequate steps are taken to manage biorisks. For example, Canada's comprehensive, nationwide biorisk management system was promulgated in the Human Pathogen and Toxin Act, and is overseen by the Centre for Biosecurity in Public Health Agency of Canada *(60)*.

4.3.2 Stakeholder: research institutions

82. Through hosting research and employing scientists, research institutions constitute the second line of control for biorisk assessment and mitigation. Research institutions include all organisations pursuing basic and applied life sciences, including, but not limited to, universities, institutes, companies, government laboratories and community labs. In the absence of clear guidance from national governments and strong communication systems between institutions to share best practices or facilitate innovation and consensus building, research institutions may struggle with ambiguities in their responsibilities concerning biorisk management.

83. Examples of tools and mechanisms are given below:

    a. **National legislation and regulation**. Research institutions play a vital role in supporting their employees, as described above. National legislation is a tool that can set out the legal roles and responsibilities of institutions for biorisk assessment, training and internal oversight. It provides a clear legal framework for measures and activities to ensure thatresearch institutions understand their legal responsibilities for the activities of their employees and to ensure that biorisk management is not secondary to their academic, commercial or other objectives. The ability of research institutions to undertake research safely, at different levels, will vary among Member States. A regulatory system through which research institutions are registered as suitable for certain types of activity (e.g. genetic modification) could help research institutions in reducing biorisks, providing for external regulatory audit and providing specific guidance when an institution undertakes or proposes to undertake new types of work. Some countries already recognize certain areas of life sciences research or kinds of technology (e.g. human genome editing and genetic modification of human pathogens) as being of concern. However, other areas of biorisk are rapidly evolving, due to advances in technology, and are not as clearly defined or governed. In the United States, the Select Agent Regulations provide the legal framework for laboratory biosecurity while several government-wide policies on dual-use research oversight have been implemented over the last decade. In the United Kingdom, the Health and Safety Executive requires all organisations involved in genetic manipulation to register with them and seek approval for particular types of work. Under their Compendium of Guidance, it is a legal requirement for all organisations undertaking genetic manipulation research to have an internal committee to review the research, with the power to refuse permission to proceed *(76)*.

    b. **Institutional oversight**. Scientists have many demands on their time; thus, even within a robust research culture, there is the possibility of substandard risk assessment and risk management by scientists. Institutional oversight of scientist-led risk assessments (e.g. through internal audits, peer review and committee approval) is a tool that can be applied to standardize processes within an institution, to improve or ensure the quality and timeliness of risk assessments. For example, in Germany, institutions that receive funding from the German Research Foundation (DFG) must create a committee to review security-relevant research. This review process is overseen by the Joint Committee on the Handling of Security-Relevant Research, which is a collaborative biorisk management initiative run by DFG and the German National Academy of Sciences Leopoldina *(59)*.

4.3.3 Stakeholder: funding bodies

84. Most research institutions are dependent for some of their research funding on external grants, philanthropic funding or contract-awarding bodies.

85. Examples of tools and mechanisms are given below.

    a. **Research design review.** Although funding bodies are not typically involved in the design of research, they can help to mitigate biorisks through their research applications processes. Many leading life science funders have developed questions on their funding applications explicitly asking applicants whether they have considered safety, security and dual-use aspects of their research. These funders also ask peer reviewers to consider biorisk aspects of the proposals they review.

    b. **Funding requirements**. For research that involves particularly risky materials, techniques or technologies, funders can make it a condition of funding that scientists: (i) proactively identify and manage risks possibly connected with their research, (ii) explain how the risks (as managed) are proportionate to the potential benefits of the research, (iii) consider whether less risky forms of research could be equally beneficial, and (iv) modify the research design, or the dissemination and publication plans (as the research proceeds or after the research has been completed) to mitigate risks. For example, in the United Kingdom, the Biotechnology and Biological Sciences Research Council (BBSRC), the Medical Research Council (MRC) and the Wellcome Trust have conditions for funding that encompass compliance with risk-related regulations *(70)*. Funders can also raise visibility by requiring disclosures of the process and presence of risk management through the research life cycle, including in publications, to facilitate knowledge sharing and instil norms of conducting biorisk management. Nascent efforts towards public reporting include the Materials Design Analysis Reporting Framework,[1] developed by a consortium of publishers, which was recently updated to include a question about dual-use, and the Visibility Initiative for Responsible Science (VIRS), developed by an international consortium of funders, publishers, researchers and oversight groups, which aims to develop improved frameworks to facilitate increased transparency in biorisk management practices through case studies and reporting frameworks *(71)*.

    c. **Agenda setting**. Funding bodies may have a role in setting the research agenda in certain fields. This is an executive function and allows funders to engage with institutions individually and collectively to provide guidance on assessment and control of biorisks, requiring institutions to undertake and maintain certain levels of biorisk assessment, education, and training as a condition of eligibility. For example, a consortium of organisations that fund and otherwise support gene drive research, including Wellcome Trust, Institut Pasteur, and Bill & Melinda Gates Foundation, developed a set of guiding principles for sponsoring gene drive research, including promoting safety and governance of the technologies, ensuring transparency in data sharing, and fostering accountability *(72)*. Another agenda-setting opportunity is for funding bodies to support lines of research dedicated to developing and evaluating tools and mechanisms to support biorisk management, including both technical and social/behavioural approaches.

[1] OSF | MDAR Framework.pdf

d. **Active accountability**. In cases of known or public examples of institutions or their researchers failing in their duties to identify, assess or control biorisks, funding bodies may consider whether a review should be undertaken of extant (as well as pending) grants should be undertaken. This would be a powerful tool to encourage scientists and institutions to take their responsibilities seriously.

4.3.4 Stakeholder: publishers

86. Particularly in academic fields, publication of research findings is an important component of the research enterprise and has a profound effect on the careers of researchers.

87. Examples of tools and mechanisms are given below:

    a. **Manuscript review**. Editorial and peer review of manuscripts is an opportunity to identify information that may pose significant biorisks or allow others to inappropriately repeat risky experiments is critical. While editors and publishers have an obligation to make scientific information (e.g. ideas, knowledge and data) accessible, this does not apply wholesale where risk assessments conclude that wide dissemination through publication poses a safety or security threat. In these cases, dissemination should be curtailed. This could mean that manuscripts are not published or are seriously modified prior to publication. To facilitate this process, the aforementioned MDAR framework has experimented with including a question related to dual-use on standardised reporting about methods. An answer to this question must accompany the paper submission. Other related initiatives like VIRS are seeking to develop improved reporting standards throughout the research lifecycle.

    b. **Guidelines**. Some publishers have established guidelines for identifying, reviewing and publishing papers that may pose a risk to health, safety and security. These guidelines require periodic revision and updating to ensure inclusion of possible novel types of risks. In 2003, editors from several renowned journals issued a statement on scientific publications and security that included recommendations on editorial processes involving publications that may pose a safety or security threat *(73)*. Moreover, in 2006, the Council of Science Editors (CSE) published a white paper on publication ethics, which has since been updated several times *(74)*. The paper includes a section on the responsibilities of editors towards the public, encompassing guidance on biosafety and biosecurity topics. In the USA, the National Science Advisory Board for Biosecurity (NSABB) has integrated guidance to publishers and editors in several reports on biosecurity, dual-use and gain-of-function research *(75)*.[1]

4.3.5 Stakeholder: national governments

[1] Gain-of-function research aims at increasing the transmissibility and/or the virulence of pathogens with the aim to improve the understanding of the diseases caused by those pathogens in order to develop medical countermeasures. For more information, see for example: Institute of Medicine and National Research Council. 2015. Potential Risks and Benefits of Gain-of-Function Research: Summary of a Workshop. Washington, DC: The National Academies Press. https://doi.org/10.17226/21666; Gain of function: experimental applications related to potentially pandemic pathogens, EASAC policy report 27. October 2015 2015_EASAC_GOF_Report_complete.pdf (leopoldina.org)

88. National governments are key stakeholders ultimately responsible for defining the biorisk management standards under their jurisdiction, and for enacting and enforcing relevant policies, including laws, regulations, standards, guidelines, best practices, codes of ethics, research review processes, training and education.

89. Examples of tools and mechanisms are given below:

    a. **Legislations, regulations and guidance.** These tools can set out legal responsibilities of individuals and institutions for biorisk management, training and internal oversight. However, such frameworks are often drafted in terms of accident prevention and do not necessarily focus on the dual-use nature of scientific advances. Legislation can also help research institutions understand that their responsibilities to ensure effective biorisk management is not secondary to academic, commercial or other goals.

    b. **Oversight**. A statutory governance system where institutions must be registered as suitable to conduct certain types of activities (e.g., genetic modification), or must document biorisk assessment and mitigation when new and particularly risky types of research are proposed, is a tool that can assist with setting minimum national standards, increasing oversight, enabling external audits, encouraging transparency and accountability, and, ultimately, reducing biorisks.

    c. **Flexible frameworks**. Certain life sciences research is already recognised as particularly risky in some countries, such as human genome editing and genetic modification of human pathogens. However, there are other areas of biorisk that are rapidly evolving because of advances in technology that are not as clearly defined or governed. For example, in the USA, the Select Agent Regulations provide the legal framework for laboratory biosecurity while several government-wide policies on dual-use research oversight have been implemented over the last decade *(33, 36, 37, 45)*. However, list-based approaches to governance in the life sciences can be limited. Due to the speed of advancements, lists can quickly become outdated and create holes in the biorisk management system as new technologies and their associated risks are not listed. Overarching frameworks with sufficient flexibility to apply to new technologies as they arise may escape this problem. Other countries have adopted a risk assessment-based regulatory system. In the United Kingdom of Great Britain and Northern Ireland (United Kingdom), for example, the Health and Safety Executive (HSE) requires all organizations involved in genetic manipulation to register with HSE and seek approval for particular types of research. Under the HSE's Compendium of Guidance, it is a legal requirement for all organizations undertaking genetic manipulation to have an internal committee to review the research and risk assessments, with the power to refuse permission to proceed *(64)*. While many countries have statutory frameworks regulating biosafety, and several have biosecurity-specific legislation, very few currently have legislation or regulations focused explicitly on dual-use.

    d. **Advisory bodies and outreach activities**. Several countries use advisory bodies to obtain advice and recommendations on measures to govern biorisks. For example, in France, the National Consultative Council for Biosecurity (CNCB), which was created in 2015, provides recommendations on potential misuse of dual-use research conducted in biology. The CNCB also suggests measures to prevent, detect and counter possible threats *(77)*. In the USA, the NSABB, which was created in 2004, addresses issues related to biosecurity and dual-use research at the request of the US government. The NSABB provides advice, makes

recommendations on biosecurity and the oversight of dual-use research, and has published reports covering different aspects of such oversight *(78)*. In the Netherlands, the Biosecurity Office, which is within the National Institute for Public Health and the Environment (RIVM), is a knowledge and information centre for the government and for institutions in the Netherlands working with high-risk pathogens, knowledge, information and technologies *(8)*. The Biosecurity Office also aims to increase biosecurity awareness, and develops relevant tools and web applications.

4.3.6 Stakeholder: standard-setting institutions

90. Examples of tools and mechanisms are given below:

a. **Science academies**. Local and regional science academies, such as the InterAcademy Partnership (IAP) or the European Academy of Sciences and Arts (EASA), are important in designing science policies, strategies and ethical considerations based on which universities and other research organisations to develop their own standards of scientific integrity and codes of ethics. As an example, in May 2021, the Swiss Academies of Arts and Sciences together with the Swiss National Science Foundation, the umbrella organisation of the Swiss universities, and Swiss Innovation Agency (Innosuisse) published a code of conduct for scientific integrity, which included the following sentence on dual-use research: "Researchers are obliged to proactively recognise and consider possible harms and risks in connection with their research work and to take appropriate precautionary measures. This is especially true for dual-use research of concern." *(65)*.

b. **Local and regional biosafety associations**. Biosafety and biosecurity officers are key players in assessments of biorisks and implementation of mitigating measures *(66)*. WHO recommends that all laboratories have a biosafety officer to provide advice and guidance to scientists and management. For biosafety officers to be competent and capable of supporting their institutions in biorisk management and awareness raising, they need to be sufficiently trained in these matters and to be an empowered and trusted member of the research team. Formal and informal peer-review is made possible by local and regional biosafety associations and other entities dedicated to minimizing biorisks *(67)*. The work of these associations is needed because biorisk management is still not a recognized area of study or profession. The Croatian Society for Biosecurity is a national biosafety association that is active in advancing biosafety and biosecurity training and information sharing between biosafety professionals *(68)*; there are also helpful examples in the Netherlands and Canada *(8, 69)*. Supporting the work of local and regional biosafety associations is key to enhancing biosafety and biosecurity globally.

c. **International standards**. In 2019, the International Organization for Standardization (ISO) released ISO 35001, a standard for biorisk management for laboratories that work with dangerous pathogens. Rather than focusing on scientific hardware, the standard emphasises commitments by top management (e.g. to provide adequate resources, to prioritise and communicate biosafety and biosecurity policy, to train staff and to establish performance expectations). The standard also stresses the need for continual improvement of practices and processes to determine the causes of incidents and other issues, to correct problems so that they do not recur, to identify opportunities for improvement, and to recognise and award improvement. Some institutions have begun adopting the standard, and its further promotion

together with awareness-raising efforts will contribute to safer and more secure biological activities.

4.3.7 Stakeholder: educators

91. Examples of tools and mechanisms are given below:

    a. **Introducing responsible science concepts, including biosafety, biosecurity and dual-use**. Integrating concepts pertinent to conducting responsible research into scientific and medical curricula can enhance awareness of risks to health, safety and security with basic and applied life sciences. Academic and scientific institutions can help by including these concepts in their courses and educational activities.

    b. **Training**. Curricula with laboratory and practical sessions can include training sessions that reinforce concepts related to best practices, to apply and reinforce concepts covered in theory sessions. Active learning is one of the best approaches for introducing of concepts such as biosafety, biosecurity and dual-use and demonstrating their utility in practice. For example, the Academy of Sciences Malaysia has developed an educational module for responsible conduct of research in the life sciences that uses active learning principles in a module on dual-use research and creating a culture of safety *(79)*.

4.3.8 Stakeholder: international organizations

92. Examples of tools and mechanisms are given below:

    a. **Guidance documents**. Many countries, regions, territories and institutions have developed regulatory frameworks that govern responsible science and offer guidance on related matters; however, others do not have similar tools and mechanisms in place. International organizations (e.g. WHO, FAO, UNESCO and OIE) can provide guidance for developing local regulations and reinforcing global best practices within their boundaries of governance. There are also multilateral efforts to establish metrics related to biorisk management and track countries' performance based on those metrics. For example, UN Security Council Resolution 1540 includes provisions relating to biosecurity and preventing non-State actors from acquiring and using biological weapons. The joint external evaluation (JEE) is a voluntary, collaborative, multisectoral process to comprehensively assess a country's capacity to prevent, detect and rapidly respond to public health risks in the framework of the International Health Regulations (2005) *(80)*. The JEE evaluates a country's biosafety and biosecurity measures based on metrics developed by the Global Health Security Agenda *(81)*. The BWC provides the normative foundation for international efforts to prevent the misuse of biology and biotechnology and the treaty's ISU provides assistance to countries in joining the treaty and implementing their obligations *(82)*.

    b. **Access to information and resources**. International organizations can facilitate access to information required, for example, for biorisk assessment, training, conducting responsible science, mitigating risk and developing regulations. These international bodies can also aid

local authorities, scientific institutions and investigators in identifying resources necessary for complying with responsible science practices. For example, the United Nations Interregional Crime and Justice Research Institute (UNICRI) has developed a global network of stakeholders invested in biorisk management. UNICRI acts as a clearinghouse to enable stakeholders to share best practices and training materials *(83)*. The annual meetings of States Parties and experts under the BWC bring together governments and nongovernment experts in biorisk management, where they can share best practices and lessons learned, and develop new ideas for strengthening global biosecurity *(84)*. The BWC's confidence-building measures – especially those related to biosafety level 4 laboratories and biodefense programmes – also provide transparency into national activities in these areas *(85)*.

c. **Communication**. The identification of novel global threats and growing sources of biorisk can be achieved by transparent communication among countries and among entities. International organizations can foster communication between stakeholders and the publication of data, research or information necessary for identifying such risks. Examples supported by civil society include the Global Biosecurity Dialogues (in particular its workstream on emerging biological risks) and the Global Health Security Agenda (including its workstream on biosafety and biosecurity).

4.3.8 Stakeholder: civil society networks

93. Examples of tools and mechanisms are given below:

    a. **Transparency**. Civil society is a stakeholder in any research or laboratory activity because the risks and potential benefits of such activity impact society at large. Hence, civil society networks should be knowledgeable about and involved in discussions related to research or laboratory undertakings that may affect the publics. The BioWeapons Prevention Project *(86)*, which has advocated universalization of the BWC and hosted trainings to raise awareness on biological risk management *(87)* has been involved in BWC meetings and discussions. For example, the Nuclear Threat Initiative's Global Health Security Index is a metric that measures the level of national biosafety and biosecurity preparedness *(88)*.

    b. **Informing and educating**. Civil society networks are important for informing the publics and educating various sectors of society; they can act as a bridge between the scientific community and the public at large.

    c. **Policy-making**. An informed public can make better decisions in support of political strategies and policies that govern scientific activities. Civil society networks can liaise between scientists and the various publics to balance competing interests like the desire for unfettered science and the desire for caution and control. For example, following the devastating 2014–2015 Ebola outbreak in west Africa, a partnership between experts and civil society networks resulted in the formation of the Global Emerging Pathogens Treatment (GET) Consortium *(89)*. This consortium played an important role in organizing the African Voices and Leadership conference on Ebola in Dakar, Senegal, in 2015; that meeting helped to identify deficiencies, including biosecurity-related ones, that permitted the outbreak. The consortium was also able to secure commitments from several governments and enter into memoranda of understanding with those governments to limit possible threats.

4.3.9 Stakeholder: private sector

94. Private companies play an increasingly important role in life sciences research and the development of biotechnology. Biotechnology, agricultural biotechnology and pharmaceutical companies conduct research to support the development of commercial products.

95. Examples of tools and mechanisms are given below:

    d. **Self-governance**. In 2009, a group of leading gene synthesis companies formed the International Gene Synthesis Consortium (IGSC) and adopted a voluntary system for the screening of customers and gene sequence orders. As part of the screening process, orders are compared against a database of nationally and internationally regulated pathogens and toxins to determine whether any ordered sequence poses a security risk. If the automated screening system detects a close match between an order sequence and a regulated agent, the order and the customer are scrutinized manually *(44)*.

e. **National legislation**. Research, development and use of GMOs is subject to national legislation in many countries; however, such oversight is typically limited to considerations related to biosafety and biodiversity. Even in countries that oversee dual-use research, that oversight is often, but not always restricted to publicly funded research. Canada's biorisk management system, promulgated in the Human Pathogen and Toxin Act and overseen by the Centre for Biosecurity in Canada's Public Health Agency, requires any entity, regardless of the source of their funding, to assess the dual-use risks of any research *(38, 60)*.

96. One way to incentivize industry could be through the use of standard-setting organizations and positive role models; another could be the identification of good practices and corporate social responsibility. Industry stakeholders are becoming increasingly aware of the need to demonstrate responsibility, safety and security in their work. In addition, industry could play a role in supporting universities and higher educational establishments, to bring issues of responsibility into professional development. The increasing role of the private sector in funding research suggests that oversight mechanisms should cover both private and publicly funded research.

4.4 Awareness-raising, education, training and capacity-building

4.4.1 Examples of awareness-raising, education, training and capacity-building

97. Values and principles provide the ethical foundations for the responsible use of basic and applied life sciences. Tools and mechanisms for biorisk management provide practical grounding for the application of the values and principles. To ensure uptake and use of these foundational elements, awareness-raising, education, training and capacity-building are required for stakeholders in the research ecosystem, including scientists, research institutions and funders, among others.

98. Much has already been done in support of awareness raising and engagement in basic and applied science and related fields.[1] For example, much exemplary work has also been done in the chemical field. Several illustrative examples—by no means a comprehensive account—are provided in Annex 3. Although some exercises have completed evaluations that demonstrate success, the extent of such activity is sometimes un- or under-acknowledged. Moreover, although some initiatives have

[1] See, for example: National Academies of Sciences. 2011. Challenges and Opportunities for Education About Dual Use Issues in the Life Sciences. Washington, DC: The National Academies Press. https://doi.org/10.17226/12958. National Academies of Sciences, Engineering, and Medicine. 2017. Fostering Integrity in Research. Washington, DC: The National Academies Press. doi: https://doi.org/10.17226/21896. National Academies of Sciences, Engineering, and Medicine. 2018. Governance of Dual Use Research in the Life Sciences, Washington, D.C.: National Academies Press: https://www.nap.edu/catalog/25154 ; National Research Council of The National Academies. 2013. Developing capacities for teaching responsible science in the MENA region: refashioning scientific dialogue. In cooperation with Bibliotheca Alexandrina, TWAS and The World Academy of Sciences. The National Academies Press. Washington D.C.https://www.nap.edu/catalog/18356/developing-capacities-for-teaching-responsible-science-in-the-mena-region

proven both successful and sustainable, it is not always clear whether all such initiatives have been either successful or sustained.

4.4.2 Lessons from past activities

99. Past efforts to undertake awareness raising, education, training and capacity-building in relation to biorisks suggest several general lessons for those seeking to undertake such activities in the future (Box 4). These include the following:

Box 4 Lessons from past efforts in awareness raising, education, training and capacity-building

a. **Purpose**. The purpose of education, training and capacity-building efforts varies from enabling self-governance to underpinning formal oversight, promoting discussion and so on. It is not always clear what is expected of those being "engaged" or "educated". Moreover, existing challenges and gaps in awareness raising and education vary from addressing accidents (biosafety) to preventing deliberate outbreaks of disease (biosecurity). For preventing accidental disease outbreaks, the work needed is largely in implementation of institutional safety procedures, whereas addressing the hostile use of biology requires considerable conceptual work to understand how to fully enable scientists to deal with the problem.
b. **Priorities**. Biosecurity and dual-use are not immediate priorities for most of those associated with basic and applied life sciences and are not necessarily well understood. For those countries grappling with severe health and environmental challenges, it is a demanding task to determine how to weigh security threats associated with the life sciences against other ongoing concerns.
c. **Definitions**. The lack of shared terminology (including the meaning of central terms such as biosafety, biosecurity and dual-use) complicates efforts to share good practice.
d. **Discussion**. No single approach can fit the needs and conditions of all; thus, there is a need to explore the strengths, opportunities and challenges with particular initiatives, assess tools and mechanisms, and consider how capacity-building can be realized.
e. **Inclusion** Past initiatives had involved a broad range of actors. Concerns about biorisks extend beyond those working with pathogens. Research organizations, funders, laboratory technicians, professional societies, data managers and curators, publishers, editors, ethics committees, institutional or repository managers, civil society networks and regulators all have roles to play – both in providing training and receiving training.
f. **Innovation**. The design and creation of awareness-raising and education materials should make use of best practices (e.g. active learning processes, including team-based learning exercises).
g. **Integration**. Material on biorisk management could be integrated into existing training courses on laboratory practice, or courses on bioethics and wider discussions around responsible conduct of research.
h. **Bottom-up versus top-down.** Some past initiatives have been bottom-up (emerging organically through individual champions), whereas other initiatives have been top-down. Both bottom-up and top-down support is required, with the latter being particularly important in institutionalizing measures.
i. **Localised materials**. Various materials have been developed for awareness raising, education and training. Organizations and countries require material that is appropriate to their circumstances. In general, promoting security can be difficult because what counts as security and for whom is context dependent. There is no one-size-fits-all approach, and scenarios need to be tailored to the local context in terms of content and delivery, made accessible and promulgated. There are currently few locally appropriate scenarios for low- and middle-income countries (LMIC). Context-specific content should be developed and should consider local risks and challenges, in additional to scenarios illustrating global biosafety, biosecurity and dual-use challenges.
j. **Champions**. The value of champions, including industry and academic leaders, has been emphasized to promote and promulgate materials. Informal and formal networks are important in creating, identifying and fostering individual champions or groups of champions. Cooperating through sustainable, resourced networks is important to capitalise on growing attention to responsible conduct of research and open science education.
k. **Resources**. Although several education-related initiatives have been launched in previous years, these efforts have proven difficult to sustain, often because of a lack of funds. Both financial and technical support will be required to undertake activities in these areas, to sustain cooperative

networks and curate educational materials. This will be particularly important for LMICs with limited resources for effective biorisk management.

l. **Enabling measures**. Awareness of concerns associated with biorisks is patchy and and there has been little training in these areas. Awareness raising, education, training and capacity-building will help to address this situation. Moreover, tools and mechanisms to respond to concerns (e.g. providing channels for whistle blowing) need to be developed in tandem with awareness-raising measures. This is particularly important in the case of reporting or responding to any suspicions raised by individual trainee, students, scientists or other relevant stakeholders.

m. **Sustainability**. Measures to support the sustainability of awareness raising, education, training and capacity-building need to be built into initiatives from the start. This requires careful consideration of possible incentives for engagement (e.g. development of relevant career metrics, which could ensure longevity and bottom-up engagement).

Source: Towards a global guidance framework on responsible use of life sciences: summary report of consultations on the principles, gaps and challenges of biorisk management. Geneva: World Health Organization; 2022 (Forthcoming).

Section 5. The framework in action

100. This section outlines how Member States and stakeholders can start implementing the framework and developing biorisk management activities. It is relevant for countries and stakeholders that aim to develop biorisk governance frameworks, and for those interested in strengthening their existing biorisk governance frameworks.

101. Because there is no one-size-fits-all approach, this section provides a checklist of the various steps to be considered for developing a biorisk management framework. The approach is designed for the many different stakeholders involved in the governance of biorisks, and it identifies several key considerations and questions. Each step lists existing resources and tools that can support stakeholders to develop biorisk management activities.

102. Implementing the framework, using the stepwise approach with the checklists will be guided by the values and principles for the governance of biorisks (Table 1). In addition, implementing the framework will be a process steered by the following key considerations:

a. *Leadership and ownership*: the process of developing and strengthening biorisk management activities will require leadership and ownership at the national and regional levels. Support, guidance, capacity building and collaboration with key stakeholders will be critical for effective implementation of the framework.

b. *Creating an enabling environment:* existing expertise and systems can be used and leveraged to facilitate the implementation of the framework. For example, existing biosafety systems and procedures can be used as avenues for implementing further biosecurity and dual-use oversight measures. The implementation of the framework and the stepwise approach will need to be adapted to the particular context. Researchers, institutions and countries will start from different points. If there is no legislation, regulations, guidance or training in place, the stepwise approach can be used to guide discussions and assess the needs of different stakeholders. The stepwise approach could also be used to identify specific national capacities that need to be developed and strengthened. This approach should be evidence-led and forward looking.

c. *Intersectoral collaboration*: the framework encourages dialogues and cooperation among different stakeholders (Figure 1, step 3). Distinct stakeholder groups are best positioned to achieve specific goals. For example, scientists are best positioned to assess the risks and potential benefits of their work.

Institutions have an essential role in the oversight of biorisk assessment and mitigation. Governments and regulators are critical in reinforcing and requiring biorisk management strategies across different stakeholders and sectors (e.g. academia, public and governmental laboratories and commercial companies). Moreover, different governance strategies, engaging different stakeholder groups, may be taken to achieve a single specific goal.

d. *Partnership and financing:* resources will be required to implement the framework, as will incentives for engaging different stakeholders in the process.

e. *Monitoring result and accountability:* biorisk management and mitigation activities should be regularly reviewed. Strategies may need to be adapted in light of new developments. Likewise, effectiveness of mitigation strategies need to be assessed and processes for accountability need to be ensured.

103. The framework will be operationalized by the implementation of the six steps approach and the checklists. Figure 1 outlines the generic six steps approach for implementing the framework. Boxes 5–11 illustrate the six steps with specific checklists applicable to different stakeholders. The checklists are illustrative and can be adapted as necessary. The checklists help clarifying the minimum expected steps in a complex process and contribute to anticipate the monitoring and evaluation process by establishing a standard of baseline performance.

Figure 1. A stepwise approach with checklists for implementing the framework and developing biorisk management activities

Box 5. Stakeholder: checklist for scientists

Important note: While the checklists identify examples of considerations targeted at different stakeholders, biorisk management is a shared responsibility between different stakeholders. Together, different stakeholders will develop robust and effective biorisk management, which is emphasized in STEP 3 of the checklist.

STEP 1: Collect information: identify and assess potential benefits and risks	**Resources**
Outputs: Potential risks and benefits of work identified and assessed before beginning the work. Key considerations and questions include the following: • What are the potential benefits of the proposed work? • What risks could the proposed work pose to humans, nonhuman animals and the environment? • Has a risk and benefit assessment been conducted for the proposed work? • Could a different methodology or experimental design have been used to make the experiment safer or less of a biosecurity risk? • Are the safety and security measures sufficient to protect laboratory personnel and others from risks? • Is the proposed work falling under the scope of export controls? • Is the proposed work following institutional, national, regional legislations, regulations or guidelines for safe, secure and responsible research? • Could the information, data and research methods generated by the proposed work be misused to cause harm? Which mitigation strategies have been put into place to reduce this risk?	Box 1 WHO JEE tools (P.6.1 and P.6.2) *(90)*
STEP 2: Identify values, principles and goals	
Outputs: Values, principles and goals identified	Table 1, Table 2 and Table 3
STEP 3: Stakeholder analysis	
Outputs: All relevant stakeholders involved in the management of biorisks are identified and actions are coordinated. Key considerations and questions include the following: • Identify all key stakeholders, their roles and responsibilities associated in the management of biorisks (e.g. the research institution; professional scientific associations; funders; publishers; government; the publics; the private sector and international organizations); • Develop a strategy to include key stakeholders in the management of biorisks; • How do you plan to communicate and coordinate your actions with these actors or groups? (risk communication plan)	
STEP 4: Risk management: minimize risks and maximize potential benefits	
Outputs: A set of tools and mechanisms is identified in accordance with the risk assessment (STEP1), principles and values (STEP 2) Key considerations include the following: • Risk mitigation strategies need to be commensurate with the identified risks; • Risk mitigation strategies cannot reduce risks to zero unless the work or research is not being undertaken; • Are there resources to address identified risks? • Different tools and mechanisms may be adopted to reinforce one goal; • Different tools and mechanisms may have different levels of formality, incentives and enforcement (e.g. legislation versus guidelines and norms); • Some tools and mechanisms can be specific to certain goals whereas others may address several goals at once.	Table 2 and Table 3
STEP 5: Implement the identified tools and mechanisms	
Outputs: The set of tools and mechanisms identified (STEP 4) is implemented taking into consideration the values and principles (STEP 2) and the various stakeholders (STEP 3) Key considerations include the following: • Consider the feasibility of the set of tools and mechanisms; • Secure the resources and identify a realistic timeframe; • Get support from key stakeholders.	
STEP 6: Review performance and adaptability	
Outputs: The approach is reviewed (STEP 1 – STEP 5) and adapted it as necessary Key considerations include the following: • Risk and benefit assessments should be regularly updated;	

• Risk mitigation strategies should be regularly reviewed during the work process. New data or unanticipated findings may require that risk mitigation strategies be adapted; • Effectiveness of mitigation strategies need to be assessed.	

Box 6. Stakeholder: checklist for institutions

Important note: While the checklists identify examples of considerations targeted at different stakeholders, biorisk management is a shared responsibility between different stakeholders. Together, different stakeholders will develop robust and effective biorisk management, which is emphasized in STEP 3 of the checklist.

STEP 1: Collect information: identify and assess potential benefits and risks	**Resources**
Outputs: Potential risks and benefits of work identified and assessed before beginning the work. Questions to consider include the following: • What are the purposes of the proposed work undertaken at your institution? • What are the potential benefits of the proposed work undertaken at your institution? • What risks could the proposed work pose to humans, nonhuman animals and the environment? • Has a risk and benefit assessment been conducted for the proposed work undertaken at your institution? • Is the personnel and institution qualified to do the proposed work? • Could a different methodology or experimental design have been used to make the experiment safer or less of a biosecurity risk? • How will the proposed work be done safely and securely? Are the safety and security measures sufficient to protect laboratory personnel and others from risks? • Could the information, data and research methods generated by this work be misused to cause harm? Which mitigation strategies have been put into place to reduce this risk? • Is the proposed work following institutional, national, regional legislations, regulations or guidelines for safe, secure and responsible research? • Is the proposed work falling under the scope of export controls? • Does the institution provide adequate education, training resources, incentives and expertise for the personnel to run safety and security risk assessments and to increase awareness of risk?	Box 1 WHO JEE tools (P.6.1 and P.6.2) *(90)*
STEP 2: Identify the values, principles and goals	
Outputs: Values, principles and goals identified	Table 1, Table 2 and Table 3
STEP 3: Stakeholder analysis	
Outputs: All relevant stakeholders involved in the management of biorisks are identified and actions are coordinated. Key considerations and questions include the following: • Identify all key stakeholders, their roles and responsibilities associated in the management of biorisks (e.g. the scientists; other research institutions; professional scientific associations; funders; publishers; government; the publics; the private sector and international organizations); • Develop a strategy to include key stakeholders in the management of biorisks; • How do you plan to communicate and coordinate your actions with these actors or groups? (risk communication plan)	
STEP 4: Risk management: minimize risks and maximize potential benefits	
Outputs: A set of tools and mechanisms is identified in accordance with the risk assessment (STEP1), principles and values (STEP 2) Key considerations include the following: • Risk mitigation strategies need to be commensurate with the identified risks; • Risk mitigation cannot reduce risks to zero unless the work is modified or not undertaken; • Are there resources to address identified risks? • What training are provided to personnel as part of their regular duties to minimize risks? • Different tools and mechanisms may be adopted to reinforce one goal; • Different tools and mechanisms may have different levels of formality, incentives and enforcement (e.g. legislation versus guidelines and norms); • Some tools and mechanisms can be specific to certain goals whereas others may address several goals at once; • Does your institution have implemented mechanisms and tools to address biorisks challenges? Does your institution have appointed a biosafety officer or established an institutional biosafety and biosecurity committee that provide oversight of the proposed work? • Does your institution provide education and training about biorisk management to the personnel? • What systems are in place to provide biorisk management education to personnel and to report any incidents and breaches?	Table 2 and Table 3

• What systems are in place to order, share, agents, tools, information, and samples safely and securely between your institution and other collaborating entities? • Is there a surveillance system in place to monitor personnel for potential exposures to pathogens when working in the lab or when these are collected in the field? • Is there a system in place to conduct audits at your institution?	
STEP 5: Implement the identified tools and mechanisms	
Outputs: The set of tools and mechanisms identified (STEP 4) is implemented taking into consideration the values and principles (STEP 2) and the various stakeholders (STEP 3) Key considerations include the following: • Consider the feasibility of the set of tools and mechanisms; • Secure the resources and identify a realistic timeframe; • Get support from key stakeholders.	
STEP 6: Review performance and adaptability	
Outputs: The approach is reviewed (STEP 1 – STEP 5) and adapted it as necessary Key considerations include the following: • Risk and benefit assessments should be regularly updated; • Risk mitigation strategies should be regularly reviewed during the work process. New data or unanticipated findings may require that risk mitigation strategies be adapted; • Effectiveness of mitigation strategies need to be assessed.	

Box 7. Stakeholder: checklist for national governments

Important note: While the checklists identify examples of considerations targeted at different stakeholders, biorisk management is a shared responsibility between different stakeholders. Together, different stakeholders will develop robust and effective biorisk management, which is emphasized in STEP 3 of the checklist.

STEP 1: Collect information: identify and assess potential benefits and risks	**Resources**
Outputs: Potential risks and benefits of work identified and assessed before beginning the work. Key considerations include the following: • Does your country have legislation, regulation or guidelines on laboratory biosafety, biosecurity and the oversight of dual-use research? • Does your country have legislation, regulation or guidelines on the transport, sharing and storage of samples? • Does this work fall under legislations on export controls? • Does your country have an inventory of pathogens and toxins storied and processed within facilities under your jurisdiction? • Does your country have an inventory of dual-use research conducted in facilities under your jurisdiction? • Do the governance mechanisms cover relevant stakeholders including public and private research institutions, funders, and scientists? • Does your country provide resources for awareness raising, education and training activities on biorisks, including on dual-use research? • Does your country require to do risk and benefit assessment for the work done at facilities under your jurisdiction? • Does your country have a system for laboratory licensing? • Is there a system in place to conduct audits at institutions under your jurisdiction?	Box 1 WHO JEE tools (P.6.1 and P.6.2) *(90)* Global Health Security Agenda action package 3 *(81)* Global health security index *(88)*
STEP 2: Identify the values, principles and goals	
Outputs: Values, principles and goals are identified	Table 1, Table 2 and Table 3
STEP 3: Stakeholder analysis	
Outputs: All relevant stakeholders involved in the management of biorisks are identified and actions are coordinated. Key considerations and questions include the following: • Identify all key stakeholders, their roles and responsibilities associated in the management of biorisks (e.g. the scientists; research institutions; professional scientific associations; funders; publishers; other governments; the publics; the private sector and international organizations); • Develop a strategy to include key stakeholders in the management of biorisks; • How do you plan to communicate and coordinate your actions with these actors or groups? (risk communication plan).	
STEP 4: Risk management: minimize risks and maximize potential benefits	
Outputs: A set of tools and mechanisms is identified in accordance with the risk assessment (STEP1), principles, values and goals (STEP 2) Key considerations include the following: • Risk mitigation strategies need to be commensurate with the identified risks; • Risk mitigation cannot reduce risks to zero unless the work is modified or not undertaken; • Different tools and mechanisms may be adopted to reinforce one goal; • Different tools and mechanisms may have different levels of formality, incentives and enforcement (e.g. legislation versus guidelines and norms); • Some tools and mechanisms can be specific to certain goals whereas others may address several goals at once; • What are the resources and capacity building support allocated at research institutions and for personnel to assess and minimize risks? • What training is provided to research institutions and personnel as part of their regular duties to assess and minimize risks? • What systems are in place to share agents, tools, information, and samples safely and securely under your jurisdiction? • What surveillance systems are in place to monitor personnel for potential exposures to pathogens when working in the laboratory or when these are collected in the field?	Table 2 and Table 3
STEP 5: Implement the identified tools and mechanisms	

Outputs: The set of tools and mechanisms identified (STEP 4) is implemented taking into consideration the values and principles (STEP 2) and the various stakeholders (STEP 3) Key considerations include the following: • Consider the feasibility of the set of tools and mechanisms; • Secure the resources and identify a realistic timeframe; • Get support from key stakeholders.	
STEP 6: Review performance and adaptability	
Outputs: The approach is reviewed (STEP 1 – STEP 5) and adapted it as necessary Key considerations include the following: • Risk and benefit assessments should be regularly updated; • Risk mitigation strategies should be regularly reviewed during the work process. New data or unanticipated findings may require that risk mitigation strategies be adapted; • Effectiveness of mitigation strategies need to be assessed.	

Box 8. Stakeholder: checklist for funding bodies

Important note: While the checklists identify examples of considerations targeted at different stakeholders, biorisk management is a shared responsibility between different stakeholders. Together, different stakeholders will develop robust and effective biorisk management, which is emphasized in STEP 3 of the checklist.

STEP 1: Collect information: identify and assess potential benefits and risks	**Resources**
Outputs: Potential risks and benefits of work identified and assessed before beginning the work. Key considerations include the following: • What are the purposes of the proposed work? • What are the potential benefits of the proposed work? • What risks could the proposed work pose to humans, nonhuman animals and the environment? • Has a risk and benefit assessment been conducted for the proposed work? • Could a different methodology or experimental design have been used to make the experiment safer or less of a biosecurity risk? • What measures are in place to mitigate safety, security, and dual-use research risks of the proposed work? • Is there a system in place to conduct audits on the proposed work? • As a funder, is there a requirement in the application for funding that grantees assess the proposed work for potential biorisks and consider means of mitigating biorisks? • As a funder, can you require that certain biorisk mitigation strategies be implemented for the proposed work? • As a funder, can you require that education and training on biorisk risk mitigation strategies be provided to grantees? • As a funder, do you have your own review process in place to assess the safety, security risks and potential misuse of the proposed work?	Box 1
STEP 2: Identify the values, principles and goals	
Outputs: Values principles and goals are identified	Table 1, Table 2 and Table 3
STEP 3: Stakeholder analysis	
Outputs: All relevant stakeholders involved in the management of biorisks are identified and actions are coordinated. Key considerations and questions include the following: • Identify all key stakeholders, their roles and responsibilities associated in the management of biorisks (e.g. the scientists; research institutions; professional scientific associations; other funding bodies; publishers; governments; the publics; the private sector and international organizations); • Develop a strategy to include key stakeholders in the management of biorisks; • How do you plan to communicate and coordinate your actions with these actors or groups? (risk communication plan)	
STEP 4: Risk management: minimize risks and maximize potential benefits	
Outputs: A set of tools and mechanisms is identified in accordance with the risk assessment (STEP1), principles, values and goals (STEP 2) Key considerations include the following: • Risk mitigation strategies need to be commensurate with the identified risks; • Risk mitigation cannot reduce risks to zero unless the work is modified or not undertaken; • Different tools and mechanisms may be adopted to reinforce one goal; • Different tools and mechanisms may have different levels of formality, incentives and enforcement (e.g. legislation versus guidelines and norms); • Some tools and mechanisms can be specific to certain goals whereas others may address several goals at once; • What resources for training, capacity building and educational activities are provided to grantees to assess and minimize biorisks, including dual-use research?	Table 2 and Table 3
STEP 5: Implement the identified tools and mechanisms	
Outputs: The set of tools and mechanisms identified (STEP 4) is implemented taking into consideration the values and principles (STEP 2) and the various stakeholders (STEP 3) Key considerations include the following: • Consider the feasibility of the set of tools and mechanisms; • Secure the resources and identify a realistic timeframe; • Get support from key stakeholders.	

STEP 6: Review performance and adaptability	
Outputs: The approach is reviewed (STEP 1 – STEP 5) and adapted it as necessary Key considerations include the following: • Risk and benefit assessments should be regularly updated; • Risk mitigation strategies should be regularly reviewed during the work process. New data or unanticipated findings may require that risk mitigation strategies be adapted; • Effectiveness of mitigation strategies need to be assessed.	

Box 9. Stakeholder: checklist for publishers and editors

Important note: While the checklists identify examples of considerations targeted at different stakeholders, biorisk management is a shared responsibility between different stakeholders. Together, different stakeholders will develop robust and effective biorisk management, which is emphasized in STEP 3 of the checklist.

STEP 1: Collect information: identify and assess potential benefits and risks	**Resources**
Outputs: Potential risks and benefits of work identified and assessed before beginning the work. Key considerations include the following: • What were the objectives of this work? • Who has been funding this work? • What are the potential benefits and risks of the work? • What risks could the proposed work pose to humans, nonhuman animals and the environment? • Has a risk and benefit assessment been conducted for the proposed work? • What kind of biorisk mitigation measures have been implemented? • Is the work subject to dual-use research considerations? • As a publisher or editor, what policy, review process and expertise are in place in your journal to identify manuscripts that contain data, methods, and information that could foreseeably be misused by others to cause harm? What actions can your journal take to minimize the risk?	Box 1
STEP 2: Identify the values, principles and goals	
Outputs: Values, principles and goals are identified	Table 1, Table 2 and Table 3
STEP 3: Stakeholder analysis	
Outputs: All relevant stakeholders involved in the management of biorisks are identified and actions are coordinated. Key considerations and questions include the following: • Identify all key stakeholders, their roles and responsibilities associated in the management of biorisks (e.g. the scientists; research institutions; professional scientific associations; funding bodies; other publishers; governments; the publics; the private sector and international organizations); • Develop a strategy to include key stakeholders in the management of biorisks; • How do you plan to communicate and coordinate your actions with these actors or groups? (risk communication plan)	
STEP 4: Risk management: minimize risks and maximize potential benefits	
Outputs: A set of tools and mechanisms is identified in accordance with the risk assessment (STEP1), principles, values and goals (STEP 2) Key considerations include the following: • Risk mitigation strategies need to be commensurate with the identified risks; • Risk mitigation cannot reduce risks to zero unless the work is not being undertaken; • Different tools and mechanisms may be adopted to reinforce one goal; • Different tools and mechanisms may have different levels of formality, incentives and enforcement (e.g. legislation versus guidelines and norms); • Some tools and mechanisms can be specific to certain goals whereas others may address several goals at once; • In your journal, what resources, training and capacity building is provided to journal's editors and manuscript reviewers to be able to flag manuscripts for biorisks, including dual-use research? • In your journal, what policies and tools are in place to enable journal editors to conduct risk and benefit analysis? • In your journal, what publication strategy (e.g. full publication, delayed publication, publication with accompanying opinion papers) is in place after a comprehensive risk and benefit analysis?	Table 2 and Table 3
STEP 5: Implement the identified tools and mechanisms	
Outputs: The set of tools and mechanisms identified (STEP 4) is implemented taking into consideration the values and principles (STEP 2) and the various stakeholders (STEP 3) Key considerations include the following: • Consider the feasibility of the set of tools and mechanisms; • Secure the resources and identify a realistic timeframe; • Get support from key stakeholders.	
STEP 6: Review performance and adaptability	
Outputs: The approach is reviewed (STEP 1 – STEP 5) and adapted it as necessary	

Key considerations include the following: • Risk and benefit assessments should be regularly updated; • Risk mitigation strategies should be regularly reviewed during the work process. New data or unanticipated findings may require that risk mitigation strategies be adapted; • Effectiveness of mitigation strategies need to be assessed.	

Box 10. Stakeholders: checklist for civil society networks and the publics

Important note: While the checklists identify examples of considerations targeted at different stakeholders, biorisk management is a shared responsibility between different stakeholders. Together, different stakeholders will develop robust and effective biorisk management, which is emphasized in STEP 3 of the checklist.

STEP 1: Collect information: identify and assess potential benefits and risks	**Resources**
Outputs: Potential risks and benefits of work identified and assessed before beginning the work. Key considerations include the following: • Is there publicly available information about the work and potential impacts? • What will be the objectives of this work? • What are the potential benefits and risks of the work? • What risks could the proposed work pose to humans, nonhuman animals and the environment? • Has a risk and benefit assessment been conducted for the proposed work? • What kind of biorisk mitigation measures have been implemented? • Have other, less risky, methods been considered? • Is there a system in place to conduct audits on the proposed work? • Who will be responsible for responding to potential consequences of the work if it is funded? • Who will be liable for any unintentional consequences that may occur?	Box 1
STEP 2: Identify the values, principles and goals	
Outputs: Values, principles and goals are identified	Table 1, Table 2 and Table 3
STEP 3: Stakeholder analysis	
Outputs: All relevant stakeholders involved in the management of biorisks are identified and actions are coordinated. Key considerations include the following: • Identify all key stakeholders, their roles and responsibilities associated in the management of biorisks (e.g. the scientists; research institutions; professional scientific associations; funding bodies; publishers; the government(s); the private sector and international organizations); • Develop a strategy to include these stakeholders in the management of biorisks; • How do you plan to communicate and coordinate your actions with these actors or groups? (risk communication plan)	
STEP 4: Risk management: minimize risks and maximize potential benefits	
Outputs: A set of tools and mechanisms is identified in accordance with the risk assessment (STEP1), principles, values and goals (STEP 2) Key considerations include the following: • Risk mitigation strategies need to be commensurate with the identified risks; • Risk mitigation cannot reduce risks to zero unless the work is not being undertaken; • Different tools and mechanisms may be adopted to reinforce one goal; • Different tools and mechanisms may have different levels of formality, incentives and enforcement (e.g. legislation versus guidelines and norms); • Some tools and mechanisms can be specific to certain goals whereas others may address several goals at once; • What resources, education and capacity building are allocated by governments, funders, institutions and researchers to inform the publics about the potential benefits and harms of life sciences research? • What resources and tools are in place for making the publics aware of the risks and benefits of life sciences and for empowering them to engage in discussions and decisions about life sciences activities?	Table 2 and Table 3
STEP 5: Implement the identified tools and mechanisms	
Outputs: The set of tools and mechanisms identified (STEP 4) is implemented taking into consideration the values and principles (STEP 2) and the various stakeholders (STEP 3) Key considerations include the following: • Consider the feasibility of the set of tools and mechanisms; • Secure the resources and identify a realistic timeframe; • Get support from key stakeholders.	
STEP 6: Review performance and adaptability	

Outputs: The approach is reviewed (STEP 1 – STEP 5) and adapted it as necessary Key considerations include the following: • Risk and benefit assessments should be regularly updated; • Risk mitigation strategies should be regularly reviewed during the work process. New data or unanticipated findings may require that risk mitigation strategies be adapted; • Effectiveness of mitigation strategies need to be assessed.	

Box 11. Stakeholder: checklist for private sector

Important note: While the checklists identify examples of considerations targeted at different stakeholders, biorisk management is a shared responsibility between different stakeholders. Together, different stakeholders will develop robust and effective biorisk management, which is emphasized in STEP 3 of the checklist.

STEP 1: Collect information: identify and assess potential benefits and risks	**Resources**
Outputs: Potential risks and benefits of work identified and assessed before beginning the work. Key considerations include the following: • What are the purposes of the proposed work/order? • What are the potential benefits of the proposed work/order? • Is the personnel and your company qualified to do the proposed work/order? • What risks could the proposed work/order pose to humans, nonhuman animals and the environment? • Has a risk and benefit assessment been conducted for the proposed work/order? • Could a different methodology or experimental design have been used to make the experiment safer or less of a biosecurity risk? • How will this work/order be done safely and securely and in line with national legislation, regulations and international guidelines and norms? What measures are in place to mitigate safety, security, and dual-use research risks of the proposed work? • Is there a system in place to conduct audits on the proposed work/order? • Does your company provide access or fund educational and training activities on biosafety, biosecurity and dual-use research for your personnel? Do you provide support to your personnel to identify biorisks, to undertake benefits and risks analysis and to identify appropriate biorisk mitigation strategies? • Does your company provide adequate education, training resources, incentives and expertise for the personnel to run safety and security risk assessments and to increase awareness of risk? • Is the proposed work/order following national and regional legislations, regulations or international guidelines for safe, secure and responsible research? • Are there any national legislation, regulations or guidelines aimed at overseeing the proposed work/order to reduce the chances of deliberate misuse? • Is the proposed work/order falling under the scope of export controls? • Could the information, data and research methods generated by this work/order be misused to cause harm? Which mitigation strategies have been put into place to reduce this risk?	Box 1
STEP 2: Identify the values, principles and goals	
Outputs: Values, principles and goals are identified	Table 1, Table 2 and Table 3
STEP 3: Stakeholder analysis	
Outputs: All relevant stakeholders involved in the management of biorisks are identified and actions are coordinated. Key considerations and questions include the following: • Identify all key stakeholders, their roles and responsibilities associated in the management of biorisks (e.g. the scientists; research institutions; professional scientific associations; funding bodies; publishers; other governments; the private sector and international organizations); • Develop a strategy to include key stakeholders in the management of biorisks; • How do you plan to communicate and coordinate your actions with these actors or groups? (risk communication plan)	
STEP 4: Risk management: minimize risks and maximize potential benefits	
Outputs: A set of tools and mechanisms is identified in accordance with the risk assessment (STEP1), principles, values and goals (STEP 2) Key considerations include the following: • Risk mitigation strategies need to be commensurate with the identified risks; • Risk mitigation cannot reduce risks to zero unless the work is modified or research is not being undertaken; • Different tools and mechanisms may be adopted to reinforce one goal; • Different tools and mechanisms may have different levels of formality, incentives and enforcement (e.g. legislation versus guidelines and norms); • Some tools and mechanisms can be specific to certain goals whereas others may address several goals at once; • Some tools and mechanisms can be specific to certain goals whereas others may address several goals at once;	Table 2 and Table 3

• Does your company have implemented mechanisms and tools to address biorisk challenges? Does your institution have appointed a biosafety officer or established an institutional biosafety and biosecurity committee that provide oversight of the proposed work? • Does your company provide education and training about biorisk management to the personnel? • What systems are in place to provide biorisk management education to personnel and to report any incidents and breaches? • What systems are in place to order, share, agents, tools, information, and samples safely and securely between your institution and other collaborating entities? • Is there a surveillance system in place to monitor personnel for potential exposures to pathogens when working in the lab or when these are collected in the field? • Is there a system in place to conduct audits at your company?	
STEP 5: Implement the identified tools and mechanisms	
Outputs: The set of tools and mechanisms identified (STEP 4) is implemented taking into consideration the values and principles (STEP 2) and the various stakeholders (STEP 3) Key considerations include the following: • Consider the feasibility of the set of tools and mechanisms; • Secure the resources and identify a realistic timeframe; • Get support from key stakeholders.	
STEP 6: Review performance and adaptability	
Outputs: The approach is reviewed (STEP 1 – STEP 5) and adapted it as necessary Key considerations include the following: • Risk and benefit assessments should be regularly updated; • Risk mitigation strategies should be regularly reviewed during the work process. New data or unanticipated findings may require that risk mitigation strategies be adapted; • Effectiveness of mitigation strategies need to be assessed.	

Section 6. Conclusions

104. Over the past decades, there has been an accelerating pace in the development and applications of the life sciences. While rapid technological change and emerging new technologies can offer great opportunities to achieve the United Nations SDGs and global health, rapid change can also pose risks to our societies, including safety and security risks.

105. Attending to the safety and security risks of life sciences research and converging technologies is a complex endeavour.

a. First, there is no one size fits all approach to mitigate these risks. Countries and various stakeholders will have different starting points and they will work in different contexts, with different priorities and resources.

b. Second, developing and implementing biorisk management activities and policies to face the opportunities and risks brought by these technological changes can be challenging. Countries and relevant stakeholders can be outpaced in their capacity to face rapid technological developments.

c. Third, mitigating these risks involves a broad range of stakeholders. The development and implementation of biorisk management activities is a shared responsibility between different actors, including scientists and their institutions, funding donors, journals and publishers, governments, security communities, the publics, the private sector and other relevant stakeholders.

106. Effective and robust biorisk management systems rely on three core pillars: biosafety, biosecurity and the oversight of dual-use research and they require a range of tools and mechanisms to address both existing and unknown risks. This framework provides a common set of values and principles (Section 3) to guide decision-making and identifies various a broad range of tools and mechanisms that could be used in different contexts and applicable to Members States and stakeholders' different starting points (Section 4). The evolving and dynamic science and technology context result in a diversification of risks that requires biorisk management systems to be flexible, responsive and proactively anticipate changes. Foresight approaches can contribute to the responsible use of the life sciences and the developments of biorisk management systems.

107. Finally, mitigating biorisks is a shared responsibility. Effective and robust biorisk management involve a broad range of stakeholders (Section 4 and Section 5). Collaboration among different actors should be sought and encouraged. We are all

concerned with mitigating biorisks. Together, we can contribute to the safe, secure, responsible use of the life sciences so all populations can truly benefit from the great potential of these technologies.

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Annex 1. Scenarios

Introduction

108. The seven illustrative scenarios[1,2] presented in this Annex are intended to demonstrate how different elements of the framework can be helpful in successfully working through very different types of situations for a variety of stakeholders. The intent is to help different audiences to develop practical and robust strategies to confront a range of plausible futures. The scenarios will bring together the different elements of the framework (values and principles, stakeholders, tools and mechanisms) and test the framework against alternative plausible futures.

109. The scenarios are hypothetical, yet realistic scenarios where robust biorisk management is needed. Each scenario poses questions from the perspectives of different stakeholders and suggests biorisk management governance gaps that scientists, institutions, countries, funders, and journals should address when designing and refining biorisk management governance tools and mechanisms. Each scenario includes a description of the situation, identifies examples of risks, values and principles and each poses questions that specific types of stakeholders should be contemplating.

110. A robust life science biorisk governance framework will engage each country, institution, funder, institutional review board, journal, and scientist in a concerted effort to mitigate the biorisks associated with advanced life science research and technology development. Stakeholders along the research continuum have rolls to play in ensuring a careful assessment of benefits, risks, and gaps and to work together to create appropriate mitigation strategies in line with international norms and guidelines set forth by WHO.

111. These scenarios were developed to also highlight various ethical values and principles that serve as the foundation and embody the framework for advanced life science research. In each of these scenarios, there are several areas of concern for biorisk management and points of intervention to mitigate biorisks. While multiple stakeholders can and should engage in biorisk mitigation strategies throughout the

[1] Within the context of this framework, scenarios are understood as descriptions of plausible alternative futures that do not predict the future but are aimed at illustrating the effectiveness of the framework by testing its robustness against hypothetical scenarios and by identifying any potential gaps and breaks that might challenge it. The main purpose of using scenarios in this framework is to show how it might work in a range of different plausible future situations.

[2] Annex 1 directly draws on the report developed by the WHO Global guidance framework for biorisk management scenario development working group 5 (unpublished). Scenario 7 was developed as part of the BSP Case Studies WHO Framework for Responsible Life Science Research (unpublished).

research continuum, each scenario limits its focus to only a subset of issues for educational purposes. Key considerations included in the scenarios likewise do not represent a full list of governance options, nor will all suggestions for governance be appropriate for all environments, especially when resources are constrained. However, the scenarios provide concrete examples of scientific research activities and walk the reader through ways to identify and address the biosafety, biosecurity, and dual-use research risks that can arise.

Scenario 1. Gene therapy

112. This scenario underscores the importance of education and training for biorisk management and dual-use research as well as the biorisk management measures that a scientist and an academic or research institution needs to consider to ensure safe and secure research conduct.

Situation

113. Scientist A at the "Cure Research Institute" studies treatments for lung cancers and specializes in gene therapy. In her research, Scientist A uses a viral vector (that is, a genetically modified version of a virus) to transport genetic material that will modify a patient's disease carrying gene into a non-disease carrying version of the gene. To do this, Scientist A has created a lentivirus-based system to deliver the genetically modified elements to cancerous cells in lung tissue. Lentiviruses usually infect blood cells, but Scientist A has created a modified lentivirus that includes two genes from the measles virus. The hemagglutinin and fusion proteins from the measles virus were integrated by Scientist A into the lentiviral particle, which allows the viral vector to target cancerous cells in the lung. However, the measles virus hemagglutinin gene produces the protein that immune systems are most likely to recognize and attack following measles vaccination. Therefore, to get this system to work properly, Scientist A had to create mutations in the hemagglutinin gene so that a patient's immune system would not attack the viral vector after recognizing the measles virus hemagglutinin protein. If not for the introduced mutations in the hemagglutinin gene that allowed the viral vector to escape immune system recognition, the gene therapy treatment might not work with patients who had previously been vaccinated against measles. Over the course of her work, Scientist A has identified several mutations that if introduced to a viable measles virus, could allow it to evade immune memory in vaccinated individuals. Scientist A is excited to publish this research and hopes that it will advance the field of lung cancer treatments.

This scenario highlights the following risks (other risks may also arise).

114. *Biosafety*: The integration of a lentiviral vector genome is a biosafety risk to lab workers, since lentiviruses can trigger cancer following exposure. Ordinarily, due to the nature of lentiviruses, lentiviral vectors cannot be transmitted via aerosols. In this scenario, a new transmission route via aerosols could be created by integrating envelope proteins enabling infection of lung epithelial cells.

115. *Dual-use research*: The information gained from this work could be misused to generate a measles virus that available vaccines are not as highly effective against as they would be otherwise. Additionally, the viral system created in this experiment could

potentially be used for further experimentation to attempt creating a more transmissible or more lethal measles virus.

This scenario highlights the following questions for selected stakeholders (other questions and stakeholders may also arise).

116. Scientist A:

a. Are the laboratory's biosafety measures sufficient to protect laboratory personnel from risks resulting from potential exposure to the lentiviral vectors?
b. Could a different, less dangerous virus be used to do the experiment instead of using measles?
c. Could the information generated from this research be misused to create a measles virus that evades immunity conferred by measles vaccination?
d. What level of detailed information, data, and research methods concerning the types of mutations and the level of immune evasion they confer should be publicly available in publications following this research?

117. Biosafety officer at the research institute:

a. Is there a biosafety mitigation strategy in place at the institute? Are biosafety measures sufficient to protect laboratory personnel from exposure, including aerosol exposure?
b. Was a risk assessment conducted prior to approving this research? Could the information emanating from this study be misused by a malicious actor to genetically engineer a measles virus that the vaccine would not protect against?
c. Could a different methodology or experimental design have been used to make the experiment safer or less of a biosecurity risk?

This scenario highlights the following values and principles (other values and principles may also arise).

118. *Responsible stewardship of science*: Responsible stewardship of science requires stakeholders, including scientists, their institutions, and funders, to adequately assess risks and benefits of potential research. Biosafety officers and institutional review boards are common institutional bodies that provide this oversight. Each of these entities must consider if the risks of the potential work are greater or less than with potential benefits that may come from the work, identify if there are less risky methods or forms of research to answer the question, and if any further steps can or should be taken to reduce risk. Not only should all local, national, and international policies and guidelines be followed at a minimum, but each stakeholder should continue to innovate and improve best practices to further reduce risk over the life of the research.

119. *Health, safety and security:* Biorisk mitigation strategies should be implemented and followed to enable life science research to improve human, animal, and/or environmental health, prevent life sciences from causing harm and promote peace.

Discussion

120. Gene therapy is a powerful technology that provides, through viral vector systems, genetic therapeutic material to treat or stop a disease. In this scenario, biosafety, biosecurity, and risk mitigation issues should be assessed before starting the research. The scientists working on the project and the biosafety officer should work together to conduct a meaningful risk assessment and create a risk mitigation plan that considers methodologies, protocols, and security measures. Both the risk assessment and mitigation strategies should be reviewed by the institutional review board before any work begins.

121. However, there is still limited information and guidelines on how to best conduct a comprehensive risk assessment of viral vector systems in human gene therapy. It is therefore extremely important to educate scientists and raise awareness about biosafety and biosecurity risks, to teach effective methods for conducting rigorous risk assessments, and to share the types of mitigation tools available to reduce biorisks, including the risk that research findings could be later misused.

122. Responsibilities of the researcher and the biosafety officer should be precise and understood from the start for better biorisk management. Both the researcher and the biosafety officer should work with the institutional review board to ensure adequate oversight. Research oversight should be done periodically to check on adherence and effectiveness of the risk mitigation strategies. Such oversight also helps to prevent misuse by monitoring the conduct of research.

123. As more gene therapy products are available, biosafety and biosecurity frameworks, guidance, and training for scientists and other stakeholders (e.g., health workers) will need to be developed as more groups will have access to such tools.

This scenario highlights the following priority actions, tools and mechanisms for selected stakeholders to be considered (other actions, tools and mechanisms and stakeholders may also arise).

124. Academic and research institutions and PIs

a. Ensure that education and training about biorisk management be available for all scientists and laboratory staff, especially PIs and biosafety officers.
b. Ensure that all research staff in their laboratory have received such training and promote awareness-raising among students and trainees on biorisk management.

c. Promote the culture of biorisk management and reduce dual-use research risks through education and trainings for basic and applied life sciences research.
d. Implement tools and mechanisms to consider biosafety challenges in research laboratories, for instance through appointing a biosafety officer and setting up an institutional biosafety and biosecurity committee and/or institutional review board.
e. Promote a culture of biosafety and biosecurity for basic and applied life sciences and the need of appointing a biosafety officer and establish an institutional biosafety and biosecurity committee for protocol review of gene therapy research studies or other kinds of higher risk research. The biosafety officer should be well trained and should carefully consider biosafety and biosecurity during the research review process. S/he should ensure that risk mitigation measures are in place before initiating this kind of research. Once the work has started, the biosafety officer should continue to work with the laboratory staff to provide support and oversight for the work.

125. Laboratory staff

a. Be aware of the potential for a new transmission route (in this case, via aerosol), and this should also be considered in the risk assessment and risk mitigation strategies surrounding this experiment. In this scenario, relevant risk mitigation strategies may include guidance for use of PPE for aerosol-generating procedures, equipment to protect against aerosol exposure, or additional personal protective equipment (e. g. FFP3 mask).
b. Have a standard operating procedure and manual for the laboratory procedures, risk mitigation in case of a mishap, and use and disposal of PPE.

126. Scientists

a. Be aware of their responsibilities regarding assessing, preventing and mitigating biosafety and biosecurity risks and potential research misuse of the information generated by their research.
b. With support from their institutions, commit to responsible communication of their research findings to ensure both equitable access to the knowledge generated and minimize risk of misuse.

Scenario 2. Neurobiology

127. The aim of this scenario is to demonstrate that many different stakeholders should contribute to minimizing risks associated with dual-use research.

Situation

128. Scientist B is a PI who has done years of funded research on a central nervous system bioregulator. The absence of this particular bioregulator in a human being is known to be the cause of a very debilitating illness. The cause of such a loss of the bioregulator is thought to relate to malfunctions of the immune system, but how this happens is unclear, and the bioregulator clearly has other complex roles. Scientist B and his colleagues are preparing publication of a paper that aims at clarifying the neuronal circuits involved in the debilitating disease and how the bioregulator functions and malfunctions within that circuit. Scientist B hopes that the information in his paper could eventually lead to methods for effective manipulation of the bioregulator and the circuit to treat people who suffer from the illness. Scientist B is committed to advancing science on the bioregulator to uncover new techniques for improving patient outcomes. He sees great potential benefit in this work and has never considered potential ways that malicious actors could use this research to do harm. Moreover, he has submitted all his projects to the university approval processes and never encountered any questions from university leadership or from funders about the dual-use nature of her work.

129. When presenting this research at a conference, Scientist B is asked by a member of the audience whether someone could use the information Scientist B has produced on the structure of the bioregulator to create a drug that inhibits the regulator. (If a drug effectively inhibited the regulator, it could cause a serious debilitating disease for the exposed individuals). Scientist B finds this question odd, but quickly answers the question and moves on. Later in the day, a colleague of Scientist B, Scientist C, approaches him at the conference and comments on the question he received during the presentation. Scientist C, who works on cannabis chemistry, mentions that the question reminded him of the time when Scientist C's mentor told him about how earlier work on the structure and function of cannabis was later misused by criminals to make stronger and stronger drugs. Scientist B and Scientist C do a quick online search for misuse of neurobiology research. They find several publications discussing potential dual-use applications of neurobiology research. Scientist B and Scientist C realize they don't know a lot about potential misuse of their research, or the risks and ethical implications of their work.

This scenario highlights the following risk (other risks may also arise).

130. *Dual-use research*: There have been cumulative advances in life and associated sciences that have enhanced the potential health benefits of neurobiology research.

Studying bioregulation of critical neuronal circuits is essential for understanding certain neurological diseases. However, these advances also could increase the possibility of misuse. There is a history of misuse in the field of neuroscience. The concern in this scenario is the potential use of Scientist B's research by another malicious actor or group to cause harm.

This scenario highlights the following questions for selected stakeholders (other questions and stakeholders may also arise).

131. Scientists B and C

    a. How could Scientists B and C learn more about the potential risks of their research and keep apprised of the latest developments and best practices they could incorporate to help minimize harmful societal implications?

132. Institution

    a. Has Scientist B received an adequate biosecurity education that would have equipped him to recognize and address dual-use concerns?
    b. Has the institution provided any incentives to its researchers to ensure that an adequate biorisk assessment is carried out before research proceeds?
    c. How can biosecurity checks be institutionally implemented to advise Scientist B of the dangers of malicious misuse of his research and to require him to consider some means of minimizing the dangers?

133. Professional scientific association

    a. What role can the association play to ensure that its members have a firm grasp of the problem of dual-use and means to deal with it?

134. Funders

    a. Does the funder have a rigorous biosecurity review process in place to assess the dangers and potential misuse of proposed research?
    b. How can the funder require Scientist B and other grantees to consider some means of minimizing biorisks?

135. Publishers

    a. What review process should potential publishers have in place to identify manuscripts that contain data, methods, and information that could foreseeably be misused by others to cause harm?
    b. What are the measures that journals could take to minimize the risk?

136. National government

a. Does the country have legislation, regulations or guidelines in place to ensure that biorisks introduced through advanced life science research, technology development, and the publication of such research are mitigated or eliminated?
b. Do the governance mechanisms cover relevant stakeholders including public and private research institutions, funders and scientists?

137. International organizations

a. What role can WHO, other agencies in the UN system, and non-proliferation treaties such as the BWC and the Organisation for the Prohibition of Chemical Weapons play in helping countries, research institutions, professional societies, journals, and other stakeholders minimize risks presented by dual-use research?

This scenario highlights the following values and principles (other values and principles may also arise).

138. *Responsible stewardship of science*: Everyone involved in science has a responsibility to prevent science from causing harm. Part of this responsibility includes educating themselves on the risks, considering how their work fits into the broader society, and understanding historical context. At each stage of the research lifecycle, multiple types of stakeholders have an opportunity to intervene to reduce biorisks; responsible stewardship of science requires each stakeholder to try to do so.

139. *Social justice*: All entities and individuals in the research enterprise have a responsibility to equitably minimize burdens of research, which includes considering potential dual-use dangers associated with their work. Understanding how science and the research could be misused is a vital component when considering how to balance risks and potential benefits. Consequences of misuse of the technology will likely affect vulnerable populations more than others but benefits of the work might not be accessible to those same populations.

Discussion

140. For over 100 years, advances in civil society research in chemistry and biology have been used to facilitate the development of chemical and biological weapons, some of which target the nervous system directly or indirectly. Advances in the life sciences are proceeding at a fast pace, and technologies are becoming cheaper and more accessible. These advances will increasingly determine the types of targets that can be attacked by novel designed agents. This scenario focuses on questions about the impact of these developments generally, not the implications of just a single experiment.

141. Some scientists and international organizations are only now beginning to recognize the dual-use nature of certain kinds of neurobiology research involving the central nervous system. The International Committee of the Red Cross (ICRC) and a variety of

States Parties have led a decades long campaign to close the possible loophole in the Chemical Weapons Convention (CWC) that could be read as allowing the use of Central Nervous System-Acting chemicals for law enforcement purposes. In November 2021, the Conference of States Parties to the CWC narrowly took a decision to prohibit such use. Potential misuse of neurosciences has been identified as a concern by some State Working Papers of the Biological and Toxin Weapons Convention (BWC), but much remains to be done in addressing this area of research through improving the relevant tools and governance mechanisms at the individual, institutional, national and international levels.

This scenario highlights the following priority actions, tools and mechanisms for selected stakeholders to be considered (other actions, tools and mechanisms and stakeholders may also arise).

142. This scenario underlines the need for improved education and training so that scientists, institutions, funders, publishers, and countries are aware of the problem of dual-use and the potential consequences for broader society. Once these stakeholders understand dual-use, they can apply their expertise to helping minimize the risk through their daily jobs, both for individual experiments and more broadly in their field.

143. Scientists

a. Responsibility to understand how their field of research fits into a broader societal context, which includes considering the risks of the research and historical examples of misuse of the field.

144. Academic institutions

a. Educate students in science, technology, engineering, arts, mathematics about biorisk management.
b. Incorporate biorisk management ideals and skills into scientific curricula from secondary school biology classes through to doctoral work in basic and applied life sciences, including in biology, biochemistry, bioengineering and other adjacent fields.
c. Provide continuing education, that includes training on dual-use research, for all members of the scientific community.

145. Professional associations

a. Take active roles in educating members about the risks associated with research in the field and history of misuse or unsafe practices.

146. National governments

a. Provide resources for education and training on biorisks, including on dual-use research.
b. Develop relevant legislation, regulation and guidelines that include oversight of research with dual-use research potential.

Scenario 3. DNA synthesis

147. This scenario considers how well-intentioned research can be used as the foundation for riskier work, the role of vendors in biorisk management, and the importance of all laboratory members in creating a safe and secure environment.

Situation

148. Student scientist D is a graduate student in Supervisor scientist E's large laboratory, where they study host immune response to pox viruses. Student scientist D is specifically focused on understanding the immune response to monkeypox. Supervisor scientist E hopes that this basic science research could eventually help to inform development of a new vaccine. For her first aim, student scientist D wants to focus on the BR-203 virulence protein, which is believed to help the virus keep the host cell from dying before it can replicate. Supervisor scientist E and student scientist D decide that the BR-203 gene, which encodes the BR-203 protein, should be inserted into a myxoma virus backbone. While myxoma has a high lethality for rabbits, it is not known to infect humans and is a close enough relative of the monkeypox virus to be biologically suitable for the experiment. To conduct the research, student scientist D and supervisor scientist E have worked with the biosafety officer at their institution, the University of Alias, to determine biosafety protocols for this research.

149. Student scientist D struggles to get traditional cloning techniques to work for inserting BR-203 into a myxoma backbone. Instead, Supervisor scientist E agrees that student scientist D can order from a de novo DNA synthesis provider the BR-203 gene with part of the myxoma genome on either side. They select a provider that is not a member of the International Gene Synthesis Consortium (IGSC) because it is the cheapest option. Once the order arrives, student scientist D is able to insert the fragment into her myxoma backbone easily and conduct her experiments as planned.

150. Five years later, a new graduate student in the Supervisor scientist E's laboratory, student scientist F, is interested in student scientist D's previous work. When reviewing her notes, student scientist F finds the de novo synthesis order information. Student scientist F also decides to study monkeypox immune response, but student scientist F wants to compare host immune responses against monkeypox and myxoma. Student scientist F decides to order the myxoma BR-203 ortholog, M-T4, with parts of the monkeypox genome on either side of it to make it easier to insert the gene into the laboratory's monkeypox backbone. Student scientist F does not check with Supervisor scientist E before ordering. Student scientist F receives the order and successfully inserts the myxoma virus M-T4 gene into the monkeypox backbone, which was obtained from the laboratory's stock of monkeypox virus. Student scientist F finds student scientist D's old constructs in the freezer and rescues the old construct to recreate the chimeric viruses used by student scientist D for her original experiments in order to compare

immune responses. Upon realizing the ease of using de novo synthesis for creating chimeric viruses, student scientist F decides to order more fragments, mixing more and more of the genomes together to see at which point the myxoma virus can infect the monkeys, which are used in other in vivo experiments in the lab and accessible to student scientist F. This way, student scientist F successfully creates a myxoma virus highly infectious for monkeys. Once student scientist F creates a chimeric virus that can infect the monkey, student scientist F considers infecting herself with the virus to see if it can also infect humans.

This scenario highlights the following risks (other risks may also arise).

151. *Biosafety*: Wild type monkeypox virus is infectious to humans whereas myxoma virus is not. Using monkeypox genes to make myxoma virus capable of infecting monkeys creates the new prospect that the laboratory experiments will lead to a myxoma virus that is capable of infecting humans and making them sick. Technical and personal protective equipment protecting laboratory and animal unit staff from infection might not be sufficient with the newly created virus and might need to be reinforced. A lack of awareness and oversight might lead to situations when laboratory staff might not be aware of higher biosafety risks and therefore could unintentionally expose themselves to dangerous pathogens. Infection might be diagnosed too late and spread from laboratory staff to other persons outside the laboratory. Deliberately infecting oneself with a novel, chimeric virus poses a severe health risk to the researcher, other laboratory staff, and members of the community.

152. *Biosecurity and dual-use research*: Engineering a virus to give it the new ability to infect a new host species is a gain-of-function experiment and an experiment of concern. Monkeypox virus is considered a potential security risk by several countries, including Australia, Canada, and the United States, which regulate access to this pathogen. In addition, export of the virus is regulated by the Australia Group, an informal forum of 43 countries that harmonize their export controls to prevent the proliferation of chemical and biological weapons.

153. The monkeypox virus genome is also covered by the International Gene Synthesis Consortium IGSC's Harmonized Screening Protocol developed by gene synthesis companies and that requires sequence provider members to screen sequence orders and ensure that customers have a legitimate need for the synthetic DNA. In 2022, 20% of gene synthesis providers around the world are not members of the consortium[1] and are not required by their countries to conduct this screening. This makes it possible for individuals or groups to order synthetic DNA fragments and potentially use it to create dangerous pathogens.

[1] Home | International Gene Synthesis Consortium

This scenario highlights the following questions for selected stakeholders (other questions and stakeholders may also arise).

154. Student scientist D

a. Should this experiment be conducted or are there safer ways of addressing the research aims?
b. What biosafety and biosecurity information does one need to know to be qualified to do such an experiment in a laboratory?
c. Whose permission is needed to order the DNA fragments?
d. How should materials be stored for future use?
e. Is this work being done safely?
f. Are there biosafety or security risks associated with this work?
g. What are the future potential consequences of creating chimeric poxviruses?

155. The supervisor scientist E

a. Should this experiment be conducted or are there safer ways of addressing the research aims?
b. What are the people in the laboratory doing and why?
c. What biosafety and biosecurity information do students need to know to be qualified to do such experiments in the laboratory?
d. What are the future potential consequences of creating chimeric poxviruses? What is the potential for misuse or accidental release from this work?
e. Is work being done safely (e. g. technical and personal protective equipment sufficient and up to date), in line with approved protocols from the institutional review board?
f. Has the risk assessment been done by someone with sufficient expertise (professional experience and/or training)?
g. Who has access to materials in the laboratory and can people access materials without the supervisor scientist E's permission or knowledge?
h. Who can order materials and can ordering occur without Dr. Kebede's permission or knowledge?
i. To whom should supervisor scientist E report safety and security concerns?
j. Is all research following institutional guidelines as well as local and national guidelines and legislation?

156. Student scientist F

a. Should this work be done?
b. What biosafety and biosecurity information does one need to know to be qualified to do such an experiment in a laboratory?

c. Whose permission is needed before ordering DNA fragments or reusing old constructs?
d. Whose permission is needed to access monkeypox, a pathogen with a higher biosafety level?
e. Are there biosafety or security risks associated with this work?
f. What are the future potential consequences of creating chimeric poxviruses?
g. What are the risks of infecting oneself with a novel virus? Could this start an outbreak?

157. Other laboratory members

a. Does the research that students scientists D and F are working on match what they say they are working on in lab meetings or when talking to others?
b. Are all laboratory animals and virus stocks accounted for as expected?
c. If student scientist F's unauthorized orders of genes, creation of chimeric viruses, and experiments with animals and himself were discovered by another member of the laboratory, would they know whom to report this behaviour to and be willing to do so?

158. Biosafety officer of the institution

a. Do the principal investigator and the staff (including students) show a sufficiently high level of biosafety and biosecurity awareness and commitment to following established biosafety and biosecurity guidelines?
b. Have the principal investigator and the staff (including students) received sufficient biosafety and biosecurity training?
c. Have there been biosafety-relevant changes in experiments run in the institution since the last time which might change the outcome of risk assessments and even lead to classification of the experiments to higher biosafety levels?
d. As a consequence of changed risk assessments, is the technical and personal protective equipment sufficient for the protection of the laboratory staff?
e. Are there rules regulating access to restricted pathogens or laboratories and animal units with higher levels of biosafety? What policies and procedures are in place to ensure compliance with these rules?
f. Are there rules governing who can order potentially dangerous gene sequences?

159. University of Alias administration

a. Is research being done safely and securely?
b. Is all research following institutional guidelines as well as local and national guidelines and legislation?
c. Has the laboratory worked with the biosafety officer and has that interaction been sufficient to assess and mitigate risks?

d. Are there rules in place about only allowing staff to place orders with vendors that are members of relevant groups, like IGSC, or that have signed onto a code of conduct?

160. de novo synthesis company

a. Who is ordering these fragments?
b. Does the individual and institution ordering the synthetic DNA have a legitimate need and the means to handle safely?
c. Do these fragments pose a biosecurity risk?
d. How could these fragments be misused by the purchaser?
e. What appropriate permissions should be sought before dispatching the order?

This scenario highlights the following values and principles (other values and principles may also arise).

161. *Responsible stewardship of science*: The responsible stewardship of sciences highlights the importance of basic and applied research in the life sciences being conducted in a rigorous and evidence-based manner for the betterment of humans, the planet's biodiversity, ecosystems, and environments. In addition, responsible researchers are expected to identify, manage, and mitigate reasonably foreseeable potentially harmful consequences of their research through a multidisciplinary review process. Researchers are also expected to exercise caution in the planning and pursuit of their research and utilize appropriate biosafety and biosecurity measures to minimize risks to health, safety, and security.

162. *Integrity*: Researchers are also expected to conduct their work with integrity which includes conducting their work in accordance with local and national biosafety and biosecurity rules and regulations. Self-experimentation without proper oversight is unsafe and potentially unethical, especially if it creates risks for other individuals. In addition, the results of such an experiment are of limited scientific utility due to methodological constraints. Finally, researchers are expected to report possible illegal, unethical, or unsafe behaviour by their colleagues to relevant institutional, national, regional, and/or international authorities

Discussion

163. In this scenario, the biosafety and biosecurity risks extreme. There are several potential points of intervention that could have created a more safe and secure laboratory. Student scientist D started her research with good intentions, but a subsequent student misused her work. The supervisor scientist E and the biosafety officer should have had many conversations with student scientist F before she got to the point of successfully creating the chimeric viruses, during any of which they should

have discussed the potential biosecurity and biosafety risks of this work and decided whether to allow the research to take place. Other people working in the laboratory were well positioned to notice inappropriate behavior or activities from student scientist F, and if they were properly trained and supported by the institution, they should have been capable and empowered to intervene. The DNA synthesis company should have been screening orders, ensuring supervisor scientist E had approved of each individual order, and keeping records of what had previously been ordered from the supervisor scientist E's laboratory.

164. Supervisor scientist E does not seem to have educated her students sufficiently on biosafety and biosecurity risks, and awareness of these issues is low. For student scientist F, access to animal experiments, dangerous infectious agents and genetic material has been made too easy, and she has not been sufficiently supervised. There is no access control for student scientist F while retrieving student scientist D's constructs and there seems to be no requirement for institutional review board approval for this new experimentation. Also, supervisor scientist E does not seem to keep track of who is working with the more dangerous pathogens in her laboratory and has not established rules on who has access to monkeypox virus. The institution's biosafety officer should have trained supervisor scientist E and her students on biosafety issues and raised awareness on these topics. In combination, the lack of awareness and training and the insufficiently regulated access to restricted material leads to a situation where persons both inside and outside the laboratory might become infected with a highly pathogenic chimeric virus that could cause an outbreak in the community.

165. This situation might have been prevented if the gene synthesis company providing the monkeypox genetic material had checked with the institution before filling the order of restricted genetic material by an individual who might not have a legitimate interest in obtaining that genetic material.

This scenario highlights the following priority actions, tools and mechanisms for selected stakeholders to be considered (other actions, tools and mechanisms and stakeholders may also arise).

166. This scenario highlights the importance of having principal investigators (PI), students, and staff aware of key biosafety and biosecurity issues, being familiar with the relevant local and national biosafety and biosecurity legislations, regulations and guidelines and being able to identify biosafety and biosecurity issues relevant to their own work (e.g., what are critical biosafety aspects of the work done in the laboratory like transmission routes or host ranges of infectious agents handled and what can result from genetic modification?). To enable this, the principal investigator, students, and staff need to be sufficiently educated regarding biosafety and biosecurity legislations, regulations, guidelines and norms. This education should be provided before the research commences and be updated in regular intervals, e.g., at least once a year.

167. Principal investigator

a. Enable and encourage students and staff to consider biosafety questions themselves and create an open atmosphere, encouraging them to discuss with the PI.
b. Be a “biorisk management role model” by following general rules such as the Good Microbiology Laboratory Practice.
c. Keep in contact with students and staff and be up-to-date on experiments running in their laboratory.

168. Institutions

a. Employ or assign biosafety officers who are responsible for oversight of experiments running in the respective institutions. They should be sufficiently educated on biosafety and biosecurity matters in order to identify, manage, and mitigate research that may pose health, safety, and/or security risks. Biosafety officers should strive to create an open culture that encourages raising awareness and facilitating exchanges on biosafety and biosecurity questions. They should also conduct regular inspections, review, audit of laboratories with the aim of ensuring that both institutional and national regulations are followed, including controls of stocks of microorganisms.
b. Establish rules governing who has the right to order genetic materials and who has the right to access agents that pose potential health, safety, or security risks. The right to order certain materials and/or access certain stocks of pathogens should be limited to a defined circle of persons with a clear process for granting and recording access to these materials, ordered at least sporadically.

169. Gene synthesis providers

a. Follow established gene sequence and customer screening protocols. Orders containing regulated pathogens should only be fulfilled if a legitimate interest can be substantiated to the company by the institution ordering it and if the institution provides evidence of the necessary permits for working with the pathogen. The signature of the principal investigator and/or an institutional authority might be required for each order of gene sequences coding for select agents/toxins.
b. Gene synthesis companies belonging to the International Gene Synthesis Consortium adhere to a code of conduct which obliges them to perform both gene sequence and customer screening. Oligonucleotides with sequences from an organism on a list of regulated pathogens are only delivered to the customer if additional customer checks are fulfilled. However, not all companies are

members of the consortium, creating a gap in biosecurity. National legislations and policies could fill this gap.

170. National governments

a. Take steps to minimize biorisks of advancing biotechnologies. Risks related to DNA synthesis can be mitigated legislatively through adopting laws requiring adequate screening of the sequences ordered and the people placing the order.

Box A1.1: Examples of biorisk governance measures in Germany

It is instructive to look to countries that have governance measures in place to address these types of issues. For example, in Germany, every institution performing genetic engineering operations is required to employ or assign biosafety officers who need to participate in mandatory training courses. Access to laboratories working with infectious agents (biosafety levels 2 - 4) is restricted to authorized personnel. Laboratory staff working with recombinant organisms must first receive education from the principal investigator on biosafety issues related to the work. Principal investigators themselves are required by law to attend a training course covering risk assessment of genetic engineering operations and related legal requirements before taking up genetic engineering operations. They are personally liable for following national legislation and can be fined for transgressions. Genetic engineering operations with pathogens (as either donor or recipient organisms) need to be authorized by local authorities who are required to consult a national expert body consisting of honorary experts (the ZKBS) on questions of biosafety. Any experiment of BSL 3 or higher must not start before receiving official authorization by local authorities. Experiments are only allowed to be performed in laboratories matching the organism's BSL, and records on any experiment leading to the creation of GMOs need to be kept by the principal investigator. Local authorities are regularly controlling laboratories and institutions (frequency depending on the BSL) and are checking biosafety measures, records and stocks.

Even if this is not required by law in other countries, scientists should be interested and act responsibly in this regard on their own and in the interests of the students and staff working in their laboratory. It is legally required by European law to regularly update risk assessments of genetic engineering operations.

Scenario 4. Mutational scanning

171. This scenario highlights the roles of journals and funders to contribute to mitigating biorisks and the unique positions of private institutions.

Situation

172. Researcher G is working at a private company on treatments for infectious diseases. Researcher G is passionate about doing research that could lead to finding better treatments for patients. In particular, he is trying to understand how quickly mutations can arise that allow a pathogen to avoid existing antibodies against the pathogen, which make antibody-based treatments ineffective. To conduct this research, Researcher G does deep mutational scanning (DMS) to evaluate possible point mutations in the pathogen genome and determine which mutations may enable the pathogen to evade antibodies. To conduct this research, Researcher G makes a library of variants of the pathogen and passages those variants with a selection pressure, usually the antibody treatment, to find the variants that continue to replicate despite the presence of the antibody. Following passaging, the pathogen libraries are sent for genetic sequencing and key mutations, or combinations of mutations, that may contribute to evading antibodies are identified.

173. Following identification of these mutations, Researcher G sends results to his collaborator, Researcher H, who is a protein engineer based at a government research institution in another country. Researcher H uses Researcher G's DMS data to computationally design new antibodies that are then synthesized and tested for therapeutic usage. Both researchers wish to publish the unique pipeline and methodology they have created for an emerging pathogen, and they write up their results and methods in a manuscript and submit it for publication to a scientific journal. One of the reviewers who received their submission has concerns that the level of information they are sharing could be misused by someone wishing to create a drug that inhibits efficacy of existing broad-spectrum antivirals used to treat patients.

This scenario highlights the following risks (other risks may also arise).

174. *Biosafety*: This scenario presents biosafety risks that stem from creating variants for which existing treatments are not effective. The risk that such variants might be accidentally released is a biosafety risk. The level of risk depends on how transmissible and virulent each variant is and whether there are effective countermeasures available.

175. *Biosecurity and dual-use research*: There are multiple biosecurity risks. The risks of misuse should be divided into risks stemming from the information generated by this research (and that might be published), risks stemming from the methods described,

and risks stemming from the products created. In terms of the informational risks stemming from this research if published (or that one would somehow acquire the knowledge it generated), there is the risk that the mutational information can be misused to create variants for which treatment is not yet widely available. Another risk is that the information about which mutations are likely to arise and the antibody treatment that might address them could be misused to create drugs that harm these potential treatments.

176. The second type of risks stem from the methodology published. This methodology could be misused by malevolent actors to create pathogens that evade existing treatments. If the pipeline created by this research is easy to replicate it might be misused to create similar pipelines for other pathogens. Finally, the variants created by this research might be misused if malevolent actors were to access them.

177. All of these risks need to be thoroughly assessed to determine whether they should be a source of concern or can be sufficiently mitigated or tolerated because they are risks of very low likelihood.

This scenario highlights the following questions for selected stakeholders (other questions and stakeholders may also arise).

178. Manuscript reviewer

a. Could the manuscript as written plausibly be used as instructions for how to do harm by a malicious actor?
b. Who should be informed about the risks presented by the paper and how should that be done?

179. Journal editor

a. How should we assess the risks of this paper?
b. Are the risks serious enough to merit a special review? How should we determine that? (How easy or difficult it is to misuse the information in the paper? Are there actors who have shown intentions to misuse such info? Are the benefits large enough to offset the risks?)
c. Who can we ask to review this paper and assess the potential risk of sharing this information through publication? Who are the experts on such topics (science and biosecurity)?
d. How could we publish this paper but minimize the potential risk? (Should the publication be delayed to put into place a risk mitigation plan?)
e. Can we publish results but only include a vague methodology? Redacted?

180. Private institutions

a. How should we vet collaborations and ensure appropriate oversight is not slipping through the cracks due to miscommunication?
b. How should we monitor and react to collaborations when a project begins to show signs of dual-use research potential?

181. Funders

a. Have we provided a careful level of oversight to this public-private partnership to reduce biosafety, biosecurity, and dual-use research risks?
b. Was there a procedure built into the application for funding to assess the proposal for potential biorisks?
c. Should we require that certain biorisk mitigation strategies (including biosafety measures) be implemented?

This scenario highlights the following values and principles (other values and principles may also arise).

182. *Responsible stewardship of science*: Journals and publishers, public and private institutions, and funders all have the responsibility to be sound stewards of science. Each entity should actively participate in and promote biorisk management.

183. *Fairness*: Journals and publishers, public and private institutions, and funders should have mechanisms built into their processes to ensure fair outcomes from their work. Journals and publishers should have protections in place for reviewers who report biosecurity or dual-use research concerns in a manuscript they are reviewing. Institutions, regardless of if they are private or public, should have whistleblower protections and foster an environment that allows staff to question if work already in progress has become unsafe or a potential biosecurity threat. Staff that raise biosecurity concerns about their work or others' work should not be punished and such action should be encouraged. Funders should not penalize groups that have previously halted research due to safety or security concerns or groups that require more money to adequately implement safety and security measures.

Discussion

184. Journals and publishers, funders, and private institutions are often overlooked in biorisk management discussions despite having vital roles to play. Funders and publishers are uniquely positioned to intervene before a project begins and before potentially risky information is widely disseminated.

185. In some countries, national policies concerning biorisk management may not apply to private institutions or may only apply to work funded by specific funders. In such cases, it is vital that private institutions, other funders, and publishers are proactive in reviewing proposals or work for safety and security risks.

This scenario highlights the following priority actions, tools and mechanisms for selected stakeholders to be considered (other actions, tools and mechanisms and stakeholders may also arise).

186. Journal editors

a. Responsible for what they publish.
b. With the peer reviewers of manuscripts, consider how the paper submissions they work with are contributing to broader society, including considering the current and future biorisks that may arise from the paper.
c. Identify experts (in house or external) for reviews and questions as needed.
d. Determine if a manuscript submitted may need further review.
e. Have clear policies in place that lay out the steps to screen papers for biosecurity risks and a protocol on how to assess them and determine the best approach (full publication, delayed publication, publication with accompanying opinion papers). The first step for determining whether a paper has biosecurity risks depends on journal editors as well as reviewers' awareness of biosecurity risks and their ability to flag them for further assessment. The same applies to the institutions and funders. The process of awareness raising and education is ongoing and complex. Yet it is necessary if the risks of misuse are to be addressed. Further tools are needed in order to enable journal editors (and the experts they would solicit) conduct a proper risk- benefit analysis. In other words, after flagging a paper for appearing risky, a comprehensive review should be conducted, following a publication strategy informed by the assessment.

187. Funders

a. Assess proposals for biorisks and rely on external expert review and advice in this area.
b. Assess how proposed work may be used and any relevant history of the field of study.
c. Identify options to require stronger biorisk mitigation measures.
d. Consider potential biosecurity and dual-use research risks when assessing proposals. Even if the funding agency (or private funder) is unable to conduct a thorough risk assessment themselves, they should be capable of noting there may be a concern and know who to ask for further review.

188. Public and private research institutions

a. Be aware of all work being done in their facility and collaborations.
b. Help their researchers screen potential collaborators as needed and consider any additional biosafety or biosecurity risks that may arise from the collaboration. Institutions must ensure that all work is adequately reviewed for biorisks; at least

one institution involved in the collaboration should review the risk assessment and risk mitigation strategy.

c. Identify the biorisks associated with research. Institutions should have in-house staff capable of conducting risk assessments with the research team and have a review board capable of reviewing the risk assessment and risk mitigation plans for biosafety, biosecurity, and dual-use potential as appropriate.

189. National governments

a. Assess possible existing gaps in coverage of biosafety, biosecurity, or dual-use research policies. If such policies exist at all, national legislation should be used to address such gaps. National legislation that applies to all research or work in the life sciences, not just publicly funded research, can strengthen the biorisk management framework in the country. When combined with other measures implemented at other stages, such legislation can create a robust biorisk management framework.

Scenario 5. Mobile public health laboratory

190. This scenario highlights the biorisks associated with field collection of biological samples, sample transport, and public health outbreak response activities.

Situation

191. Mobile laboratory Director Z oversees setting up several mobile labs that could quickly move into an area when an outbreak of a newly emerging disease occurs. These mobile labs will be responsible for contributing to the creation of diagnostic tests and initial characterization of the pathogen, as well as conducting diagnostic testing and molecular surveillance. Additionally, the staff of these labs will help collect and process environmental and wild animal samples to assess zoonotic potential and potential spillover events. Part of mobile laboratory Director Z's job is developing safety and security protocols for these mobile labs and creating trainings for a pool of people who may be called upon to deploy with these labs with little advanced warning. Mobile laboratory Director Z knows the people who will be tasked with staffing these labs have experience working in diagnostic laboratories or working in research laboratories in their day-to-day jobs, but the mobile laboratory director Z is concerned that they may not have experience working with a potentially high consequence pathogen daily. Mobile laboratory Director Z is also concerned that potential staff will not be familiar with the potential security risks associated with working with novel and/or high consequence pathogens. Mobile laboratory Director Z must ensure the mobile labs are using appropriate security systems and following all applicable laws, regulations, and guidelines for the very different locations where the lab will be deployed and sending samples to other labs in line with export control laws.

This scenario highlights the following risks (other risks may also arise).

192. *Biosafety*: One of the key activities the mobile lab in the scenario will participate in is field collection of environmental or animal samples. Such activities often have enhanced biosafety risks compared to laboratory-based activities as there are fewer engineering controls available in the field. Staff will have to rely more heavily on PPE and best practices than they would in a laboratory to maintain a safe environment. Sampling from wild animals in the field is a particularly high-risk activity that will require extensive prior training and biosafety protocols.

193. Working with novel pathogens or samples of unknown origin may have a higher risk than working in research laboratories; samples may contain unknown or uncharacterized agents. Similarly, staff may be exposed to an unknown agent in the field. All staff of the mobile labs will need extensive training in how to handle samples at higher levels of containment than they may need in their normal jobs. Protocols should

include advanced safety measures for samples that may unknowingly contain an infectious agent with altered transmission pathways or risk level than the agent expected to be in the sample.

194. *Biosecurity*: Mobile laboratories may be temporarily located in locations with security risks, such as civil unrest. Additionally, such laboratories may be targeted by individuals or groups if the situation becomes politicized. The mobile laboratories will need strong security measures to keep staff, samples, equipment, reagents, and information safe from potential theft or harm. While people and samples are being transported to the mobile laboratory from the field, or from the mobile laboratory to other facilities in the public health system, they are extremely vulnerable to potential threats and adequate planning and coordination will be necessary to allow safe and secure transportation.

195. Information generated from these mobile laboratories will be critical for responding to a public health threat. Protocols for sharing the information must be implemented to ensure privacy of people in the community, the correct people receive the information, and sensitive information is not prematurely released to entities who may wish to misuse or discredit it.

This scenario highlights the following questions for selected stakeholders (other questions and stakeholders may also arise).

196. Mobile laboratory director

a. Where can the mobile laboratory director recruit personnel with sufficient biosafety expertise and build a global network of people ready to step in in case of an emergency?
b. What lessons can be learned from outbreaks and outbreak responses in the past?
c. How will information, samples, and people be protected and secured in the mobile lab, field, and transport?

197. Public health and health system laboratories and institutions

a. What training should be provided to staff as part of their regular duties in preparation for potential deployment to the mobile laboratory?
b. What capacity do these institutions have to support the mobile laboratory?
c. What systems are in place to share reagents, tools, information, and samples safely and securely between this facility and the mobile facility?
d. Is there a national or international standard for safely collecting samples from wild animals and transporting them to the mobile laboratory?

e. How do national or international biosafety standards designed for laboratories in buildings need to be modified for unique challenges posed by the design, construction, and operation of mobile laboratories?
f. Is there a protocol in place to ensure secure communication and sample transportation between mobile labs and other entities in the public health system?
g. Is there a surveillance system in place to monitor field collection and laboratory staff for potential exposures to pathogens collected in the field or when working in the mobile laboratory?

198. Local, regional, national governments

a. What guidelines are in place to direct the development of safety and security protocols?
b. Who has jurisdiction of the lab, and ownership and responsibility for samples, at different times?
c. How should samples be stored, transported, and shared?

This scenario highlights the following values and principles (other values and principles may also arise).

199. *Inclusiveness and collaboration*: Processes must be in place to ensure that relevant authorities are consulted before a laboratory is moved into their jurisdiction. Moreover, as information generated by mobile laboratories are likely to be relevant to local, national and international stakeholders, equitable dissemination of and access to the information to all relevant partners is important. As these laboratories are designed to move from location to location, there must be consideration of varying cultural and social context at each location to which the laboratories is moved. Different collection procedures or reporting practices may be needed with location and the organizers of the laboratory must be flexible in implementing changes and adapting protocols, without compromising safety and security.

Discussion

200. Research is often the primary activity considered when discussing biorisk management. However, public health, medical and veterinary clinics and laboratories also conduct work with biological samples that require practitioners to consider biosafety, biosecurity, and dual-use potential.

201. One of the most high-risk activities in the life sciences from a safety perspective is field work, especially with wild animals. There are often many opportunities to unknowingly be infected by an unidentified agent. Similarly, transportation is often one of the most vulnerable stages in a sample's lifecycle; transportation is one of the hardest

times to secure materials. Such safety and security concerns are only amplified in emergency situations, such as during an outbreak.

This scenario highlights the following priority actions, tools and mechanisms for selected stakeholders to be considered (other actions, tools and mechanisms and stakeholders may also arise).

202. Mobile laboratory director

a. Responsible for coordinating the development of processes and overseeing implementation and training in the mobile labs.
b. Establish an advisory group consisting of individuals from the countries the mobile laboratories may be deployed in, including people who have experience developing mobile labs in other countries, members of the public health systems the mobile labs will collaborate with, and people with experience and expertise in conducting fieldwork and research with highly pathogenic organisms.
c. Responsible for finding personnel to potentially staff the mobile laboratories.
d. Coordinate with public health and research institutions to find potential personnel who may be called upon to staff the laboratories s as needed.

203. Public health, medical laboratories and other institutions

a. Coordinate with mobile laboratory director to assess risks and capacity.
b. Use their biorisk management experts and resources to help develop protocols for the mobile laboratories. They may also run protocols and plans through their own review boards to ensure it meets standards.
c. Identify how the mobile laboratories will communicate and fit into the larger public health system and consider how to do so safely, securely, and equitably. The public health systems should build their capacity to support biorisk management, both in case the need arises to deploy the mobile laboratories but also in their day-to-day activities.
d. Provide to all staff biosafety and biosecurity training. Additionally, such staff should be made aware of the how expectations may differ between normal activities and emergency situations. Special care should be taken to ensure that even during chaotic emergencies, protocols are in place to uphold biosafety and biosecurity.

204. National governments

a. Identify rules in place to govern security of information and samples, especially during transportation.

b. Coordinate with one another and international agencies to ensure the mobile laboratories are meeting their public health needs while following best practices for safety and security.
c. Have clear guidelines and policies governing how the mobile laboratories should operate in their country, including regarding how to conduct their field collection and laboratory work safely and securely. Rules for hazardous waste disposal and transportation of samples, information, and waste should be explicit.
d. Ensure that any existing legislation for biorisk management is written in such a way that public health and medical laboratories, including mobile laboratories, are included in relevant requirements. Guidelines put out by OIE can be an enormously helpful resource to countries in planning for the appropriate and safe deployment of mobile labs related to the collection of wild animal samples.

Scenario 6. Gene drive

205. This scenario focuses on responsibilities towards public empowerment, environmental stewardship, and intergenerational justice with an emerging technology that has the potential to spread freely in the environment if released.

Situation

206. Scientist Y is an ecologist concerned about the expanding range of black rats, an invasive species. Scientist Y is interested in developing a gene drive to control the black rat population. She has designed a gene drive system which would theoretically eliminate 98% of black rats in a given population within 3 years. Scientist Y has modeled the gene drive and conducted preliminary studies to assess which genes should be targeted by the drive but has not yet constructed the full gene drive cassette. After reading an article about the severe problems the black rat is causing in another country, Scientist Y decides to begin planning for her gene drive to be released in that country and set up a secondary laboratory in that country. Eventually, Scientist Y is ready to create the full gene drive cassette and test it in black rats in her secondary laboratory. Scientist Y is unsure what approvals are needed and from whom before she can conduct this experiment, so Scientist Y reaches out to the national authority responsible for managing invasive species in the country where his primary laboratory is located. Officials in the agency are unsure what their responsibilities are regarding Scientist Y's proposal and are unable to tell her who else she must contact before the gene drive can be tested.

This scenario highlights the following risks (other risks may also arise).

207. *Biosafety*: Appropriate biosafety and animal husbandry measures must be in place for experiments in animals or insects as this work is often higher risk than cell culture work. Such measures are especially critical if field testing begins, as the field test is a less controlled environment than the lab.

208. *Biosecurity*: If a gene drive is eventually released, depending on its design, it may be able to self-propagate through the environment. The impacts on the host species, ecosystem, and environment may not be predictable and could be severe. Such impacts may last for several generations. Additionally, it will be difficult, if not impossible, to control how far the gene drive spreads in the wild or to stop it once it has been released. Recalling a gene drive post release will likely not be effective. There is significant uncertainty related to potential consequences and the severity of such consequences for gene drives and similar technologies.

This scenario highlights the following questions for selected stakeholders (other questions and stakeholders may also arise).

209. Scientist Y

a. How are the risks of the gene drives most appropriately assessed? For example, are there species in the same habitat possibly crossing with the gene drive rat, possibly creating unintentional spreading of the gene drive? Are there ecological webs in which the black rat may have a role?
b. Is the region intended for the intentional release suitable? (e. g. a region with a very limited exchange between different populations (small island) would be desirable to limit the spread of recombinant animals)
c. Is the gene drive stable and if not, what is the effect on possible offspring?
d. How are genetically modified rats in the laboratory prevented from escaping?

210. Governments

a. How are the risks of the gene drives most appropriately assessed?
b. What regulations or guidelines are needed to ensure the work is done safely and securely – both in the laboratory (controlled environment) and eventually at any release sites?
c. Are export controls needed on the technology?
d. What agreements are needed between the government of the researchers, the government of the country where the gene drive will be released, and governments of other countrieswho may be impacted?

211. The publics

a. Is there publicly available information about the research and potential impacts?
b. Are there options for members of the public to voice concerns, debate and potentially block the release of this gene drive?
c. What assurances are in place to keep the gene drive from being spread before it is approved to do so, while research is occurring?
d. Who will be responsible for responding to potential consequences of the gene drive once it is release and funding any required remediation?
e. Who is liable for any unintentional consequences that may occur?
f. Have other, less risky methods to control this invasive species been attempted?
g. How could release of this gene drive affect Indigenous populations and have they been consulted?

This scenario highlights the following values and principles (other values and principles may also arise).

212. *Intergenerational justice*: When considering technologies with the ability to alter ecosystems, intergenerational justice is particularly important to consider when assessing risks and conducting work. The health, safety and security of humans,

nonhuman animals and the environment for future generations is of particular concern with these technologies that have extensive unknown risks towards the environment and ecology.

213. *Public empowerment*: The public is a stakeholder in all life science research. However, as gene drives and related technologies have vast potential to spread in the wild and uncontained to a single facility, the public is a critical stakeholder in such work. It is the responsibility of scientists, funders, institutions, and countries to ensure the public is empowered to respond to such work. Furthermore, scientists, funders, regulators, and institutions have the responsibility to educate the public about the potential benefits and harms, limitations, and capabilities of all basic and applied life sciences, especially for self-propagating genetically engineered agents, in ways that balance competing influences and demands. All involved must exhibit respect for communities, including indigenous populations.

Discussion

214. Gene drives and other technologies designed to have self-sustained spread in a population are of particular concern to public and environmental health both now and in the future. As such technologies are relatively new, there are significant unknowns related to potential consequences of such technologies if they are released into the wild. Due to the potential environmental and ecological impacts in the near or far term, special attention must be paid to safely and securely conducting such work. The Cartagena Protocol on Biosafety to the Convention on Biological Diversity includes provisions for gene drives and similar technologies. However, not all countries are signatories to the Convention or Protocol, creating substantial gaps in oversight for gene drive and similar technologies in those countries. As a gene drive could spread across national borders, the lack of policies and oversight in some countries is a risk to all countries.

This scenario highlights the following priority actions, tools and mechanisms for selected stakeholders to be considered (other actions, tools and mechanisms and stakeholders may also arise).

215. Scientists

a. Carefully assess risks and harms. They should consider the real needs and the social value of the research proposed/ the environmental impact/ and a cautious way of proceeding (first in the laboratories, then the release of rats should be in controlled habitats, etc…).
b. Undertake a community consultation and provide understandable information to any member of the public.

c. Inform the local government and seek adequate authorizations early in the process (e.g. before setting up the satellite laboratory).
d. Be educated in biosafety and biosecurity and ecological impact on the ecosystem.

216. Governments

a. Have oversight mechanisms, with regular checks, in place.
b. Monitor and consider the assurances the researcher and funding agency or institution has as well as ask mechanisms to ensure there is funding for remediation or possible problems.
c. Create regulations concerning GMOs, of which an organism carrying a gene drive would cover. However, gene drives have risks that other GMOs do not. National legislation should include special provisions for gene drives and similar technologies specifically.
d. Have an oversight system (ideally linked to a global framework such as the Cartagena Protocol on Biosafety to the Convention on Biological Diversity). Depending on how well a country has regulated the field of GMOs and if it has ratified the Cartagena Protocol on Biosafety, information on applicable regulations including transboundary movements of GMO can be accessed via the country's profile in the biosafety clearing house (https://bch.cbd.int), which is an online platform for exchanging information on living modified organisms (equivalent to GMOs) and a tool for facilitating the implementation of the Cartagena Protocol on Biosafety. For countries that are not signatories to Cartagena, the option to implement their own registry and regulations to govern such technologies is to be considered.
e. Conduct a thorough and respectful community consultation prior to any release of the gene drive. Communities should be consulted before any field trials or full releases of GMOs.
f. Caution should be taken in using procedures that are not accepted in more regulated and controlled countries to others where such controls are weak or inexistent. Agreements and a system of oversight should be in place before proceeding with this kind of research. It is the responsibility and liability of the researcher, funding agencies, and institutions developing these procedures that should be clear from the start.

217. Institutions and funding agencies

a. Require education and training of all scientists involved in gene drive research covering potential ecological risks.

Scenario 7. International collaboration on high consequence pathogens research

218. This scenario underscores issues associated with research on high consequence pathogens and international collaboration between countries that do not have the same policies on biorisk management.

Situation

219. Two research teams, Team W and Team X, are interested in studying the evolutionary potential of a recently emerged subtype of influenza virus. The research they are interested in conducting is considered dual-use research because it could result in the creation of a more transmissible, virulent, infectious, and/or pathogenic strain of influenza. Team W is based in Country A, where there are dual-use research guidelines that require a risk assessment in advance of the research as well as strict monitoring and reporting requirements about the experiments. Team X is based in Country B, where there are few rules specifically aimed at reducing biorisks associated with dual-use life science research.

220. Team W and Team X decide to collaborate on research studying the evolution of influenza. Team W has viral stocks and experience conducting similar research on other viruses that are not covered by the dual-use research policies of Country A. Team X has worked with other subtypes of influenza in the past, but only to study immune response to the virus.

221. Together, the two teams develop a strategy to study potential evolutionary pathways of the viruses. The planned experiments will include passaging the virus in different environments to understand the impacts of different selection pressures, genetically modifying stock viruses with mutations that increase or decrease transmissibility and/or pathogenicity in other influenza subtypes, and infecting animal models with the different viruses created via passaging or direct genetic modification to assess differences in pathogenicity and transmissibility in vivo.

222. Team W conducts the *in vitro* work in their lab in Country A, which has fewer reporting requirements than *in vivo* work under Country A's dual-use of concern guidelines. Once they have generated the mutated viruses, they send the viruses to Team X in Country B. Team X conducts the *in vivo* studies in their lab without needing to report any specifics of the research to Country B authorities.

223. Over the course of their work, the collaborating researchers find that they have created new strains of influenza that are more pathogenic than the original strain. They characterize the enhanced pathology and improved fitness of these strains in the Team X laboratory. When the research teams go to publish their findings in a top-tier journal,

they are surprised to receive an email from the journal editor saying their research has been flagged as a biosecurity concern that will require extra review.

This scenario highlights the following risks (other risks may also arise).

224. *Biosafety*: Recently emerged influenza strains are often considered high consequence pathogens due to the potential for influenza to jump between species, high transmissibility, and differing levels of pathogenicity. The host range of newly emerged pathogens may be unknown, so extra precautions must be taken to minimize the risk of the agent accidentally infecting a wild animal or instigating an outbreak in humans via a laboratory source.

225. *Biosecurity*: Transporting samples of infectious diseases, especially across national borders, can increase the risk of theft. Export control regulations must be followed. In the course of their work, the teams have created new strains of influenza that are more pathogenic than the strains occurring in the wild. Neither Country A nor Country B is aware of these developments.

226. *Dual-use research*: Information learned during studies evaluating the evolution of viruses may include information that could be misused to genetically engineer a strain of virus that can evade existing therapeutics or prophylactics. Differences in regulations between the two countries can lead to confusion and gaps in oversight. In this case, neither the governments of Country A nor Country B may be aware of the work being conducted by the collaborators once the samples are in Country B.

This scenario highlights the following questions for selected stakeholders (other questions and stakeholders may also arise).

227. Members of Teams W and X

    a. What are the potential benefits of this research and what are the risks?
    b. Was a risk assessment done and do the benefits outweigh the risks?
    c. What changes could our experiments cause to the virus?
        i. How will we monitor these changes?
    d. What will we do if we identify new strains that are more transmissible, virulent, pathogenic, or infectious?
    e. To whom do we report the creation of a more transmissible, virulent, pathogenic, or infectious agent?
    f. Is it ethical to look for a location with fewer guidelines to conduct research of concern?
    g. Are all team members sufficiently trained to conduct the research safely?

228. Institutions

a. Is the research conducted at this institution and by the staff of this institution being done ethically and in accordance with any relevant international, national, and/or local governance measures?

229. Countries A and B

a. What research is being done in this country?
b. Are there gaps in oversight of biological research in this country?
c. Is potentially dangerous research being exported to other countries with different rules for oversight?

This scenario highlights the following values and principles (other values and principles may also arise).

230. *Responsible stewardship of science*: Life science research should be undertaken with appropriate biosafety and biosecurity measures to promote health and the betterment of humans, biodiversity, ecosystems, and environments. Before work with agents that could pose a threat to any of the entities above is started, it is imperative that risks associated with the work and any mitigation strategies be identified and assessed to determine if the risks are proportionate to potential benefits.

231. *Inclusiveness and collaboration*: Risk assessments and appropriate biosafety and biosecurity practices should be adopted regardless of the country where work is occurring; the same biosafety and biosecurity practices used in Country A should be applied in Country B if the risk of the work being done in both countries is equivalent. The phase of work being completed in Country B is the *in vivo* phase, and animal work typically has higher risks associated with it than cell culture work. Team W and Team X should be increasing or strengthening their biosafety and biosecurity protocols for the phase of work in Country B, even if Country B does not require such efforts to be made.

Discussion

232. Research with infectious diseases, especially high consequence infectious diseases, is vital for preparedness and response to public health threats. However, care must be taken to conduct the research responsibly and minimize the potential for harm. One area of great concern is the potential to generate new strains or variants of a pathogen in the laboratory that is more transmissible, virulent, infective, and/or pathogenic than strains or variants occurring naturally. Even routine experiments can generate altered strains, variants, or viral populations. While most of the new strains, variants, or populations will have little, if any, quantifiable changes from the original sample, there is the potential that the new samples could exhibit a higher risk to the human, animal, or environmental health. Researchers must be cognizant of the potential changes their

experiments could be causing and adequately address the risks their experiments may pose in their risk assessments.

233. In their work, Team W and Team X created strains of influenza that were more pathogenic than their original influenza stocks. Such research can be useful to understanding evolutionary pathways of viruses, which can inform surveillance, testing, and therapeutic development, but also creates higher risks. If the new strains were to infect laboratory staff, that could pose a risk to not only the individual's health but also broader public health as it could seed an outbreak. The same information that could help inform public health surveillance could also be misused by nefarious actors hoping to create more dangerous pathogens themselves.

234. Team W decided to seek a collaboration with a laboratory in a different country to circumvent the laws in Country A. Not only is this unethical behavior, but in doing so, they also created a situation where there is no governmental oversight to highly risky work with a high consequence pathogen.

This scenario highlights the following priority actions, tools and mechanisms for selected stakeholders to be considered (other actions, tools and mechanisms and stakeholders may also arise).

235. International organizations

a. Create international guidelines for responsible life science research. An international minimum standard for oversight of life science research would ensure Team W's and Team X's research had some biosafety and biosecurity guidelines applicable to the work in each country. Adopting an international minimum standard could also help countries streamline the development of their own, more comprehensive governance mechanisms with other countries to create a simpler regulatory environment for scientists and their institutions.

236. Institutions and principal investigators

a. Create training modules required for all team members. All team members should receive thorough training on how to assess the risks of the work, appropriately implement mitigation measures, and safely and securely conduct the work.
b. Ensure all team members working on the project have training in biosafety and biosecurity, regardless of the individual's home institution.

237. Governments of Country A and Country B

a. Have guidance for safe and secure life science research, especially research with potentially high consequence pathogens. Guidelines for such research, including

the dual-use guidelines of Country A, should be regularly reviewed for gaps in oversight, and revised as needed. Once it becomes apparent that high consequence work is being exported to another country, governments should work together to address any gaps in oversight.

238. Institutions of Team W and Team X and biosafety officers

a. Responsible for ensuring the work conducted by their researchers is in line with all international, national, and local regulations.
b. Help the teams conduct risk assessments and implement mitigation measures. The institutions should also be aware of the collaboration. The institution of Team W should make sure that their collaboration and export of samples to Team X is not prohibited by laws in Country A or Country B.

239. Team W and Team X members

a. Responsible for conducting the research with the novel influenza pathogen. They are responsible for understanding the risks associated with the work and the biosafety and biosecurity protocols in place to mitigate the risks. They are responsible for conducting the research ethically and legally.

Annex 2. Case studies[1]

Case study 1. Chemical Synthesis of Poliovirus cDNA

240. In 2001, a researcher in the USA announced his lab had synthetically created a full-length poliovirus complementary DNA (cDNA) construct without the use of living cells, template DNA, or template RNA. Results of this work were published in Science in 2002 (*1*) and marked the first publication for chemically synthesizing a virus de novo. At the time, this work was flagged within the virology and biosecurity communities as potentially problematic and sparked a debate regarding whether this work should be conducted and, if so, how it should be published, if at all.

241. The lead investigator for this work was originally trained as an organic chemist before venturing into virology. In 1991, his lab published the empirical chemical formula of poliovirus in an article (*2*) that argued that viruses were non-living entities, specifically chemicals that had a life cycle, a view he maintains today (*3*). To complete this work in 1991, the lab synthetically created the poliovirus using template RNA from an already existing poliovirus but without the use of living cells. To support the argument that viruses were chemicals rather than living entities, the lab wanted to demonstrate a functional virus could be synthesized without the use of living cells or template genetic material.

242. The sequence of many viruses, including the poliovirus, are publicly available online. In order to complete the de novo chemical synthesis, researchers used the publicly available sequence to create their synthetic virus. The lab segmented the poliovirus sequence into fragments with an average length of 69 nucleotides. These sequence fragments were then ordered from a commercial company that creates synthetic genes for customers based on supplied sequences. The company then shipped the synthesized fragments, called oligonucleotides, to the laboratory. Once the lab had the oligonucleotides, the fragments were combined and sequenced. The lab found they had successfully created a full-length cDNA for poliovirus.

243. To test whether the cDNA strand they had synthetized could create functioning virus proteins, the team transcribed the cDNA into RNA and then incubated the transcribed RNA with cytoplasmic extracts from an un-infected human cell line. The incubation mixtures were then applied to human cells to determine if the transcribed and translated RNA produced infectious virus particles. The incubation mixtures were able to infect the human cell line, confirming that the synthesized cDNA could create infectious poliovirus in cell culture. To confirm that the synthesized cDNA could create poliovirus that was pathogenic in animals, the lab injected the incubation mixture into transgenic

[1] Annex 2 directly draws on the case studies developed in the report BSP Case Studies WHO Framework for Responsible Life Science Research (2022, unpublished).

mice to assess if the synthetically derived viruses displayed altered pathogenicity to wildtype virus. The team found similar pathology between the chemically derived virus and the wildtype virus, though the chemically derived virus required higher doses to cause death compared to the wildtype viruses.

244. In 2002, several publications commented on this experiment. Some in the security community and public criticized the publication of the work as giving bioterrorists the tools they need to create a bioweapon (*4, 5, 6*), such as someone with malicious intent synthetically creating smallpox or Ebola viruses. The lead researcher said (*7*) his work highlighted the risks of having virus sequences publicly available, as anyone could make any virus from published data, and that his work was not contributing additional risk as others had previously published that this was theoretically possible (*6*). There was disagreement over the amount of risk the publication actually posed; poliovirus was relatively easy to synthetically create without templates or human cell lines due to its relatively small, unsegmented genome. Viruses with larger, more complex genomes, such as poxviruses or Ebola virus, would be much harder to synthesize using the approach published. There was also concern (*6*) amongst viral geneticists that the publication and its surrounding controversy could cause the US government to implement new restrictions on research, especially considering the anthrax attacks that occurred a year earlier in 2001.

245. In addition to questions about whether this work should have been completed and published, there was also concern (*8*) that the publication included no discussion of the ethics or risks associated with the work. The lead researcher for this experiment later published a manuscript (*9*) discussing the controversy surrounding his work in which he explained that originally, his team included a discussion of ethics and security risks, but the editors at Science demanded those sections be removed. Science defended publishing the manuscript as it had been through the usual peer-review process at the time. There was also no external ethics review before the experiments started (*4*). The funder of the work was the US Department of Defense, via DARPA. The lead researcher later reported that no one approached him or his team about the 1991 paper that described synthesized poliovirus using cell-free extract. He also said that Science did not raise any security concerns over the 2002 publication.

246. Since this 2002 publication, synthetic biology technology has rapidly advanced. There are more people than ever working in synthetic biology, there has been an explosion in the number of DNA synthesis companies from which oligonucleotides can be ordered, and many more viruses have been synthetically generated or modified. However, there have also been several changes in how such research is governed by several stakeholders. In 2003, several editors from life science journals released a statement discussing biosecurity and how their journals would start reviewing manuscripts for biosecurity risks (*10*). In the US, the PATRIOT Act made it a criminal offense to knowingly

possess a biological agent in a quantity that could not reasonably be for peaceful purposes. A 2004 report (*11*), commonly known as the "Fink report", from the US National Research Council's committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology recommended that the US Department of Health and Human Services create a new review system for 7 categories of experiments regarding microbial species, in addition to the recombinant DNA reviews conducted by the US National Institutes of Health (implemented in 1976) (*12*) before experiments begin. The 2004 report also recommended that the Department of Health and Human Services create a National Science Advisory Board for Biodefense (NSABB) that would review proposals or manuscripts, serve as a resource to the US government concerning biosecurity risks, and periodically review governance measures related to biosecurity.

247. Since 2002, the editors of many major high-impact scientific journals have instituted new mechanisms to review submitted manuscripts for security risks and consider what ethical or contextually information should be included in publications for responsible reporting of the work. The US Department of Health and Human Services also created the NSABB, which subsequently created several documents regarding governance and oversight of life science research of concern (*13*). Policies such as the 2012 United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern (*14*) and 2017 Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO) (*15*) have been adopted to reduce biosecurity risks associated with research with certain pathogens.

248. Limitations and gaps in governance of research like that conducted in the 2002 paper continue in the US. While the NSABB has previously been active in reviewing and advising on biosecurity considerations, the board has not met since January of 2020 and before that meeting, had last met in 2017. The 2012 dual-use research of concern (DURC) and 2017 P3CO policies don't cover all research of potential concern, including the work done in the 2002 paper as poliovirus is not on either policy's list of agents. Not all journals have the expertise in-house to conduct thorough reviews for potential biosecurity risks. Both within the US and internationally, the debate on how to best address governance of life science research continues.

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Case study 2. 1918 Spanish Influenza Reconstruction

249. In 2005, a group of scientists from the Centers for Disease Control and Prevention (CDC), Mount Sinai School of Medicine, Armed Forces Institute of Pathology, and United States Department of Agriculture (USDA) worked together to generate a reconstruction of the 1918 pandemic influenza virus (*1*). The reconstruction study was published in the journal Science in October 2005 (*1*). Coding sequences published in prior literature were used to rebuild each gene of the 1918 pandemic influenza virus, and the virus was reconstructed from those genes using a reverse genetics system followed by infectious virus being generated in cell culture (*1-8*).

250. Once the 1918 pandemic influenza virus was reconstructed, the scientists tested for infectivity, pathogenicity, and viral growth. Infectivity of the virus was examined in mammalian cells in both the presence and absence of trypsin (*1*). Growing the virus in the presence and absence of trypsin is important because the capacity of an influenza virus to replicate in vitro without trypsin to cleave the hemagglutinin (HA) molecule is commonly believed to be a determinant of pathogenicity in mammals (*9, 10*). The study determined that the 1918 pandemic flu neuraminidase (NA) protein was responsible for cleavage of the HA protein in the absence of trypsin, but the mechanism for this action was not similar to previously studied influenza viruses (*1*).

251. Pathogenicity was examined through infection of mice with the reconstructed 1918 pandemic flu virus (*1*). The intranasal infection resulted in high viral titers in the lungs, high lethality, and rapid weight loss (*1*). The animal study was able to determine that the virus did not spread to the brain, heart, liver, or spleen and that the development of severe lesions in the lungs was caused by a mechanism related to the 1918 pandemic flu HA gene (*1*).

252. The growth of the virus was examined through the infection of a polarized human lung epithelial cell line (*1*). Titers of the 1918 pandemic flu virus were primarily found on the apical side of the cell, and they were significantly higher than any of the control viruses tested (*1*). The results of this experiment were two-fold in showing that the HA and polymerase genes were responsible for optimal virus replication in lung epithelial cells and in confirming that high viral titers are present in the lungs during infection (*1*).

253. The work performed in the 1918 Spanish influenza reconstruction study was quickly scrutinized by a subset of other scientists and the public, but researchers pre-emptively provided a list of justifications for what could be seen as a risk-intensive project. The primary justification provided by authors included the beliefs that a future influenza pandemic is likely, better understanding the 1918 pandemic flu virus could aid our understanding of potential novel flu viruses, and the research could identify targets for

therapeutic development (*1, 11*). The justification that a future influenza pandemic is possible is supported by an Intergovernmental Platform on Biodiversity and Ecosystem Service report claiming that future pandemics are likely to emerge more often and spread quickly due to factors such as the disruption of ecosystems and the proximity of humans to wildlife (*12*). Despite increases in influenza surveillance, the emergence of an entirely new strain of influenza with pandemic potential is still possible (*13*).

254. The second justification from the authors was that understanding the 1918 pandemic flu virus better could aid our understanding of potential novel flu viruses that may emerge in the future (*1*). One of the key findings from the 1918 Spanish influenza reconstruction study was that the NA protein was responsible for the cleavage of the HA protein through a mechanism that had not been identified previously (*1*). The discovery of a novel mechanism had the potential to open a new avenue of research that could put the field a step ahead of a novel influenza virus that uses the same HA cleavage mechanism. The final justification was that the research could identify new targets for therapeutic development (*1*). The study identified that the HA and polymerase genes were important virulence factors, and subsequent research has focused on the development of polymerase inhibitors (*1, 14, 15*). Viral polymerase inhibitors could be a crucial therapeutic should a 1918 influenza or novel influenza A pandemic occur in the future (*15*).

255. Critics of the 1918 Spanish influenza reconstruction study expressed concerns that the published article could serve as a blueprint for malicious actors to construct a bioterrorism agent due to the detailed methodology and the public availability of the viral genome (*16*). Additional criticisms claimed that the benefits of reconstructing a virus with such a deadly history are not well defined and that there are plenty of other influenza viruses that could be studied for the purposes of pandemic preparedness (*16*). The National Science Advisory Board for Biosecurity (NSABB) reviewed the article and unanimously voted to endorse publication (*17*). However, the board stated that the decision was made to encourage further research in the field of influenza pandemic preparedness and that the risk of misuse was outweighed by the potential benefits to scientific understanding (*17, 18*). The criticism that the benefits of reconstructing the 1918 Spanish influenza virus were not well defined are partially addressed by the improvements in influenza pandemic preparedness that resulted from the discovery of novel mechanisms, virulence factors, and drug targets, though the threshold for what level of benefit outweighs the risk will change between stakeholders (*1, 14, 15*). The criticism that there are other influenza viruses that could be examined to achieve the same goals sought by this study was also partially addressed by the discovery of a new mechanism for NA cleavage of HA, which was only possible using the full-length 1918 reconstruction, as this mechanism had not been observed in any other influenza viruses (*1, 19*). However, it is possible that this mechanism could have been discovered in a different influenza virus if the proper screening had been performed.

256. Support and funding for the 1918 Spanish influenza reconstruction process were provided by the US Department of Agriculture, the National Institutes of Health, the Armed Forces Institute of Pathology, and the CDC (*14*). The reconstruction of the virus was performed at CDC facilities (*14*). The CDC required that the project be approved by an Institutional Biosafety Committee and an Animal Care and Use Committee before work was allowed to commence (*14, 20*). The committees sought to mitigate risk by ensuring that all work with any virus containing one or more genetic elements from 1918 Spanish influenza be performed in a Biosafety Level 3 laboratory with enhancements (BSL3-E) (*14, 20, 21*). The viruses were handled in a manner consistent with recommendations from the US Federal Select Agent Program, even though 1918 Spanish influenza was not registered as a select agent when the research occurred (*14, 22*). Only one scientist was allowed to access the laboratory during the reconstruction process, and that scientist was taking a daily prophylactic antiviral to mitigate infection risk. No other influenza viruses could simultaneously be handled in the same laboratory as the 1918 Spanish influenza virus to prevent cross-contamination, and the scientist worked with the understanding that he would be placed in quarantine if he became infected with the virus (*20*).

257. The journal Science consulted with external experts who had experience in the field and asked the authors to discuss their results with federal officials before the publication was released (*23*). The debate around whether the results should have been published ranged from concern over the publications being used as a blueprint for bioterror to declarations that scientific journals had the right to publish whatever content they wished under the protection of the first amendment (*16, 23*).

258. Current government policies that govern the type of research performed in the 1918 Spanish influenza reconstruction project include the United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern, Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO), and the Select Agent and Toxins Regulations (*21, 24, 25*). The United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern establishes a review mechanism for government-funded research with dangerous pathogens that could potentially be misused by malicious actors (*24*). The policy states that any government-funded research that aims to resurrect an extinct select agent or toxin must be reviewed (*21, 24*). The Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO) provides further guidance on criteria a project must meet before approval can be granted (*25*). The reconstructed 1918 Spanish influenza virus was added to the Select Agent and Toxin Regulations list after the research was published (*21*). As a result, all research involving the virus must meet the standards of the Federal Select Agent Program (*21*).

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Case study 3. Environmental surveillance for Nipah Virus

259. Environmental surveillance of infectious diseases is a process that can involve collecting biological samples from humans, local animal populations, or directly from surfaces. Environmental surveillance of infectious diseases is often used (*1*) to monitor risk areas for disease and identify risk factors for pathogens spilling over into a human population. The goal of collecting environmental surveillance data typically involves preventing future outbreaks due to a spillover event. The transmission of an infectious disease from an animal population into a human population is commonly known as a zoonosis (*2*). The rate at which new diseases emerge has been on the rise due to factors such as global warming and human encroachment into unsettled territories (*3*). Approximately 60% of all novel emerging infectious diseases are the result of zoonoses (4).

260. Nipah virus is the infectious agent behind a zoonotic disease characterized by cough, fever, headache, and vomiting with coma, confusion, encephalitis, and death occurring in more severe cases (*5*). Outbreaks of the disease are believed to originate due to transmission of Nipah virus from Pteropus bat species to humans through the consumption of bat secretions in fresh date palm sap (*6*). As a result, numerous efforts have been made to perform environmental surveillance of Nipah virus in Pteropus bat species in Bangladesh (*7, 8*). The goals of these previous studies were to characterize the dynamics of Nipah virus in its natural reservoir over space *(8*) and time and to characterize the nucleocapsid protein evolution over time (*7*).

261. Environmental surveillance of Nipah virus has been performed through two primary methods in recent years. The first method involved placing tarps below the roosts of Pteropus medius bats to collect urine (*7*). Urine samples were pooled in the tarps and collected in 50 mL Falcon tubes. Limitations of the first method include the inability to guarantee that all samples are from P. medius bats and the dilution of Nipah virus positive samples with negative ones. The second method involved capturing individual bats in custom made nets attached to treetops near P. medius roosts (*8*). The bats were removed while wearing proper personal protective equipment (PPE), anesthetized, and taken to a field lab for sampling. Weight, age, and sex measurements were taken for each captured bat then blood, throat swabs, wing biopsies, and urine samples were collected. Potential limitations of the second method include a greater risk of infection for the field researcher due to the handling of a live wild animal.

262. Justifications for performing the environmental surveillance research included determining the risk of viral spillover into human populations, better understanding determinants of viral transmissibility, providing molecular targets to better gauge the pandemic potential of Nipah virus in environmental samples, and targeting interventions

to prevent a spillover event from turning into a global pandemic. The studies were able to partially support their justifications (*8*) by determining that Nipah virus transmission is not exclusively confined to a region previously known as the "Nipah Belt" (*9*) between November – April. This information highlights that public health officials may need to look at herd immunity levels in P. medius populations around Bangladesh instead of certain calendar dates in a specific region when implementing spillover prevention interventions. The studies were also able to partially support their justifications (*7*) by characterizing the evolutionary rate of the Nipah virus nucleocapsid gene. In the 2021 publication, the authors claimed that this information will help determine whether an environmental sample of Nipah virus has pandemic potential, but the article calls for future studies to better understand outbreak risks.

263. Criticism of environmental surveillance research tends to focus on the risk posed to society if a field researcher is infected with a pathogen with pandemic potential. The risk of viral exposure is most prevalent when collecting samples directly from living wild animals. These risks can include needle sticks while taking blood samples, exposure of animal excreta to open wounds, and bites or scratches from improperly anesthetized animals. The first environmental surveillance collection method (*7*) limits the risks posed by needle sticks and bites or scratches, but the data quality is sacrificed as a result. Lower data quality may reduce the impact the study results can have on preventing or mitigating Nipah virus spillover events. The second environmental surveillance collection method (*8*) produces high-quality and specific data, but the risk to field researchers is considerably enhanced. The unintentional infection of a researcher with Nipah virus has the potential to result in a global pandemic if proper precautions are not followed. The study that used the second environmental surveillance collection method did follow proper precautions, and all researchers were equipped with nitrile gloves, P100 respirators, safety glasses, Tyvek suits, and welding gloves while handling the bats. The use of this PPE can greatly reduce the risk of infection, but it does not completely eliminate the potential threat to the researcher or society at large.

264. International guidance on how to perform environmental surveillance research in a safe and efficacious manner is limited. The 4th Edition of the WHO Laboratory Biosafety Manual (*10*) contains a section that advises researchers to treat all collected materials as potentially infectious when performing environmental surveillance in a disease outbreak situation. This advice was followed by the researchers performing the second environmental surveillance collection method (*8*) since they wore adequate PPE while handling all bats, but more specific international guidance related to environmental surveillance research in non-outbreak scenarios is needed. Continual medical surveillance of all researchers during and after sample collection events, the use of adequate PPE to avoid exposure to potentially infectious animals or biological materials, and making an effort to minimize sample collection events without sacrificing data quality should be considered the minimal standards for safe environmental surveillance

research. Pre-exposure preventative treatments should be utilized during environmental surveillance if available.

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Annex 3. Illustrative examples of awareness raising, education, training and capacity building in the life sciences and related fields

Argentina	The Argentine National Authority for the Chemical Weapons Convention developed a national project on education and outreach to (i) to improve the level of knowledge about the role of the treaty and the national legislation that implements it, (ii) to help raise awareness about the dual-use nature of knowledge in the chemical sciences and the risks that this implies, and (iii) to promote a culture of responsible use of technical and scientific knowledge.[1] These efforts were taken up by, for example, the chemistry department at the University of Rosario, where chemical safety, security and responsible conduct of science are incorporated into the chemical curricula. This is carried out through a range of curricular activities, elective subjects (bioethics, green chemistry, educating for sustainable future, etc) and complementary activities (workshops, seminars, etc.). New activities to improve how these topics are discussed in the chemical curricula have been designed (and design continues) with their impact evaluated through a research project supported financially by the university.
Australia	The Biosecurity Emergency Response Training Australia (BERTA) was established through a collaboration between several Australian state and territory governments, the Commonwealth of Nations, Animal Health Australia (AHA) and Plant Health Australia (PHA). To maintain consistency in biosecurity training, the National Biosecurity Committee funded Tocal College to develop the BERTA Training and Assessment Materials.
Canada	Several governmental agencies such as the Centre for Biosecurity of the Public Health Agency of Canada and the Office of Biohazard Containment and Safety of the Canadian Food Inspection Agency have developed biosafety and biosecurity training materials, as well as an online training portal. *Tri-Agency framework: Responsible conduct of research* is a key reference document for the three major Canadian funding agencies and guides all funded research as well as research institutions eligible for funding. It sets out the responsibilities and corresponding policies for researchers,

[1] See https://www.cancilleria.gob.ar/es/iniciativas/ancaq/proyecto-nacional-de-educacion/actividades-de-educacion-y-divulgacion

	institutions and the Agencies in order to support and promote a positive research environment.[1]
China	The Tianjin Biosecurity Guidelines for Codes of Conduct for Scientists are high-level principles that serve as a reference for a broad range of stakeholders to develop or amend national- or institutional-level codes of conduct, practices, protocols or regulations. Inspired by the Hague Ethical Guidelines that were developed by the Organisation for the Prohibition of Chemical Weapons, the Tianjin Biosecurity Guidelines emerged from foundational work by China and Pakistan, and were developed collaboratively by InterAcademy Partnership leaders, Tianjin University's Centre for Biosafety Research and Strategy, and Johns Hopkins University's Center for Health Security, with input from scientists from 20 geographically diverse countries.
France	Established in 2011, the 'Agence Nationale de Sécurité du Médicament et des produits de santé' (ANSM) aims to strengthen the safety of medicines and health products and to support health policy decision-making for the safe use of drugs and biological products. It is responsible for the inspection of manufacturing sites of medical and health products, and it regulates and inspects work with microorganisms and toxins. A National Consultative Council for Biosecurity (CNCB) was created in 2015.[2] CNCB develops guidance to mitigate misuse and dual-use research in the life sciences.
Kenya	Academic chemistry institutions in Kenya have traditionally emphasised safety training to the detriment of security concerns. But gaps in chemical security awareness and implementation have resulted in reported cases of theft and attacks involving chemicals. Over the past five years, the Kenya Chemical Society has conducted chemical security training and outreach campaigns in academia and industry to address this gap. These engagements have uncovered a lack of basic knowledge among chemical practitioners about chemical security sufficient to prevent misuse, theft, and diversion of hazardous and dual-use chemicals.[3]
Lebanon	Several biosafety and security-related initiatives have been undertaken in Lebanon, including the establishment of a biosafety and biosecurity

[1] Tri-Agency Framework: Responsible Conduct of Research: The Interagency Advisory Panel on Responsible Conduct of Research (PRCR) (ethics.gc.ca)

[2] http://www.sgdsn.gouv.fr/missions/lutter-contre-la-proliferation/le-conseil-national-consultatif-pour-la-biosecurite-cncb/

[3] Ellene Tratras Contis, Dorothy J. Phillips, Allison A. Campbell, Bradley D. Miller & Lori Brown [eds]2018. Responsible Conduct in Chemistry Research and Practice: Global Perspectives. American Chemical Society. https://pubs.acs.org/doi/book/10.1021/bk-2018-1288

	association and outreach to perpetuate responsible science concepts. The outreach initiatives have primarily targeted faculty and students/trainees at universities and hospitals and has provided education on basic biosafety principles and biosecurity measures through seminars, symposia, poster sessions, workshops, online courses/forums as well as train-the-trainer events.
Malaysia	The Responsible Conduct of Research (RCR) education agenda in Malaysia was initiated by the Educational Institute on Responsible Science in Kuala Lumpur. In close collaboration with the US National Academies of Sciences, Engineering and Medicine, and with support from the Malay Ministry of Education, the Young Scientists Network of the Academy of Sciences Malaysia produced the first Malaysian Educational Module on RCR (including a chapter on the culture of safety and dual-use research) in 2018. In 2019 and sponsored by the International Science Council, the two-year ASEAN RCR programme was initiated to train the first cohort of ASEAN RCR instructors.[1]
Mexico	The Mexican Biosafety Association A.C. (AMEXBIO) was established in 2009. A member of the International Federation of Biosafety Associations (IFBA), its central aim is to provide information on biosafety and biosecurity and to promote training of individuals in these fields.
Morocco	The Moroccan Biosafety Association has partnered with the US Biosecurity Engagement Program, the Task Force for Global Health and Gryphon Scientific to organise biosafety and biosecurity training workshops, meetings and train-the-trainer events.
The Netherlands	The Dutch government established a Biosecurity Office in 2013 as an information centre for biosecurity.[2] The office collaborates with many international organisations and an internal working group provides lectures, webinars and workshops, as well as tools and web applications, that provide biosecurity education and helps identify potential biorisks. The office also organises an annual Biosecurity Knowledge Day. On request from the Dutch Ministry of Education, Culture and Science, the Royal Netherlands Academy of Arts & Science (KNAW) developed a

[1] See https://aseanysn.org/blog/call-for-applications-for-asean-responsible-conduct-of-research-project. See also: Chau, D.M., Chai, L.C., Azzam, G., Chan, S.C., Thahira Begum S.A Ravoof., Normi, Y. M., Ong, B.H., Zulkharnain, A., Abdullah, N., Abdullah, N.S., and Veerakumarasivam, A. (2018). Malaysian Educational Module on Responsible Conduct of Research. Kuala Lumpur, Malaysia: Academy of Sciences Malaysia.

[2] https://www.bureaubiosecurity.nl/en/news/biosecurity-office-international-2

	Biosecurity Code of Conduct for Scientists.[1] The Code aims to prevent life sciences or its application from directly or indirectly contributing to the development, production or stockpiling of biological weapons, as described in the Biological Weapons Convention, or to any other misuse of biological agents and biological material.
Pakistan	In collaboration with international actors, *Quaid-i-Azam* University (QAU) of Pakistan has been carrying out awareness-raising activities and producing educational materials on bioethics, biosafety, biosecurity and dual-use since 2010. These activities are aimed at strategising and promoting awareness of biorisk management in Pakistan, and emphasise a 'holistic biosecurity' approach, not limited to laboratory biosecurity.
Ukraine	In 2018, the Organization for Security and Co-operation in Europe (OSCE) conducted a thorough review of biological safety and security in Ukraine, identifying major gaps in the systems in place. One of these gaps was an appropriate training levels for biosafety and biosecurity. Several projects were launched to address these gaps including one that entails training and bolstering risk awareness for life scientists. In 2019, the Council of the European Union issued a decision to support strengthening biological safety and security in Ukraine including awareness-raising, education and training.
UNICRI	The United Nations Interregional Crime and Justice Research Institute (UNICRI), in collaboration with the United States Federal Bureau of Investigation (FBI), administers the International Network on Biotechnology (INB). The INB is a global network of academic and research institutions committed to advancing education and raising awareness about responsible and secure conduct in basic and applied life sciences. The INB supports the (co-)development and sharing (via an online portal accessible to network partners) of modular educational resources (awareness-raising videos, scenarios, active learning exercises, etc.) covering the themes of biosafety, biosecurity and bioethics.
United Kingdom	A decade ago the University of Bradford produced an education module resource which is still available on the Federation of American Scientists website, and *Preventing Biological Threats: What You Can Do* and *Biological Security Education Handbook: The Power of Team-Based Learning* in 2015. Recently London Metropolitan University has produced an innovative set of biological security education cartoons. These products have been made available in different languages.

[1] https://www.knaw.nl/en/news/publications/a-code-of-conduct-for-biosecurity

United States	The US Department of State Bureau of International Security and Nonproliferation Office of Cooperative Threat Reduction (ISN/CTR) initiated the Biosecurity Engagement Program in 2006. This programme has supported training activities as well as capacity-building efforts both at home and abroad. Since 2010, the Biosecurity Engagement Program (BEP) has supported several institutions committed to advancing awareness-raising and education about responsible and secure conduct in the life sciences. For instance, the US National Academy of Sciences, Engineering and Medicine co-organised with local partners three international meetings on conducting responsible science in the Middle East and North Africa (MENA) region, and workshop training on responsible conduct of science and bioethics for stakeholders working in the life sciences. Gryphon Scientific organised several workshops and produced modular educational resources (biorisk assessment videos, scenarios, and mock research review exercise), and developed an on-line platform, Bio-Chem COMPASS, dedicated to provide a safer and more secure work environment for bio/chem professionals in the MENA region.[1] The Frontline Foundation organised an online course on biorisk management accredited by the International Association for Continuing Education and Training across MENA countries.

Source: Towards a global guidance framework on responsible use of life sciences: summary report of consultations on the principles, gaps and challenges of biorisk management. 2021 (forthcoming).

[1] https://bccompass.org