Roadmap for Biosecurity and Biodefense Policy in the United States

Full Report

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This project was supported by a grant from the U.S. Air Force Academy and Defense Threat Reduction Agency under their Project on Advanced Systems and Concepts for Countering Weapons of Mass Destruction.

ROADMAP FOR IMPEMENTING BIOSECURITY AND BIODEFENSE POLICY IN THE UNITED STATES

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Acknowledgements: The project partners thank the U.S. Air Force Academy for supporting this project and all working group members for their contributions, insights, and peer review of all project methodologies, analyses, case studies, and final report. We thank all of the stakeholders with whom we spoke to ensure that the analyses and conclusions described in the report are accurate, relevant and appropriate. We thank U.S. government staff at the White House and Departments of Defense, State, Health and Human Services, and Agriculture, and Environmental Protection Agency for providing us opportunities to discuss our interim analyses. We thank the American Biological Safety Association, Association of Public Health Laboratories, American Society for Microbiology, Biotechnology Industry Organization, Engineering Biological Research Consortium, American Association for the Advancement of Science, Council on Government Relations, National Association of County and City Health Officials, and Association of State and Territorial Health Officials for helping us to engage their members during the course of the project.

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Executive Summary

The U.S. policy landscape for countering biological threats is split into two main groups: 1) biosecurity, which specifically focuses on preventing theft, diversion, or deliberate malicious use of biological sciences knowledge, skills, materials, and technologies to cause harm; and 2) biodefense, which involves the development of capabilities and knowledge-based to assess, detect, monitor, respond to, and attribute biological threats. Policies in both groups often affect the same stakeholders, which may result in mutual benefits among defense-oriented policies or counteract (or limit achievement of) defense and/or security objectives. Complicating the system for countering biological threats is the rapidly changing biotechnology landscape, which simultaneously presents new opportunities for building technological capabilities for defending against biological threats and for enabling security risks and vulnerabilities. As the U.S. government finalizes its new National Biodefense Strategy and begins preparing its Global Health Security Strategy, understanding the current policy landscape and the potential ability or inability of policies to achieve biodefense objectives is crucial to ensuring that the new strategies address long-standing gaps. Despite all of this activity in biodefense and biosecurity policy, systematic evaluation of existing policy and implementation to identify gaps and policy solutions for addressing those gaps has not been conducted, until now.

This report presents a roadmap for implementing biosecurity and biodefense policy to leverage the capabilities of science and technology advances and minimize security risks. Supporting the conclusions and suggestions in the Roadmap chapter are detailed analyses of the overall system of U.S. biosecurity and biodefense policy, existing methodologies for evaluating successful implementation of policies, and historical case studies with which to develop an analytic framework for assessing potential opportunity costs of biosecurity policy requirements. This study presents two analytic frameworks, one for developing and evaluating policy implementation and a second for examining direct costs, indirect effects arising from those costs, and their downstream consequences.

Changing Biotechnology Landscape

Four primary changes have occurred during the past 10-15 years that have, and will continue to, alter the biotechnology landscape: 1) expansion of the funding landscape to include cross-over venture capital firms and public crowdsourcing in addition to private industry, philanthropic organizations, and government funders; 2) increasing convergence of physical, computational, materials, and life sciences; 3) broadening of practitioners of biology to include citizen scientists and non-life scientists and engineers; and 4) globalization of biotechnology capabilities. These changes are driven by many factors, including, but not limited to, social acceptance of health applications and increased agricultural needs. Together, these factors lead to transformative changes in biotechnology that enable new knowledge gain and new applications. Examples of biotechnologies that have altered current life science capabilities include precision medicine, systems-level analysis, bio-based systems for chemical production, synthetic biology, tissue printing, additive biomanufacturing, neural networks, and artificial

intelligence. Government and non-government funders have recognized the potential for these advances to improve health, agriculture, environmental monitoring, and energy.

Findings from Systems-based Evaluation of the Biosecurity and Biodefense Policy

The systems-based policy analysis conducted in this study revealed several limitations of the current policy landscape and highlighted gaps in capabilities, implementation, and infrastructure. Limitations were identified in scope and relevance of policies, consistency of policy development and implementation, and in stakeholder engagement.

Priority Gaps and Consequences of the Limitations	
Gaps	**Consequences of the Limitations**
The need for greater investment, innovation, and workforce development for microbial forensics.	The decreasing ability of the U.S. government to be a leader in scientific and technological advancement and application.
The need to improve the input data for biosurveillance and early warning.	An inability to identify mutually-beneficial policies, such as worker protection and laboratory biosafety, and counteracting policies, such as biodefense research investments and the Biological Select Agents and Toxins (BSAT) regulations.
The need for greater attention to the security implications of scientific and technological advances beyond those associated with pathogens and toxins.	Difficulties of stakeholders to implement policies with many mandated activities and little, or no, financial support.
The lack of financial and technical resources to support local implementation of biosecurity policies.	Challenges of local stakeholders to understand their roles and responsibilities in implementing biosecurity and biodefense policies.
The continuously changing regulatory landscape for BSAT.	
Annual and inconsistent investments in nonproliferation activities, which can limit sustainability of activities.	
Effective measures for evaluating policy implementation and examining opportunity costs of new policies.	
The lack of programs for promoting resiliency within the research sector, including at the regional and national biocontainment laboratories, despite the key role it plays in preventing, detecting, and assisting with response to biological threats.	

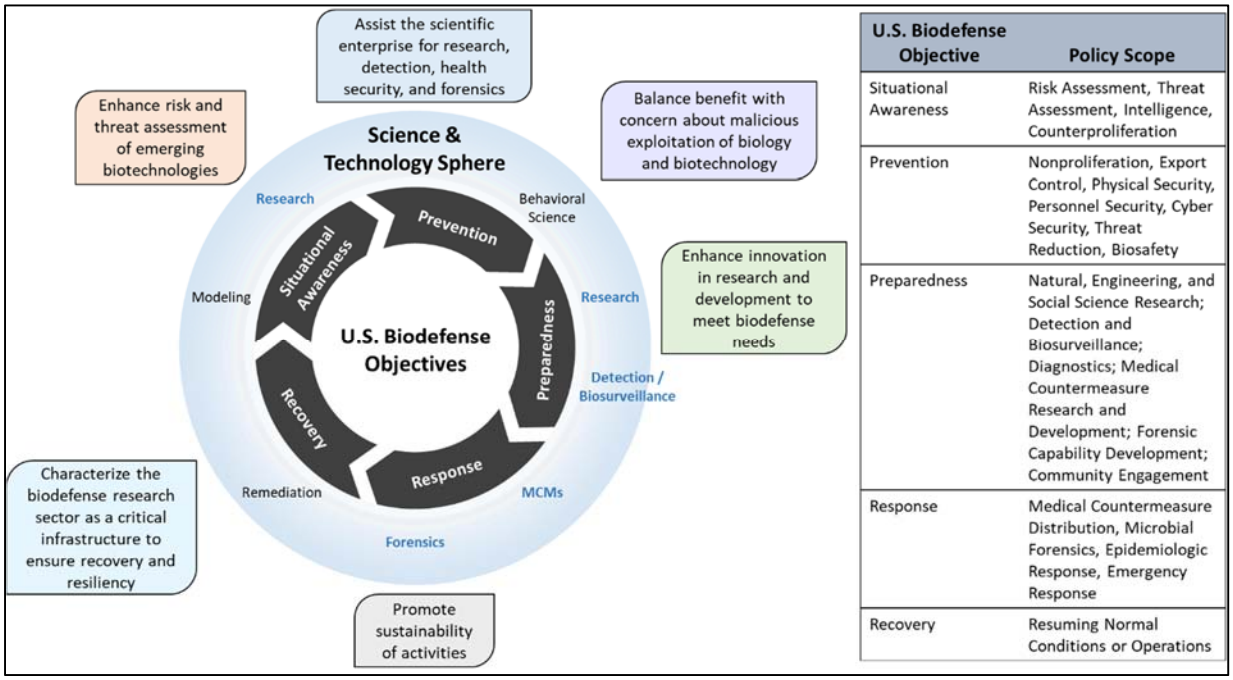
In addition to these limitations and gaps, several key *findings* were observed from the policy analysis:

- The U.S. biosecurity and biodefense policy landscape is a system of intersecting components, which can lead to mutually reinforcing policies or counteracting policies. Therefore, approaching U.S. policy development, analysis, and implementation in a systematic way enables more thorough understanding of the indirect costs, trade-offs, and feasibility of policies and their implementation.

- No single strategy describes the full range of biosecurity and biodefense objectives of the U.S. Therefore, the U.S. biosecurity and biodefense enterprise would benefit from the development of a comprehensive, inclusive strategy that recognizes the interconnectedness of existing policy, depth of implementing and affected stakeholders, and outstanding gaps.
- On occasion, local stakeholders voluntarily have developed and implemented policies and practices to address biosecurity and biosafety risks, and biodefense knowledge and technological gaps. These voluntary actions play a major role in risk reduction and capability building for the U.S.
- Several barriers may prevent policies from being fully or adequately implemented, limiting their abilities to meet U.S. biodefense objectives. These barriers include counteracting policies, lack of support for compliance with high-burden requirements, and lack of cross-sectoral and cross-disciplinary stakeholder involvement in the policy development process.

System-wide Roadmap

The roadmap for implementing biosecurity and biodefense policy addresses the identified limitations and gaps, builds on the key policy findings, and focuses on six primary actions that federal and local stakeholders have responsibility in implementing. The figure highlights the key elements of the roadmap.



Roadmap for implementing biosecurity and biodefense policy in the United States to leverage science and technology advances and simultaneously, minimize security risk.

Given the Department of Defense's role in implementing biodefense and biosecurity policies more broadly, several of these actions apply to DoD.

Roadmap

In 2001, Nobel Prize laureate, Matthew Meselson, called the 21st century the age of biotechnology.(13) The most recent market predictions suggest the global market for biotechnologies will reach $727.1 billion by 2025, with the largest growth in the health and agriculture sectors.(12) The rapid pace of change within the life sciences and biotechnology challenges current systems designed to leverage new capabilities and to prevent harms. These changes are driven by many factors, including, but not limited to, the influx of non-traditional practitioners, investment by a diversity of funders, social acceptance of health applications, increased agricultural needs, and the increasing convergence of physical, computational, and life sciences. Together, these factors lead to transformative changes in biotechnology that enable new knowledge gain and new applications. Examples of biotechnologies that have altered current life science capabilities include precision medicine, systems-level analysis, bio-based systems for chemical production, synthetic biology, tissue printing, additive biomanufacturing, neural networks, and artificial intelligence. Government and non-government funders have recognized the potential for these advances to improve health, agriculture, environmental monitoring and remediation, and energy. Within the U.S. government, the Department of Defense has been a leader in promoting and investing in these and other similarly transformative technologies to improve warfighter health and capabilities. Their efforts are enhanced by the National Institutes of Health, National Science Foundation, and Department of Energy Office of Science investments in basic research in these fields. In addition, these funders benefit from a few creative scientists and technologists who are willing and able to undertake high-risk, high-reward research, several of which involve integrating different disciplinary approaches, technologies, and information to achieve something new.

At the same time, research and development in these and other areas of biology and biotechnology are being supported to address current societal needs in health and defense. For example, the Fiscal Year 2018 Omnibus Appropriations Bill includes: a) $37.1 billion for the National Institutes of Health (NIH) to support basic research on Alzheimer's disease, opioid addiction, map of the human brain (through the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative), precision medicine, combatting of antibiotic resistant bacteria, and a universal flu vaccine;(14) b) $5.26 billion for the National Institute of Allergy and Infectious Disease (NIAID), the primary institute within the NIH that funds biodefense research; c) $22 billion for the Department of Defense to support a variety of research and facility maintenance activities, including funding basic and applied research, development, testing, and evaluation; and d) $509.8 million for the Department of Homeland Security Science and Technology Directorate to support research and development.(15)

Specifically focusing on biodefense (i.e., capabilities for countering biological threats), fundamental research (i.e., basic and applied research whose results are intended to be shared with the scientific community) includes identification and characterization of pathogens considered as priority threats to the United States, development of modeling, knowledge, and technologies for pathogen detection and monitoring (i.e.,

biosurveillance), pre-clinical research and development of medicines against high-priority pathogens (i.e., medical countermeasures), and development of new methodologies for attribution (e.g., microbial forensics). Based only on funding levels of basic and applied research and development, the primary U.S. government entities that support biodefense or health security activities are NIAID, Centers for Disease Control and Prevention (CDC), Food and Drug Administration, Biomedical Advanced Research and Development Authority (BARDA), and the Department of Defense, specifically the Defense Threat Reduction Agency, U.S. Army Medical Research Institute of Infectious Diseases, and Defense Advanced Research Projects Agency. On occasion, other U.S. government agencies (e.g., Department of Homeland Security Science and Technology Directorate and U.S. Department of Agriculture Animal and Plant Health Inspection Service) have supported basic and applied research for biodefense. Most of the biodefense funds have been appropriated for broader preparedness and response efforts, agriculture and food defense, advanced product development, and risk, threat, and vulnerability assessment.[1]

Implications of the Evolving Biotechnology Landscape

The potential for benefit and harm exists within the global context of biotechnology research, development, and application, where individuals, institutions, and countries have significant influence over whether and to what degree science advances, how science and technology are applied, and who owns information and technologies. Four primary changes have occurred during the past 10-15 years that have, and will continue to, alter the biotechnology landscape: 1) expansion of the funding landscape to include venture capital firms and public crowdsourcing in addition to private industry, philanthropic organizations, and government funders; 2) increasing convergence between life-science and non-life-science disciplines; 3) broadening of practitioners of biology to include citizen scientists and non-life scientists; and 4) globalization of biotechnology capabilities. Box 1 describes each of these changes in detail. In addition, increased access to scientific publications through open access journals and policies, and experimental videos through online journals and YouTube (and other similar platforms) are enabling greater access to biological research and helping to lower the barriers of entry to working with biology. Furthermore, as calls for improving reproducibility in science increase and acted upon, the reliability and replicability of published experimental research also will increase. Together, these changes and trends define the current landscape in the biological sciences and biotechnology.

[1] Before 2001, biodefense research was conducted by a small group of scientists, in large part because annual funding levels were extremely low. The Department of Defense, which was responsible for medical defense research, was appropriated $60 million annually in fiscal years 1999, 2000, and 2001. At the same time, the NIAID supported basic research on overlapping pathogens at a funding level of $270 million in fiscal year 2001. Shortly after the 9/11 attacks, DoD received an annual increase of $30 million in biodefense funding whereas HHS received a budget increase of more than $1.5 billion. Funding for biodefense continued to increase over the past 17 years, fluctuating annually because of scope and political interest.

Box 1. Changes in the Biotechnology Landscape

The **funding landscape** for research conducted in the United States has expanded well beyond U.S. government funders and disease-specific philanthropic organizations to include Silicon Valley venture capitalists, and foreign governments, and the general public through crowdsourcing platforms such as Kickstarter and Experiment.com. Along with funding professional scientists, these sponsors have provided financial support for teams of undergraduate or high school students participating in the International Genetically Engineered Machine Competition. In addition to these new sponsors of biological science and technology, private industry, academic institutions, and other research institutions have begun supporting research that the U.S. government is not willing to support (e.g., modification of live human embryos(1)) and outside the traditional disciplinary boundaries (e.g., synthetic biology and big data analytics). The change in the funding landscape simultaneously enables innovation and entrepreneurship within the amateur and professional science and technology communities, while also demonstrating the limitations of federal requirements that are tied to U.S. government funding. (See Appendix 1 on the synthesis of horsepox virus.)

The **convergence of life-science and non-life-science disciplines** are leading to new scientific discoveries, capabilities, and applications. In some ways, this convergence involves the support for and conduct of cross-disciplinary science such as data science and the life sciences, which has enabled the fields of systems biology and precision medicine, or material science and the life sciences, which has led to additive biomanufacturing (i.e., 3D and 4D printing of tissues). In other ways, convergence involves the use of engineering principles to "design" and "build" biological systems. This description of convergence is most closely associated with synthetic biology, which at its foundation is the application of engineering concepts (specially, the design-build-test cycle) to biology; the actual methods and materials involved in synthetic biology are common to genetic engineering, which first emerged in the late 1960s. A third way convergence has been used is the repurposing of biological organisms and molecules from their natural functions to a man-made function. For example, DoD has invested in research to create bio-based sensors that can detect radioactive and non-radioactive molecules,(5) and Microsoft Corp has supported research to use DNA molecules to store data, including image, video, and audio information.(6) New educational and research programs have been established to promote and drive innovation in multidisciplinary science.

The demographic of **practitioners** who work with biological organisms and molecules has expanded well beyond the interdisciplinary life scientists and clinicians to include researchers with expertise in engineering, computer, data, materials, physical and chemical sciences; artists; citizen scientists; and community laboratory members. The influx of practitioners into biology has pushed the boundaries of scientific achievement and risk, enabling innovation and entrepreneurship in biology and biotechnology while also creating new vulnerabilities that may result from careless, uninformed, or malicious individuals. A timely and illustrative example of this is the field of synthetic biology, which emerged when a group of computer scientists and engineers at MIT asked whether functional biological systems could be created using standardized biological parts. This initial question, which was asked of undergraduate engineering students taking a summer course at MIT, led to the creation of the International Genetically Engineered Machine (iGEM) competition, which has encouraged unconventional thinking about biology, development and sharing of genetic engineering materials and methods, and entrepreneurial spirit.(7) In fact, on its website, iGEM highlights synthetic biology companies that started out as teams in the competition. At the same time, the statements about creating new or unnatural biological organisms in a deliberate and predictable manner has elicited significant concern among the biosecurity community in the United States and internationally. In addition to the synthetic biology community, entrepreneurial members of the amateur biology community (so-called Do-it-yourself Biology (DIY Bio) community) have created companies to provide laboratory equipment and materials that fellow citizen scientists cannot obtain from the established biotechnology companies. Still other amateur scientists have created companies that conduct extremely risky, and ill-advised activities (e.g., amateur biologists injecting themselves with DIY genome editing tools or viruses(8-10)).

Global investment in the biological sciences and biotechnology has increased because of two primary drivers: 1) national-level interest in addressing human health needs (specifically, reducing chronic and infectious disease incidence and burden), improving agriculture and food availability and quality, and promoting economic growth;(11) and 2) international interest in building capabilities to promote development and to prevent, detect, and treat communicable and non-communicable disease. The global biotechnology market in 2016 was $369.62 billion with the largest market share in North America followed by Europe and the Asia Pacific region.(12) China and Brazil are among the countries actively growing their biotechnology investments.

The dramatic changes in the biotechnology landscape presents new opportunities for building U.S. capabilities to counter biological, chemical, and radiological threats and new challenges to established assessments and concerns about biological threats. This dichotomy has led some national security experts in the U.S. government to question the need for certain types of science fearing the risk may be greater than the reward, whereas others focus more on the benefits and promise of new advances and applications in biotechnology for addressing critical capability gaps in civilian and military preparedness and response efforts. Still others, continually raise concerns about "technology surprise" and the inability to stay ahead of changes in science and technology, including biotechnology, that could cause an unmatched advantage to a U.S. adversary. Congress has passed laws attempting to address some of these concerns. For example, the May 2017 Consolidated Appropriations Act includes a section requiring the intelligence community to assess new advances and applications of biology and biotechnology as they relate to U.S. "competitiveness in the global bioeconomy", including an evaluation of "the risks and threats evolving with advances in genetic editing technologies" and their implications on biodefense needs.(16) Just five months earlier, Congress passed the National Defense Authorization Act of 2016, which included a section requiring the Departments of Defense, Health and Human Services, Homeland Security, and Agriculture to develop a new biodefense strategy for the United States.(17) The law specified a review of existing policy and programs, articulation of biological threats, evaluation of agency roles and responsibilities, and development of recommendations to improve biodefense capabilities. This law encompasses the two main way in which the United States seeks to counter biological threats: 1) biosecurity, which specifically focuses on preventing theft, diversion, or deliberate malicious use of biological sciences knowledge, skills, materials, and technologies to cause harm; and 2) biodefense, which involves the development of capabilities and knowledge-based to assess, detect and monitor, treat (or vaccinate against), and respond to biological threats.

In addition to the congressionally-mandated activities, the Environmental Protection Agency, U.S. Department of Agriculture, and Food and Drug Administration updated the Coordinated Framework for Regulation of Biotechnology in 2017.(18) The purpose of the update was to increase confidence in the system for regulating biotechnology products and to prevent "unnecessary barriers to future innovation and competitiveness" in the biotechnology sector. Although this Framework focuses on safety and environmental protection regulations, it overlaps with investments in biological products to enhance U.S. capabilities to detect, prepare for, and respond to chemical, biological, radiological, and nuclear threats. For example, the Department of Defense has invested in synthetic biology research to develop bio-based sensors of biological and nuclear materials, improved medical countermeasures against biothreat agents, and organisms that can be used for bioremediation. Beyond genetic modification technologies, DoD has supported the application of big data analytics to establish and improve early warning of biological threats (i.e., biosurveillance),(19-22) genomics to improve medical care for the warfighter and veteran,(23-26) and neuroscience and mechanical engineering to create neuroprosthetics for military personnel who have lost limbs in combat.(27)

The broader implications of the changing biotechnology landscape are not well-understood, in part because advances are occurring at an alarming pace and increasingly off-shore. Harnessing new capabilities afforded by biotechnology may become challenging if new applications are being explored in unfriendly countries. Similarly, detecting and mitigating vulnerabilities or risks associated with new biological sciences advances and applications often is difficult, particularly if the international community is unaware of these advances or applications until after they are published. The shifting landscape exacerbates these and creates new challenges to any policy or programmatic efforts for maximally leveraging science and technology (S&T) advances and reducing national security risks. These challenges include: 1) variability in funder priorities and ethical, safety, and security norms; and 2) disproportionate economic and commercial advantage to adversarial countries investing in (or stealing) scientific information as was observed by the semiconductor industry. Within the biotechnology sectors, transfer of technology, skill, and knowledge to foreign countries (through funding and/or theft) is occurring. Lessons for countering this problem may come from non-life-science fields, such as the information technology sector, which incentivizes scientists to maintain the knowledge base, research capabilities, and skills in the U.S.

The Current State of Biosecurity and Biodefense Policy

As a part of this study, the authors conducted a systems-based analysis of the U.S. biosecurity and biodefense landscape in 2017 and 2018. The figures included in this section were created as part of this analysis, which is described in detail in the Policy Analysis chapter.

The current state of biosecurity and biodefense policy in the United States is bifurcated with one group of policies focused on preventing theft, diversion, and deliberate malicious use of biological materials, knowledge, skills, and technologies in the United States and internationally, and a second group of policies focused on building scientific and technical capabilities for early warning, preparedness, and response to natural, accidental, or deliberate biological threats. (Figure 1) This two-group system has resulted from the iterative and responsive process of biosecurity and biodefense policy-making during the past one hundred years.

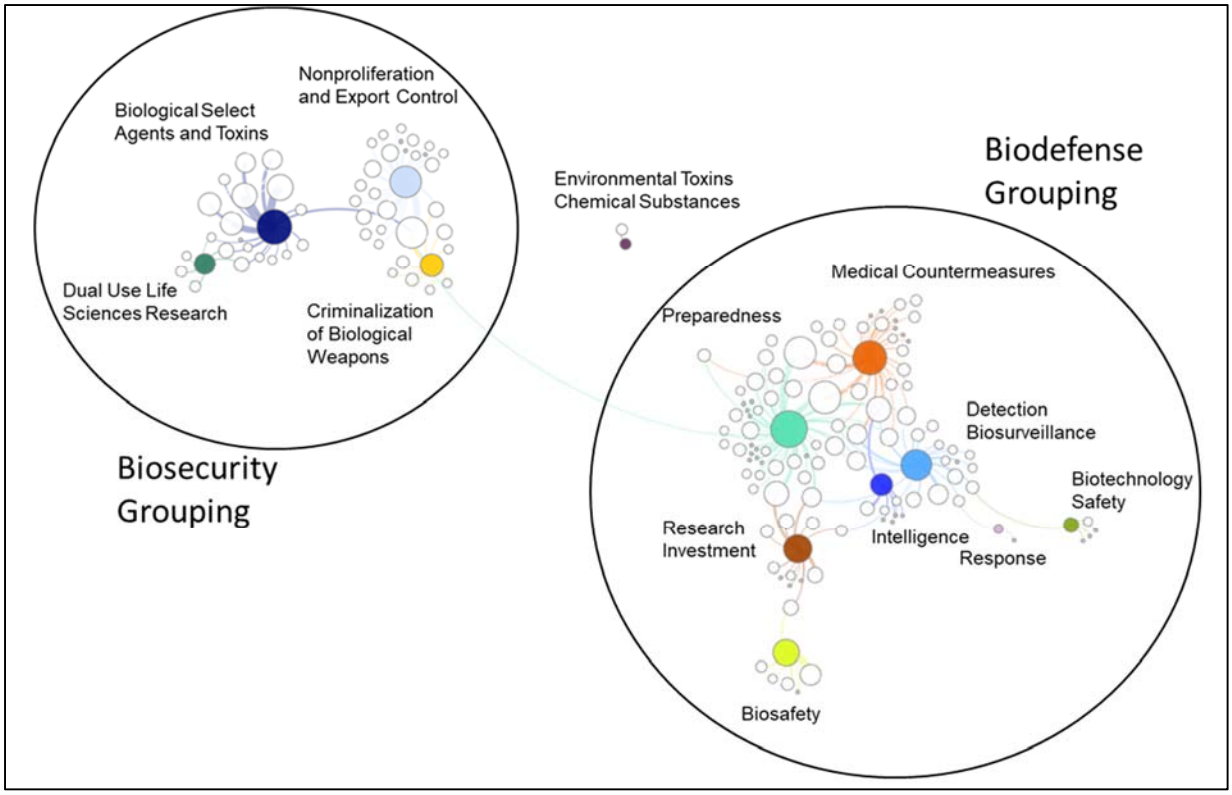


Figure 1. Relational map of U.S. biosecurity and biodefense policy by policy subject. Each white circle is a unique U.S. Code, international agreement or partnership, Executive or agency-level policy, program activity (if not already associated with a U.S. Code, international partnership, or agency-level policy), guidance, and guidelines. The size of the circles reflects the number of policies that are associated with a biosecurity or biodefense subject area. The colored circles are nodes signifying subject area. The size of the nodes reflects the number of policies associated with each subject area and the distance between nodes reflects the degree to which policies are linked based on the underlying relational database. The lines reflect direct relationships between policies and subject areas based only on existing policies. This map does not reflect associations of subject area based on conceptual similarities, but rather associations by direct links between existing policies.

As new technologies that change extant scientific capabilities are developed, as harmful incidents involving biological agents occur, or as security experts raise concern about experiments and/or information, policy-makers initiate efforts that have led to new laws and regulations, guidance, guidelines, or programs. Figure 2 illustrates the reactive nature of U.S. policy for biosecurity and biodefense. Several U.S. government agencies, local public health stakeholders, and members of the broader scientific community are responsible for implementing these policies.

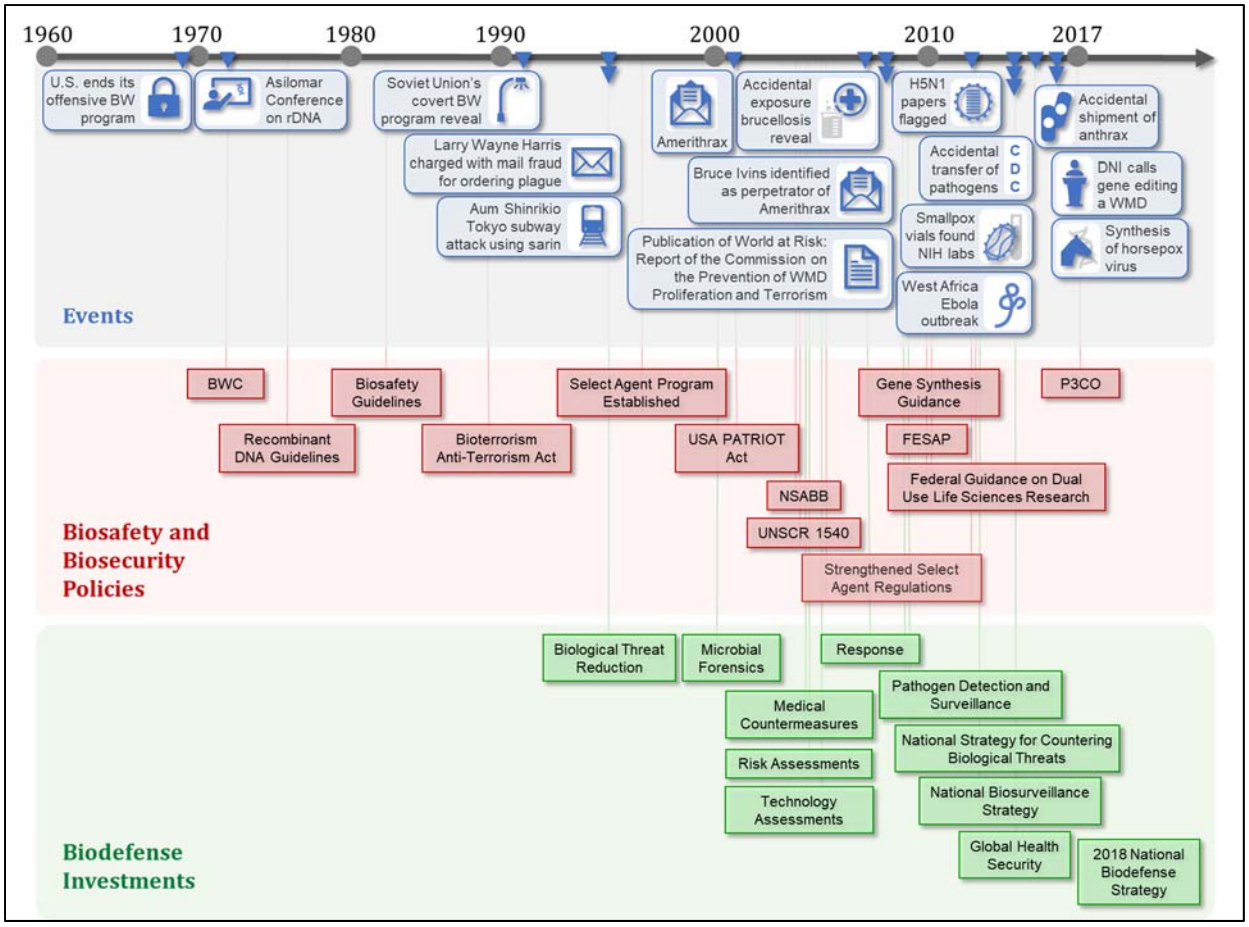


Figure 2. Schematic illustrating the reactive nature of U.S. biosecurity and biosafety policies and biodefense investments during the last fifty years.

Oversight of biological science activities, whether research or diagnostic, are governed in three ways. The first is legal authorities, which are provided by statutes and may be implemented through regulations. These laws pertain to any activities or entities that are specified in statutes and regulations, and often are not tied to funding source. Examples of these include the Biological Weapons Anti-terrorism Act of 1989, Project Bioshield Act of 2004, export control regulations, Biological Select Agents and Toxins Regulations, and occupational health and safety regulations. The second way biological activities are governed is through guidelines and guidance that are required of entities that receive funding from the federal government. These policies include the U.S. government policies on dual use research of concern, NIH Guidelines for Recombinant and Synthetic Nucleic Acids, and the HHS Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens. Because these policies are tied to federal funding, they have no ability to govern research activities not funded by the U.S. government. The third governance approach involves voluntary policy implementation of unregulated science or entities. For example, approximately 40% of private industry in the U.S. voluntarily have created institutional programs and policies to review and oversee research involving recombinant or synthetic nucleic acids. For pharmaceutical, biotechnology, and other private companies

which do not receive financial research support from the U.S. government, the NIH Guidelines for Recombinant and Synthetic Nucleic Acids are voluntary. Similarly, U.S. and some internationally-based DNA synthesis companies voluntarily follow the Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA, which aligns with industry-developed guidance for sequence and customer screening of DNA synthesis orders. Many of these policies are bounded by lists of biological pathogens, toxins, scientific activities, and/or equipment of greatest concern to security, environmental safety, and/or worker safety. In addition, and not included here, are the regulations governing research integrity, human subjects protection, and welfare of animals used in research, all of which contribute to the overall governance of biological research in the U.S. Figure 3 illustrates current governing landscape for addressing scientific responsibility in and ethical, safety, and security risks of biological research.

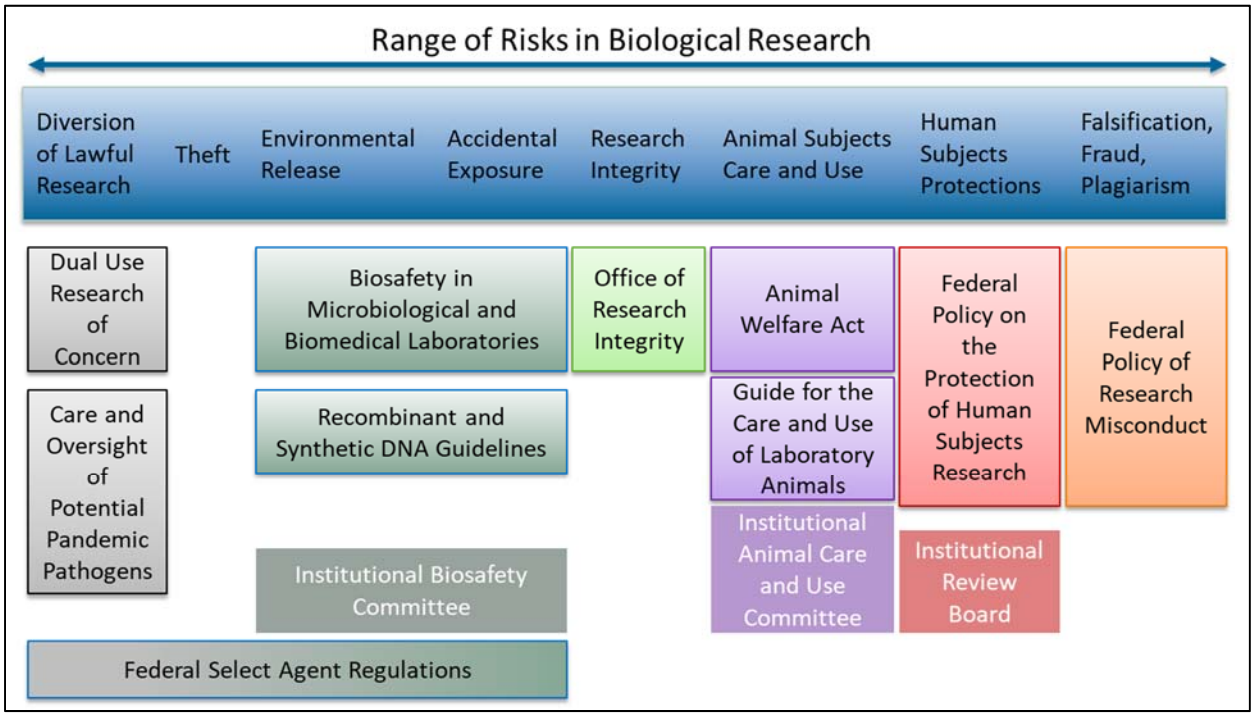


Figure 3. Schematic illustrating the current framework for governance of scientific responsibility and ethical, safety, and security risks associated with biological research.

Unlike the policy landscape for biosecurity, policies promoting investment in biodefense capability-building have sought to promote innovation within the science and technology community to generate the needed knowledge and tools. For example, several U.S. government entities, including the Centers for Disease Control and Prevention (CDC), NIH, DoD, Department of Homeland Security (DHS), and Intelligence Advanced Research and Development Activity (IARPA), have invested in biosurveillance capabilities to detect the emergence of unusual biological incidents involving biological agents, new pathogens, or laboratory-developed pathogens in animal and human populations. These efforts, which continue today, have sought to leverage advances in computer and data science to develop data analytics platforms that can integrate, sort through, and analyze vast amounts of information. In 2013, the

White House issued a National Biosurveillance Science and Technology Roadmap to help implement its 2012 National Strategy for Biosurveillance.(28, 29) Another example is DoD's interest in harnessing a variety of biological sciences, including systems biology, ecology, and behavioral sciences, to enhance military capabilities to prevent and defend against biological threats.(30) The importance of biology and biotechnology to the DoD mission was further supported by the establishment of the Biological Technologies Office of the Defense Advanced Research and Development Activity (DARPA), which seeks to harness biology and biotechnology advances to enhance national security.(31) These and many other U.S. biodefense initiatives promote development and application of cutting-edge, multi-disciplinary science to develop creative and effective solutions for countering biological threats.

Several new policy activities are anticipated in 2018. In January 2018, the Department of Health and Human Services (HHS) released its policy on care and use of enhanced potential pandemic pathogens (P3CO).(32, 33) At the present time, no other U.S. agency that funds biological research has created a corresponding P3CO policy. In March 2018, U.S. Representatives Susan Brooks and Anna Eshoo established the Congressional Biodefense Caucus to raise awareness about biosecurity and biodefense issues among members of Congress, to strengthen U.S. biosecurity and biodefense efforts, and to identify and address gaps in capabilities.(34) Also in March 2018, the 2018 Omnibus Appropriations acknowledged HHS's interest to shift oversight of the Strategic National Stockpile to HHS Assistant Secretary for Preparedness and Response (ASPR) and required the development of a U.S. strategy for global health security.(15) The Department of State (DoS) and HHS are leading efforts to define the next four years of the Global Health Security Agenda, which is an intergovernmental initiative designed to identify and address gaps in prevention, detection, and response to natural or man-made biological threats. The new National Biodefense Strategy, which was called for in the 2016 National Defense Authorization Act (NDAA), and a new National Health Security Strategy and Implementation Plan are anticipated to be released in 2018. Finally, DoD, DoS, and the U.S. Agency for International Development were involved in a Stabilization Assistance Review since May 2017, which is intended to develop a framework for foreign assistance in conflict zones and fragile states. The report of this review was delivered to Congress in April 2018 and is expected for public release later this year.(35)

Despite this high level of activity in biodefense and biosecurity policy, systematic evaluation of existing policy and implementation to identify gaps and policy solutions for addressing those gaps has not been conducted. The 2016 NDAA has called for a review of existing policies and programs, the results of which are not publicly available. In addition, the Pacific Northwest National Laboratory has identified implementing agencies of several national strategies and the Public Health Security and Bioterrorism Preparedness and Response Act of 2002.(36) To the best of our knowledge, neither of these efforts have taken a comprehensive approach to biosecurity and biodefense policy analysis. Therefore, the authors conducted a comprehensive analysis of all U.S. biodefense and biosecurity policy to identify limitations in the current policy landscape, implementation gaps, synergistic policies, and counteracting policies as a foundation for

developing the roadmap, which is described below. The full policy analysis is included in the next chapter.

Limitations of Current Policies

The policy analysis conducted as part of this study has revealed several limitations associated with the development and implementation of biosecurity and biodefense policies. These limitations fall into three main categories: a) scope and relevance of policies; b) consistency of agency-level policies promulgated to achieve government-wide objectives; c) and stakeholder contributions in policy implementation. (Table 1) Detailed descriptions of these limitations are included in the Policy Analysis chapter.

Table 1. Limitations of the Biosecurity and Biodefense Policy Landscape in the United States.

Limitations of the Scope and Relevance of Policies	Limitations to Consistency of Policy Development and Implementation Across the U.S. Government.	Limitations to Stakeholder Engagement in Policy Implementation.
Expansive policies may lack clarity about what is or is not covered under the policy, which promotes variability in policy implementation at the federal and local levels and risks affecting sectors and activities in unanticipated ways.	The current policy system is not suitable to evaluate the broader consequences of investments or regulations.	Stakeholders do not necessarily understand their roles in achieving biosecurity and biodefense objectives.
Narrow policies, especially those based on defined lists of restricted items, often prevent thorough analysis of research to anticipate and address risks early and to maximize benefits.	Federal and local stakeholders of overlapping policies may not be the same	Limited or no additional funds are available to assist key stakeholder groups comply with biosecurity regulations.
Policies that are required only at institutions that receive U.S. government funding do not necessarily cover scientific activities that are not federally funded regardless of whether they are conducted in the United States or another country, adversely affecting awareness about technological advances and of research oversight.	No consistent or common process for reviewing and overseeing research with potential for exploitation by malicious actors. Oversight of research is agency-specific.	Some tools for prioritizing biological threats result in the identification of the same agents regardless of country or situation.

Significant Gaps in Biosecurity and Biodefense Policy

During the analysis of U.S. biosecurity and biodefense policy, several capability, policy implementation, and infrastructure gaps were identified. Table 2 highlights the key gaps in each category. Detailed descriptions of these gaps are included in the Policy Analysis Section.

Table 2. Gaps in the U.S. Biosecurity and Biodefense Policy		
Capability Gaps	**Policy Implementation Gaps**	**Infrastructure Gaps**
Microbial forensics is an underinvested field in the United States and internationally.	Insufficient funds are available to support local implementers comply with biosecurity regulations, leading many to choose not to participate in research or diagnostic activities involving restricted agents.	The regional and national biocontainment laboratories are not considered critical infrastructure preventing efforts for their protection in case of an emergency.
Systems for scanning scientific advances leading to new technologies exist in offices that support or conduct research and development, but generally do not exist at the end-user or operational levels	The continuous changes to the BSAT Regulations resulted in significant challenges and delays in federal implementation and local compliance.	Very few policies and programs exist for enabling or promoting resiliency in the biodefense, health, and research sector.
Despite significant investment in biosurveillance approaches and platforms, the underlying data used to develop effective early warning methods is highly variable and uncertain.	Practical resources that enable program managers, research reviewers, and scientists assess the risks and benefits of research currently is lacking.	Very little, if any, funding has been provided for research to generate data on the effectiveness of different biosafety and biosecurity measures.
The increasing convergence of scientific disciplines, changing funding paradigm, and expansion of biotechnology practitioners suggests that greater attention is needed on evaluating the broader security implications of advances and applications that are not only focused on pathogens and toxins.	Annual and inconsistent investment in nonproliferation activities, specifically for cooperative threat reduction programs, limits long-term sustainability of partnerships and outcomes.	
	Effective measures for evaluating biosecurity policy implementation have not been developed. However, measures for evaluating a few biodefense investments do exist, each different from another.	
	No analytic framework currently exists for assessing opportunity costs of biosecurity policy development.	

The Roadmap for Implementing Biosecurity and Biodefense Policy

Drawing on the limitations and gaps identified, several *key considerations* emerge for the development of plausible roadmap that seeks to leverage the advances in science and technology while also minimizing risk. These considerations include:

- Since 2002, the U.S. government has funded significant amounts of research on high-risk, restricted pathogens to increase scientific knowledge, develop medical countermeasures (vaccines, drugs, and diagnostic tools), and develop detection methods and technologies. Many of the scientists, technologists, and engineers involved in these studies also are held responsible for compliance with U.S. biosecurity policies, including the BSAT Regulations, dual use policies, and export control requirements. This situation may result in a misalignment between scientific investment and regulation, which ultimately presents significant barriers to reaping the benefits of science and technology advances for U.S. biodefense objectives.
- The biology and biotechnology landscape has changed dramatically during the past twenty years. New funding models, practitioners, countries, and societal drivers have completely changed this landscape, but are not included as key considerations of the current biosecurity landscape. Domestic and international engagement with non-traditional funders, practitioners, international counterparts, and end-users (including the public, if appropriate) is needed to promote an environment of global support for and governance of biological science activities. This dual goal is consistent with the BWC, which prohibits only efforts and delivery systems that are intended for weapons use, and with recent calls for cross-disciplinary efforts for global health security.
- Advances in biology and biotechnology have the potential to enhance U.S. capabilities for preventing, detecting, and responding to biological threats. In some cases, these advances have been applied to specific problem-sets, such as the development of bio-based sensors using synthetic biology approaches and early warning systems using advanced biological data analytics. However, the mechanisms used to scan for promising advances, enable further innovation to address specific defense needs, and transition to operational use are limited. Improving this process would enhance opportunities for promoting creativity and communication among the biodefense and scientific communities, enabling greater harnessing of science and technology advances and applications. Furthermore, communication between the defensive and security experts could improve current capabilities for technology assessment, ultimately reducing concerns about technology surprise.
- Balancing risk and benefit objectively (i.e., without placing unsubstantiated weight on one or the other) is absolutely critical at all levels – federal, local, and international – to ensure that fears about risk or blind hope about benefits do not adversely influence any assessment of risk and benefit. Furthermore, practical resources are needed to help policy-makers, program managers, security experts, research reviewers, and scientists conduct objective assessments and learn from previous assessments. This balancing act is particularly critical given the interests in encouraging creativity and innovation within the scientific and technological communities to design, build or develop, and apply new advances to enhance biodefense, health, agriculture, and other sector-specific capabilities.

These considerations establish the premise for the following roadmap.

System-wide Roadmap

Because the biosecurity and biodefense landscape is extremely diverse and involves stakeholders from different sectors and disciplines, the roadmap articulates clear actions across all relevant stakeholder. Figure 4 presents six primary actions that the U.S. government can undertake to address current limitations and gaps of U.S. biosecurity and biodefense policy. The six actions included in this roadmap are:

- Enhance assessments of emerging biotechnologies;
- Assist the scientific enterprise for research, detection, health security, and forensics;
- Balance benefit with concern about malicious exploitation of biology and biotechnology;
- Enable innovative research and development to meet biodefense needs;
- Promote sustainability of activities;
- Characterize the biodefense research sector as a critical infrastructure to ensure assistance and guidance on recovery and resiliency.

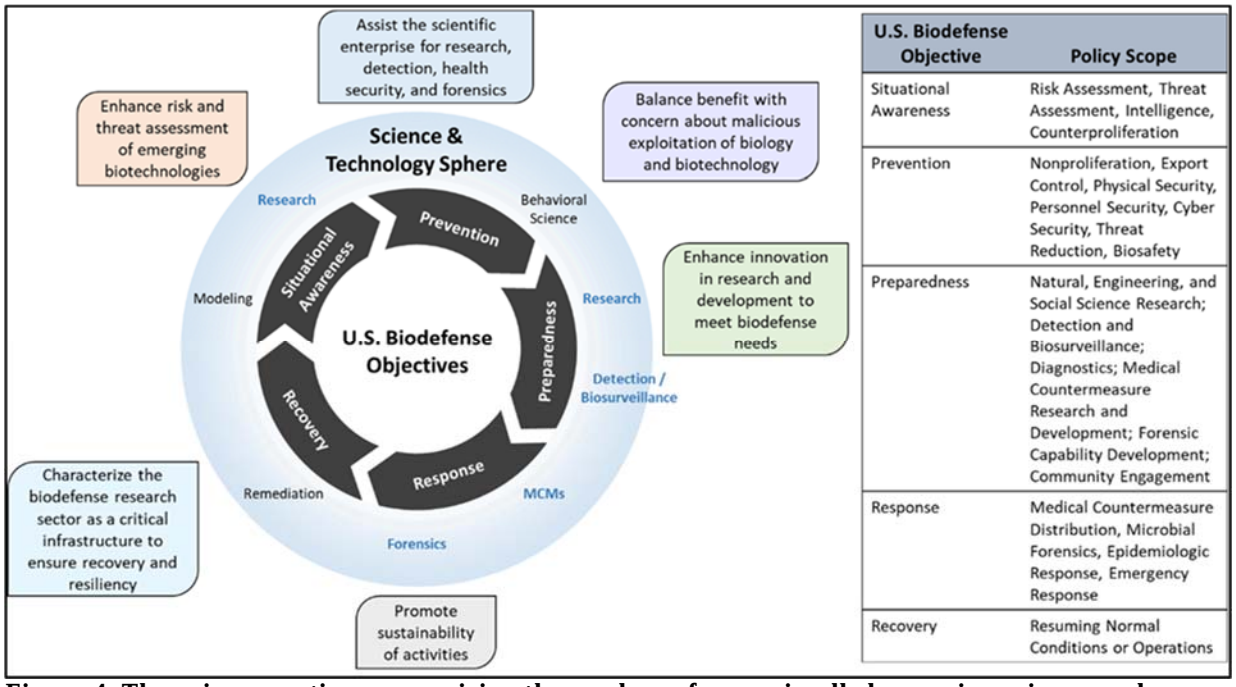


Figure 4. The primary actions comprising the roadmap for maximally leveraging science and technology advances for biodefense and minimizing biosafety and biosecurity risks. The placement of the six actions correlates with the most relevant biodefense objectives. All but one of these actions have been divided into sub-actions that contribute to their achievement. The science and technology capabilities are listed in the grey circle and placed close to the objective with which they correlate. The capabilities written in blue are discussed further in the policy analysis. The capabilities written in black are included because each is associated with one policy document. Other capabilities may exist, even though they are not included in this figure. Various U.S. government agencies have varying degrees of responsibility for each of the actions listed.

Figures 5a through 5e highlight specific steps that could be used to implement the first five actions. The primary implementor for each step is at least one U.S. government agency. Most of these actions and steps involve coordination and communication among

U.S. government stakeholders. However, a lead agency may be identified based on mission relevance, resident expertise, and available funding to support implementation and evaluation. Federal and local stakeholders, alike, may be well-suited to evaluate direct, indirect, and opportunity costs. Subsequent chapters of this report provide analytical frameworks for developing evaluation metrics of policy implementation and for examining implementation costs to various stakeholders.

The roadmap action of *enhancing risk and threat assessment of emerging biotechnology* focuses on capabilities to enhance the U.S. objectives involving situational and threat awareness. These capabilities involve providing opportunities for security experts and government personnel, more broadly, to learn about new advances in biotechnology, new applications they enable, and their technical limitations. Figure 5a includes two steps that could enhance biotechnology assessment.

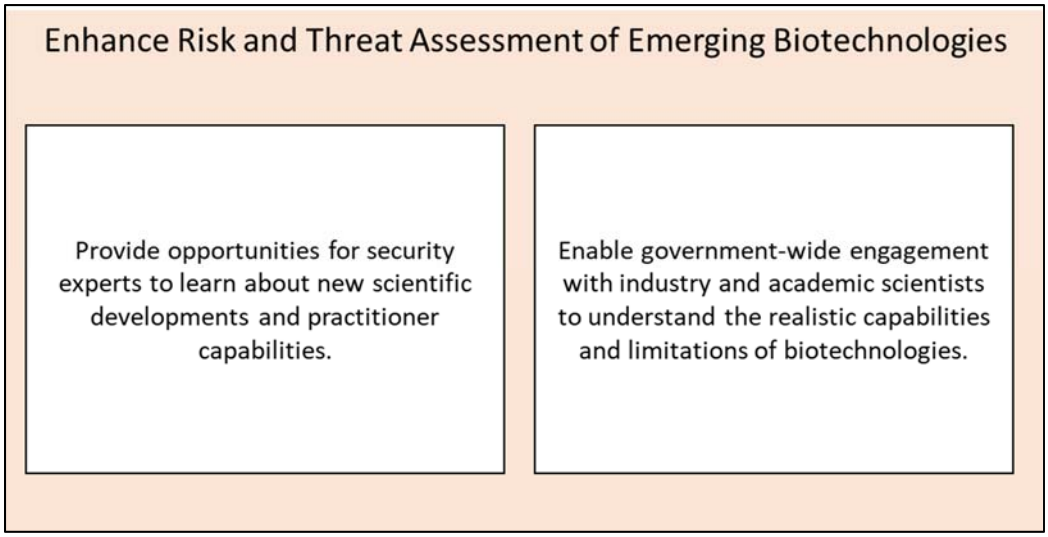


Figure 5a. Steps towards achieving enhanced emerging biotechnology assessments. The two steps listed can be conducted in parallel.

The roadmap action of *assisting the scientific enterprise involving research, detection, health security, and forensic methods* involves efforts that enable federal and local stakeholders comply with biosecurity regulations. Figure 5b includes two steps that could improve compliance with regulations through guidance and financial assistance. These steps could be done sequentially because defining changes that need to be implemented comes before needs for financial support.

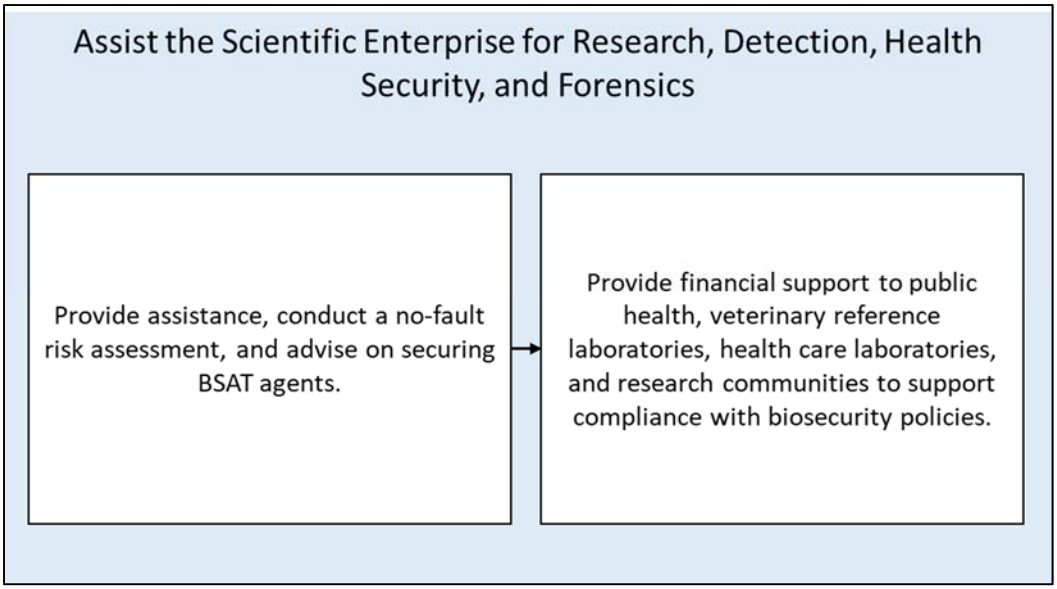


Figure 5b. Steps towards assisting the scientific enterprise that is involved in research, detection, health security, and forensics implement practices in compliance of federal biosecurity policies. The steps listed can be conducted in sequentially.

The roadmap action of *balancing benefit with concerns about malicious exploitation of biology and biotechnology* focuses on the development of resources that help federal and local stakeholders assess benefits and security risks of research objectively and share lessons learned from reviews. The steps involving stakeholder assistance for identifying and analyzing potential risks of exploitation of knowledge, skills, or technologies involves the clear articulation of outcomes of concern to ensure that guidance is not outdated as new technologies and information are created. Figure 5c presents several sequential steps towards implementation of risk and benefit assessments to maximally leverage scientific knowledge and technologies while also reducing associated security risks. These steps align most closely with prevention objectives. But, if done well, this action can result in realized benefits for preparedness and response.

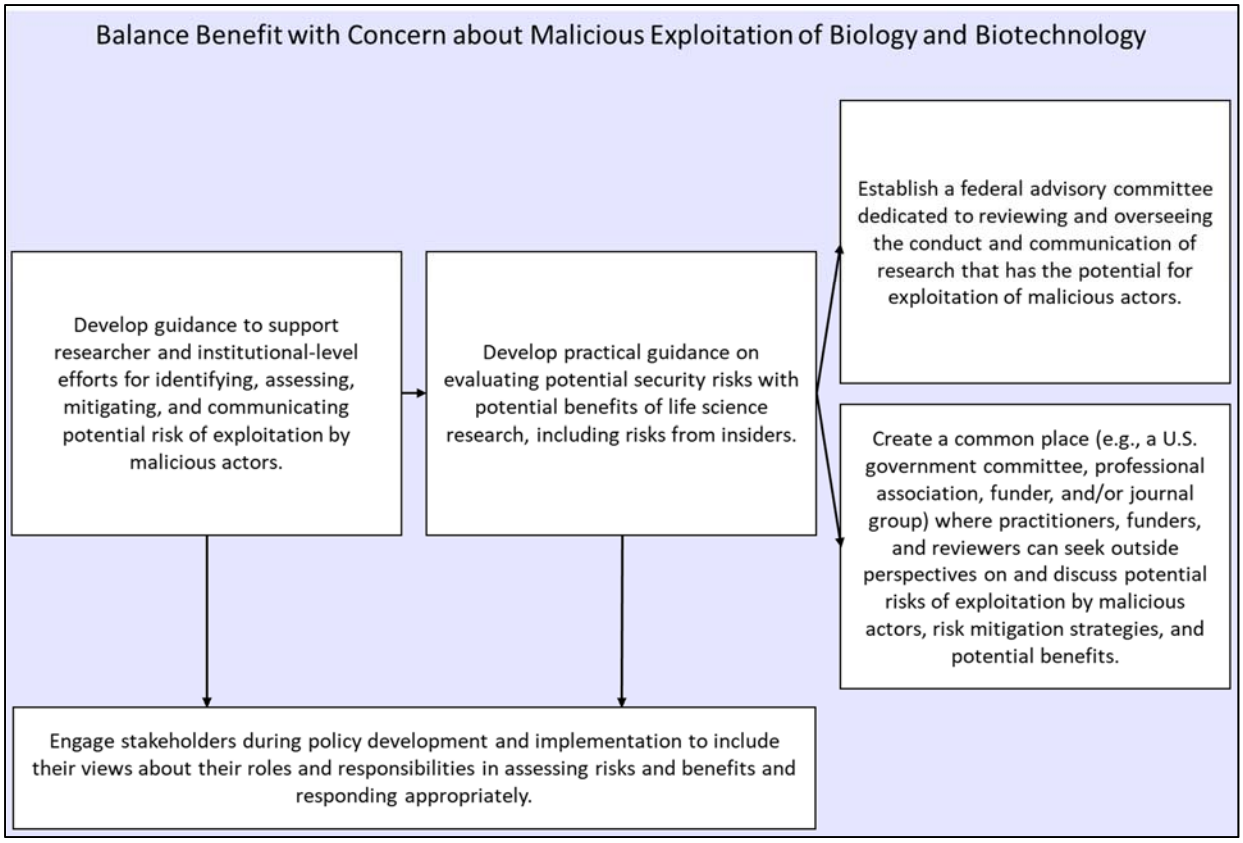


Figure 5c. Steps towards assessing and balancing the risks and benefits of biodefense and health security-relevant research. These steps could be conducted sequentially starting with the development of guidance to local stakeholders on assessing risk followed by guidance on evaluating this risk with the stated or speculated benefits. The potential benefits either are assumed from the funding initiative or project goal and rationale. These steps would be conducted in consultation with local stakeholders to ensure that the guidance reflects accurately stakeholder roles and responsibilities. A federal advisory committee that is dedicated to overseeing the conduct of research and a forum that allows opportunities for stakeholders consider different perspectives and share risk mitigation strategies could enhance objectivity in risk and benefit assessment.

The roadmap action of *enhancing innovative research and development to meet biodefense needs* focuses on enhancing the United States' ability to identify unmet or unaddressed capabilities at the national and end-user levels for which science and technology could provide solutions, support activities that enhance research capacity and workforce development, and develop approaches for encouraging more scientists and engineers to participate in the biodefense enterprise, whether as researchers, subject matter experts, and/or as policy-makers. In 2018, the Blue Ribbon Study Panel on Biodefense highlighted the need for cross-cutting budget analysis for U.S. biodefense activities,(37) a recommendation that is repeated in this roadmap. In some fields, such as vaccine and drug development, the process for basic, applied, and advanced (or translational) research is well-defined. But, in other fields, where program managers are seeking to leverage newer biological science approaches or biotechnologies to address end-user needs, the process is less well-defined, inconsistent with other processes, or not well communicated to researchers and technologists. Figure 5d includes the steps toward achieving a more informed and involved science and technology community.

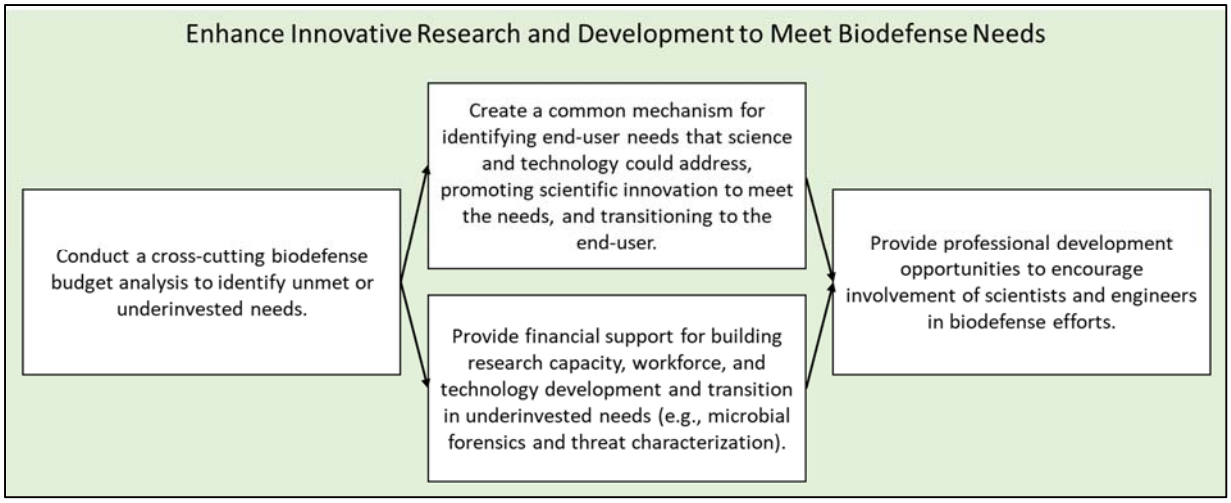


Figure 5d. Steps for enhancing research capacity to meeting unmet, underinvested, and/or end-user needs. These steps are sequential starting with cross-cutting budget analysis of biodefense and ending with opportunities to encourage involvement of scientists and engineers in the biodefense activities.

The roadmap action of *promoting sustainability* applies to all activities and stakeholders. However, the individual steps included are focused on promoting sustainability of specific activities while the U.S. government is providing financial support and well-after U.S. support ends. These steps can be conducted in parallel. The step on the left focusing on international engagement efforts with biological scientists, human and animal health practitioners, and law enforcement and emergency response personnel. The step on the right focusing on domestic efforts for maximizing benefit and minimizing risk. Figure 5e includes steps towards promoting sustainability of activities.

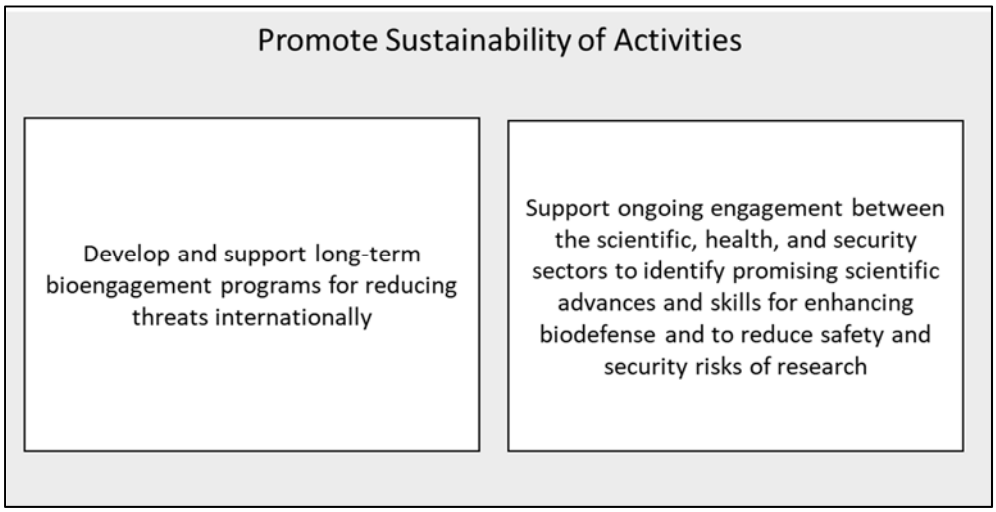


Figure 5e. Steps for promoting sustainability of activities. These steps can be conducted in parallel and apply to several stakeholders and activities.

The sixth roadmap action of *characterizing the U.S. biodefense sector as a critical infrastructure* addresses a clear gap in recovery and resiliency in this sector. Researchers regularly assist with outbreak and emergency response, lending their scientific knowledge and skills to identifying and characterizing unusual or newly

emerging biological pathogens and toxins. They conduct the foundational studies that are intended to inform medical countermeasure development, detection and monitoring of pathogens, and the development of new forensics approaches. However, the research sector is not part of the existing U.S. critical infrastructure sector, limiting federal engagement and guidance on local development of recovery and resiliency plans after disasters. In 2017, the National Academies of Sciences, Engineering, and Medicine recommended that the biomedical research sector be included as a sub-sector under the Healthcare and Public Health Critical Infrastructure Sector.(38, 39) The roadmap action encompasses this recommendation and includes other biological sciences and biotechnology fields that may fall outside the biomedical research scope.

The *federal and local stakeholders* that, based on their organizations' missions and other responsibilities, may be responsible for implementing policies in accordance with these actions are included in Figure 6. Stakeholders from several federal agencies and local entities are responsible for implementing some aspect of the first five actions. Some of these stakeholders are responsible for implementing activities that are similar to biosecurity or biodefense activities, but are not considered part of these initiatives. Examples include policies for occupational health and safety and Biosafety in Microbiological and Biomedical Laboratory (BMBL), which is used to inspect laboratories approved for BSAT. Coordination and communication among government agencies and non-governmental stakeholders is crucial for successful implementation of policies developed based on these actions.

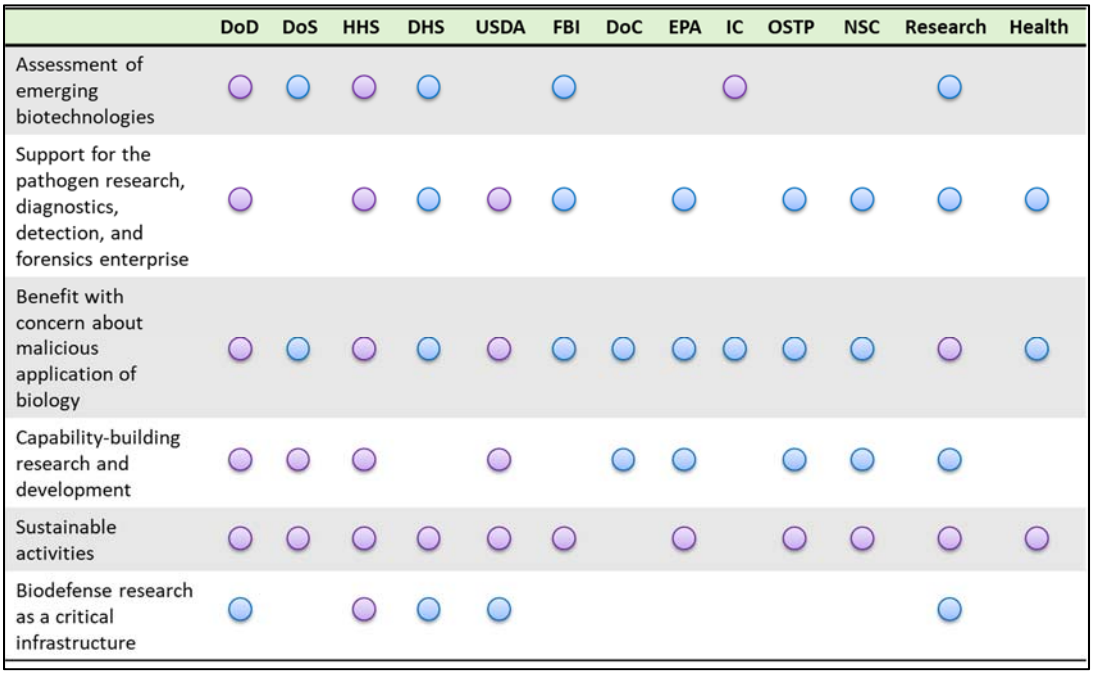


Figure 6. U.S. government and local stakeholders that may implement policies developed for each of the actions. The blue bubbles indicate responsibility of specific federal or local stakeholders for each of the roadmap actions. The purple bubbles indicate stakeholders who may have leadership roles in implementing the corresponding roadmap action.

DoD-Specific Roadmap

The Department of Defense supports a variety of science and technology activities assessing, preventing, detecting, and responding to natural, accidental, and deliberate biological incidents. Its programs span military health, research and development by the services and broader DoD, intelligence, CBRN (chemical, biological, radiological, and nuclear) homeland response,(40) outbreak response,(41) and CBRN threat reduction. Several of these DoD agencies overlap in their roles in biodefense and biosecurity. For example, the Defense Threat Reduction Agency (DTRA) supports research in chemical and biological defense to develop technological capabilities for detection and biosurveillance, early warning, medical countermeasures, and diagnostics.(42) DTRA works with other DoD entities, such as the United States Army Medical Research Institute of Infectious Disease (USAMRIID), which conducts basic and applied biodefense research.(43) DTRA also supports a variety of threat reduction activities, including global health security and cooperative biological engagement. Other DoD entities also engage in epidemic surveillance activities to gain awareness of potential biological threats.(44) Still others support research and development in biology to enhance military capabilities and to prevent harmful consequences of biotechnology.(30, 45-47) The DoD research enterprise that supports basic, applied, and translational research for any of these activities includes agency-level regulations for biosafety, biosecurity, and ethical treatment of human and animal subjects. These biodefense and biosecurity efforts enable DoD to meet its mission to safeguard the U.S. and its allies from biological threats by enhancing capabilities for threat awareness, prevention, and research and development for preparedness and response.(48)

Given DoD's role in implementing biodefense and biosecurity policies more broadly, several of the actions included in the stakeholder-wide roadmap apply to DoD. Figure 7 highlights the roadmap steps that most closely align with DoD mission areas of: threat assessment, threat prevention, research and development for biosurveillance and medical countermeasures, and response. Implementation of the steps highlighted in Figure 7, in coordination with the other responsible stakeholders (See Figure 6) could enable greater success in harnessing the capabilities and knowledge generated by science and technology advances and in reducing risk of theft, diversion, and deliberate malicious use of biology and biotechnologies.

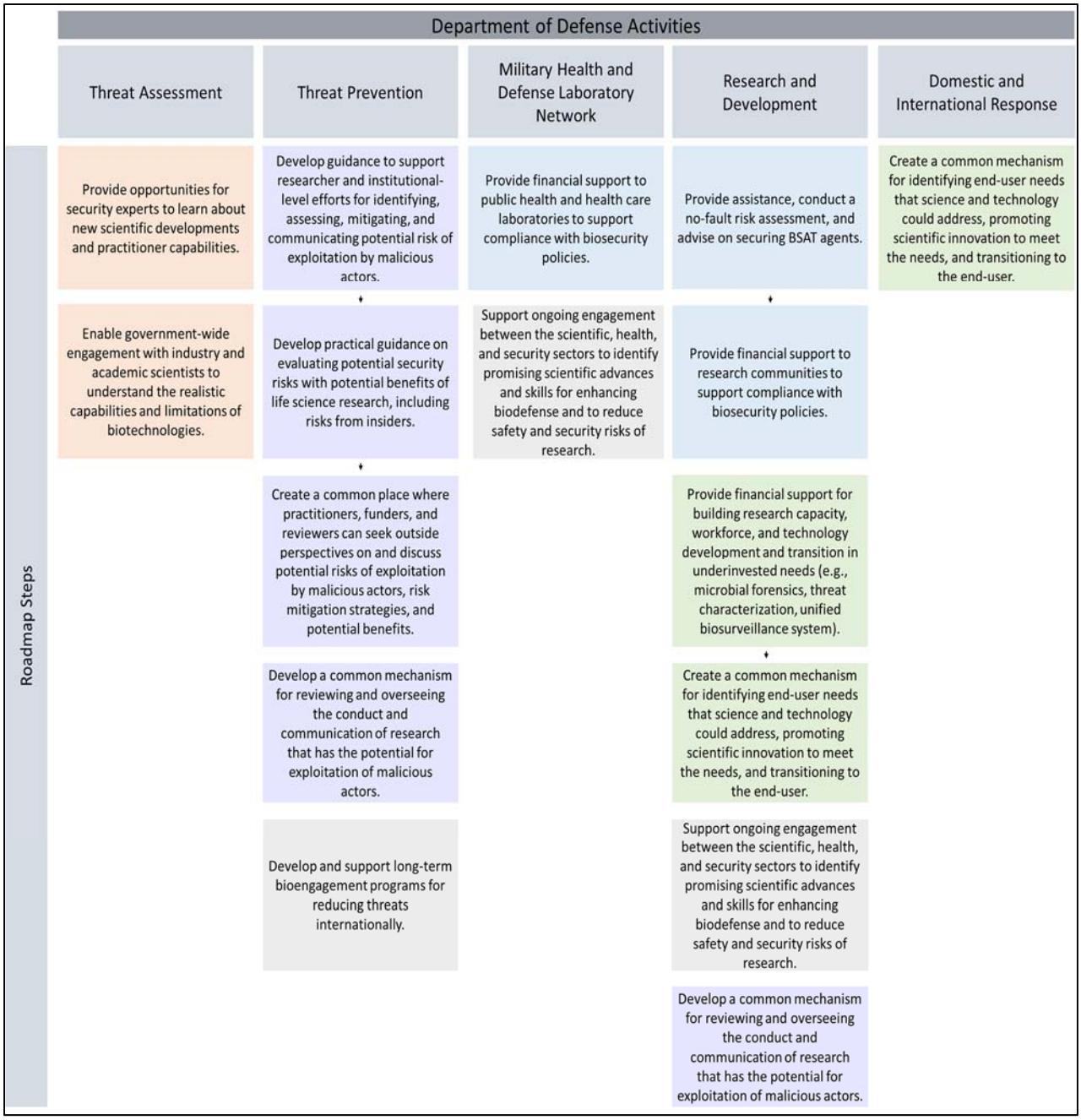


Figure 7. The steps in which DoD plays a leadership role. These steps are color coded with the six actions described in the broader roadmap and mapped to specific DoD biodefense missions.

Conclusions

The U.S. policy landscape for countering biological threats is split into two main groups: 1) biosecurity, which specifically focuses on preventing theft, diversion, or deliberate malicious use of biological sciences knowledge, skills, and technologies to cause harm; and 2) biodefense, which involves the development of capabilities and knowledge-based to assess, detect and monitor, treat (or vaccinate against), and respond to biological

threats. These two groups often affect the same stakeholders, which may result in mutual benefits among defense-oriented policies or present barriers to achieving either defense or security objectives. At the same time, the biotechnology landscape is changing dramatically, simultaneously presenting new opportunities for building technological capabilities and for enhancing security vulnerabilities. The policy analysis undertaken to inform this roadmap involved a systematic evaluation of existing policies for harnessing new advances in the biological sciences and biotechnology and for preventing malicious or accidental harms caused by pathogens, toxins, and scientific advances. This systems-based approach allowed for the identification of limitations and gaps in the current policy landscape, including those emerging from federal and local-level implementation. In addition, this analysis highlighted clear steps that could be undertaken by U.S. government, academic, and human, animal, and plant health stakeholders to address the critical limitations and gaps identified.

As new policies for biosecurity and biodefense are developed, their success and costs of implementation likely will be evaluated. To date, few evaluation metrics have been developed for evaluation of biosecurity and biodefense policy implementation. Those measures that have focused on quantitative or prescriptive assessments of required or recommended activities, such as the number of individuals trained in a course or the presence of locks on doors. Few have incorporated measures for evaluating achievement of program outcomes. For example, in 2015, the DTRA Cooperative Biological Engagement Program commissioned the development of metrics with which to evaluate its bioengagement activities. The final product included several activity and outcome-based metrics for assessing achievement of specific bioengagement activities. We have adapted this, and other similar, approaches to the evaluation of policies (See Evaluation Metrics Framework chapter). Using this framework, policy-makers and other stakeholders can begin to identify the types of data needed to evaluate the successful implementation of activities and the degree to which program outcomes or goals have been achieved.

A crucial determinant of success of a given policy is the feasibility of stakeholder implementation and potential downstream consequences. The U.S. government has two primary ways of calculating costs of new policies, both of which rely on economic data. The first involves the Congressional Budget Office estimates the costs of new legal mandates to governmental and non-governmental stakeholders.(49) The second involves regulatory agency review of the expected direct financial costs of implementing specified activities of a new or revised regulation. Neither of these assesses potential indirect costs to research, workforce, or any other intangible parameter or potential trade-offs that implementing stakeholders may make to off-set the direct costs. These indirect costs have downstream consequences to achievement of policy objectives. Some universities and researchers have calculated the direct financial costs of compliance to federal regulations. To the best of our knowledge, we are not aware of any analysis that has attempted to measure direct, indirect, and opportunity costs of policies. Therefore, we have developed an opportunity cost analysis that includes parameters for assessing each of these costs. The goal of this framework is to help policy-makers and other stakeholders identify the types of data needed to assess direct and indirect costs of a new

policy and the downstream consequences resulting from the indirect costs. Calculating these costs is important for determining the burden of implementing new measures and its potential effects on the advancement and application of research.

The roadmap, evaluation analysis framework, and opportunity cost framework described in this report seek to harness science and technology advances while simultaneously minimizing risk.

Policy Analysis

The multi-use nature of emerging biotechnology presents several unique challenges to biosecurity policy and governance. Biosecurity and biodefense—broadly conceptualized—will be affected by emerging biotechnologies in a variety of ways which only now are beginning to be understood. In 2016, the National Defense Authorization Act (NDAA) required the U.S. government to create a new "National Biodefense Strategy", along with an implementation plan that encompasses the well over 100 existing biodefense and biosecurity policies and programs. The NDAA also requires an assessment of all existing governance to date, the analysis for which has not been made public. Although some have done work to evaluate the landscape of policies, no one yet has done a comprehensive relational analysis of their implementation. However, without a system-wide evaluation of all policy, the immediate and longer-term consequences to U.S. objectives for countering biological threats may never be understood.

To better understand biosecurity and biodefense policy implementation and broader consequences, the authors have undertaken a comprehensive, relational analysis of all biodefense and biosecurity policies since 1913. The creation of such a relational "landscape" of policy enabled the authors to: 1) make fundamental observations about the biodefense policy landscape as it currently exists; 2) provide direction for the analysis of opportunity costs associated with the implementation of policies; 3) support the evaluation of policies; and 4) delineate clear needs for incorporation in the roadmap. Included in the analysis were U.S. Code, international agreements and partnerships, guidance, guidelines, and agency and executive-level strategies as primary components. U.S. Code, which encompasses enacted legislation and regulations, was used to prevent double-counting of policies. Once assembled, each policy was tagged by policy type, subject area, primary biodefense objective for which the policy was created, and the biodefense objectives that the policies indirectly affect after implementation. Figure 8 illustrates our approach used to analyze U.S. biodefense and biosecurity policies. Gephi was used to create the network maps and Tableau was used to create the dot graphs.(50, 51) All policies included in this analysis are publicly available through the U.S. Code, Code of Federal Regulations, Government Printing Office, White House archives, PHE.gov, and individual agency websites.

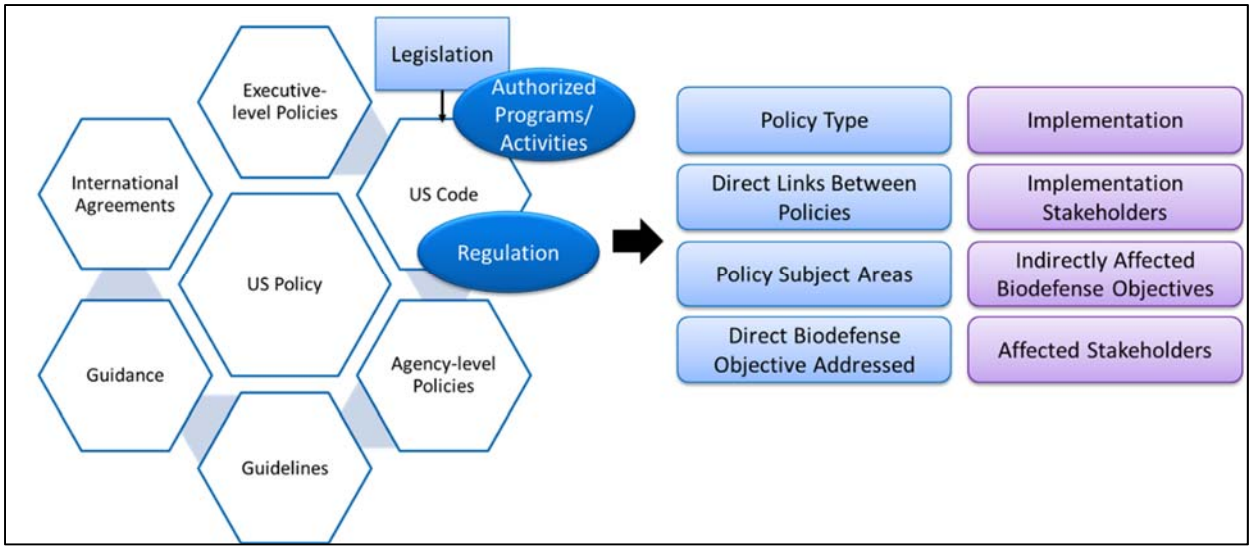


Figure 8. An illustration of the approach used to analyze U.S. biodefense and biosecurity policies. Policies were tagged by subject area, direct and indirect biodefense objective, and implementing and affected stakeholders. Links between related policies (specifically, the issuance of one policy led to the development of another) were indicated to enable the development of a relational database of U.S. biosecurity and biodefense policies, which was used to create the network maps and dot graphs.

To map policies to biodefense objectives, the authors evaluated the utility of using either the four pillars of biodefense in the 2004 Homeland Security Presidential Directive 10/Biodefense for the 21st Century or the seven objectives in the National Strategy for Countering Biological Threats. However, neither of these objectives included the full range of biodefense objectives. Therefore, the objectives used in this analysis are listed below and cover the full spectrum of biodefense activities:

- Situational Awareness, which includes threat assessment, risk assessment, and intelligence
- Prevention, which includes export control, physical security, personnel security, cyber security, nonproliferation, and threat reduction
- Preparedness, which includes preparedness planning, community engagement, research and development of medical countermeasures, and detection and biosurveillance activities
- Response
- Recovery

Science and technology capabilities supporting biodefense objectives are:

- Natural, engineering, and social science research
- Medical countermeasure research and development
- Biosurveillance and detection
- Forensics

The science and technology capabilities often fall under more than one biodefense objective and therefore, are included as separate objectives in our policy analysis.

In addition, biosafety is listed separately in the policy analysis primarily because both of its definitions – measures to prevent laboratory exposure or release of pathogens *and* to prevent environmental release of genetically modified organisms for the protection of biodiversity – may help to address biosecurity risks. Laboratory biosafety measures provide overlapping benefits for laboratory biosecurity. Furthermore, U.S. policies on safety of biotechnology products and recombinant and synthetic nucleic acids are part of the overall governance landscape of biology and biotechnology, including research about which security concerns are raised. For example, synthesis of the extinct horsepox virus using commercially-synthesized DNA has elicited significant concern among security experts about its dual use potential. This research would not be covered under any U.S. biosecurity policy if conducted in the U.S. because horsepox is an animal only pathogen that went extinct on its own. However, this research would be covered under U.S. biosafety and worker protection policies if conducted in the United States. Because of its complexity and the concern it has generated among some national security experts, the authors have developed a policy case study on this research.

Findings from Policy Mapping and Analysis

U.S. biosecurity and biodefense policy development is reactive and often has been implemented inconsistently. (See Figure 2 in the Roadmap chapter.) When a major incident occurred, the U.S. government typically has responded in a reactive mode to counter that particular risk. For example, the illegal acquisition of plague bacteria by a member of a white supremacist group resulted in creation of the Federal Select Agent Program (FSAP). This program significantly changed in 2005 in response to calls for strengthened security around BSAT after 9/11 and the subsequent Anthrax letters, and again in 2012 after Dr. Bruce Ivins was identified as the perpetrator of the 2001 Anthrax letters. Today, FSAP controls access to and regulates certain research involving high-risk pathogens. This iterative and reactive policy-making process has resulted in delays and abandonment of research involving BSAT agents at several institutions because of high financial and time burdens associated with the continuously-changing policy and implementation requirements. (Appendix 3 includes a historical analysis of BSAT regulations.) This example illustrates some challenges that the U.S. biosecurity and biodefense sector has encountered during the past 20 years.

Policy Analysis Based on Subject Area

The relational analysis performed reveals that policy and governance are divided into two primary, interdependent domains: actions intended to prevent biothreats, and actions intended to prepare for and respond to biothreats. (See Figure 1 in the Roadmap chapter). Activities in one domain can influence the other for benefit or counteraction. For example, guidelines for export control may counteract the need to share information, variants, and genetic sequences of restricted pathogens to increase scientific knowledge about how the agents cause disease and how to prevent or treat an infection. At the same time, activities within the same domain also can benefit each other. For example, compliance with the Biological Select Agents and Toxins regulations

may enhance laboratory biosafety, in addition to laboratory biosecurity, at approved facilities and successful development of medical countermeasures and distribution plans enhance preparedness and response capabilities.

The group of policies on preventing theft, diversion, or deliberate malicious use of biological knowledge, skills, and technologies primarily are focused on high-consequence pathogens, most of which are listed on U.S. export control, Australia group export control, and BSAT lists. This focus highlights the inadequacy of the current biosecurity and nonproliferation policies for evaluating and reducing potential vulnerabilities and threats associated with emerging biotechnologies that do not involve restricted pathogens and toxins. The group of policies on building U.S. capabilities to defend against natural, accidental, or biological threats often seek to leverage newly generated scientific knowledge and technology capabilities, such as data science, additive biomanufacturing, and synthetic biology. Even research involving basic characterization of pathogens, including evaluations of immunological and host response, are beginning to incorporate non-life-science advances to enable new discoveries and applications for detection and medical countermeasure research and development. This discrepancy may exacerbate efforts to evaluate and compare potential risks and benefits of research and development activities, in part because the risk of some research may be inadvertently (and possibly, inappropriately) considered to be greater than they are and the risk of other scientific activities may be disregarded because their uses and outcomes do not conform to existing conceptualizations of biosecurity.

Policy Analysis Based on Primary Biodefense Objective

Another way to categorize U.S. biosecurity and biodefense policies is by their primary purpose. An analysis of policies based on the biodefense objectives they seek to address reveals an interconnectedness between several policies.(Figure 9) This analysis can identify those biodefense objectives that have high levels of policy action and investment, and those objectives that have low levels of policy action, which may signify priority level or capability gaps. The analysis of associations of policy and biodefense objectives shows close relationships between situational awareness (including risk and threat assessments and intelligence), preparedness, response, and medical countermeasure development policies. Several policies include sections on prevention, detection and biosurveillance, resulting in close association between these policies. Similarly, several policies on prevention also include provisions for medical countermeasure development. Policies designed to promote biodefense research are loosely associated with detection and biosurveillance, and situational awareness policies. One policy, the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, links research, prevention and preparedness objectives. The most distantly related policies to other biosecurity and biodefense policies are the biosafety and environmental safety policies.

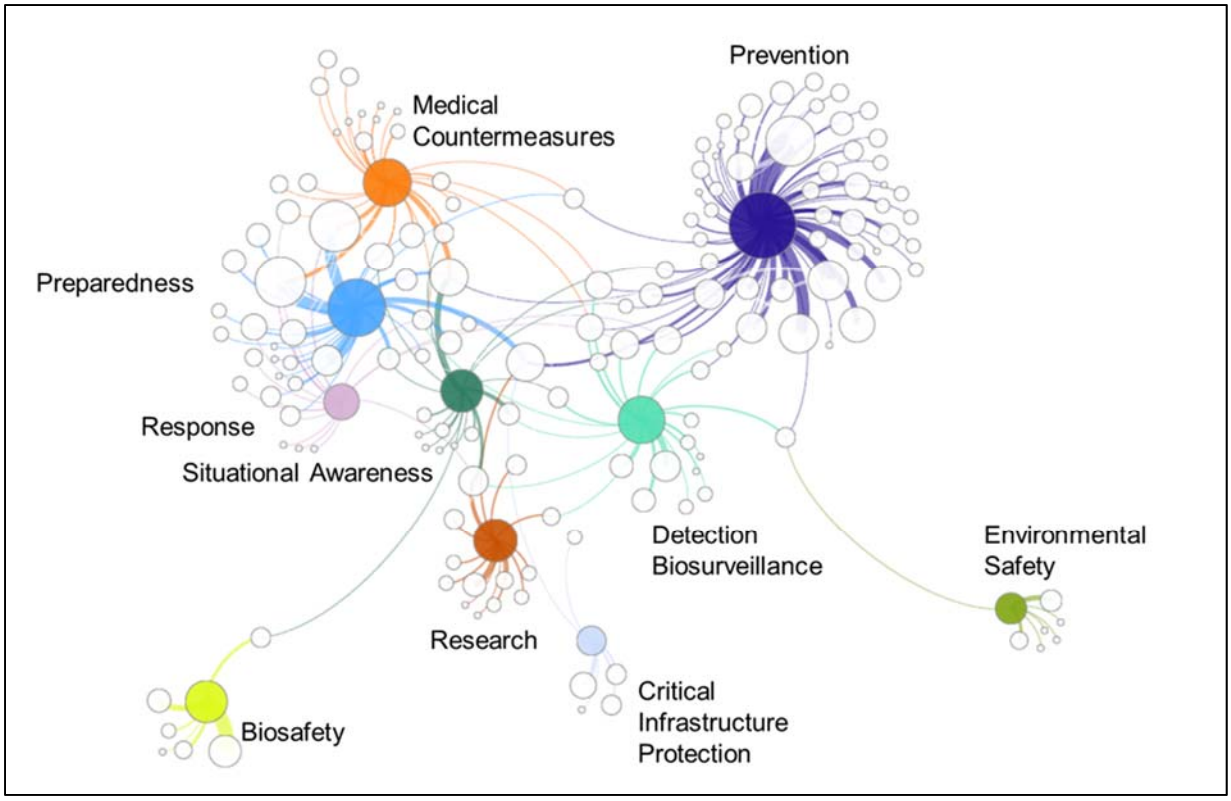


Figure 9. Relationships between policies that have been developed and implemented to achieve the same biodefense objectives. Each white circle is a unique U.S. Code, international agreement or partnership, Executive or agency-level policy, program activity (if not already associated with a U.S. Code, international partnership, or agency-level policy), guidance, and guidelines. The size of the circles reflects the number of policies that are associated with a biodefense objective. The colored circles are nodes signifying biodefense objective. The size of the nodes reflects the number of policies associated with each biodefense objective and the distance between nodes reflects the degree to which policies are linked based on the underlying relational database. The lines reflect direct relationships between policies and biodefense objectives based only on existing policies. This map does not reflect associations of biodefense objectives based on conceptual similarities, but rather associations by direct links between existing policies.

Some of these policies, such as Homeland Security Presidential Directive-10 (HSPD10)/Biodefense for the 21st Century and the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, contain sections that address several objectives including medical countermeasure development and preparedness. These policies link different biodefense initiatives together, such as prevention and detection. Other policies, such as Project Bioshield Act of 2004, are exclusively focused on a single objective. These policies may seem distantly related to other biodefense objectives, but they may be associated with several other policies that address more than one objective. For example, policies only focused on medical countermeasure development (of which the Project Bioshield Act is a part) are associated other policies on preparedness, which includes general preparedness sections and detection in addition to medical countermeasure development.

Some policies that are assumed to be linked to certain policies may not be as tightly connected. For example, biosafety and laboratory biosecurity are conceptually overlapping. But, based only on policy, the biosafety and prevention objectives are

loosely connected. The Biosafety in Microbiological and Biomedical Laboratories (BMBL) guidance, one of several policies encompassed within the biosafety objective, is the only biosafety policy that has a direct connection with biosecurity. Similarly, the prevention objective encompasses a variety of policies, one of which is the BSAT Regulations, which require physical and personnel security of regulated entities and are inspected using the BMBL. Another example is critical infrastructure protection, which has been applied to the pharmaceutical and healthcare sectors and agriculture and food sectors in accordance with HSPD10/Biotechnology for the 21st Century. This designation enables vulnerability assessments to be conducted for included sectors to identify key gaps for which activities to address gaps can be supported. However, the research community is not considered a critical infrastructure sector despite biodefense investments in the establishment and/or construction of regional and national biocontainment laboratories, which initially were intended to provide scientific and laboratory support to the public health sector in a biological event.

The policies that are associated with biodefense objectives are not only investments in new or existing programs. Figure 10 shows the types of policies associated with each biodefense objective. By far, the objective associated with the most policies is prevention. Comprising the prevention objective are a mix of policies establishing new or promoting new capability-building activities, requirements, regulations, and punishments. However, total number of requirements, regulations, and restrictions is greater than the number of policies on capability-building activities. Similarly, the number of regulations and restrictions for safety is greater than the number of activities, which includes a statute promoting research on applied biosafety (a policy which receives little attention outside the biosafety stakeholder community). All other biodefense objectives primarily are comprised of capability-building policies including medical countermeasure development. An exception are the regulations associated with the process for review and approval of drugs, devices, and biologics, which are based on the Food, Drug and Cosmetic Act. Because this Act is so broadly applied, it was not included in this analysis.

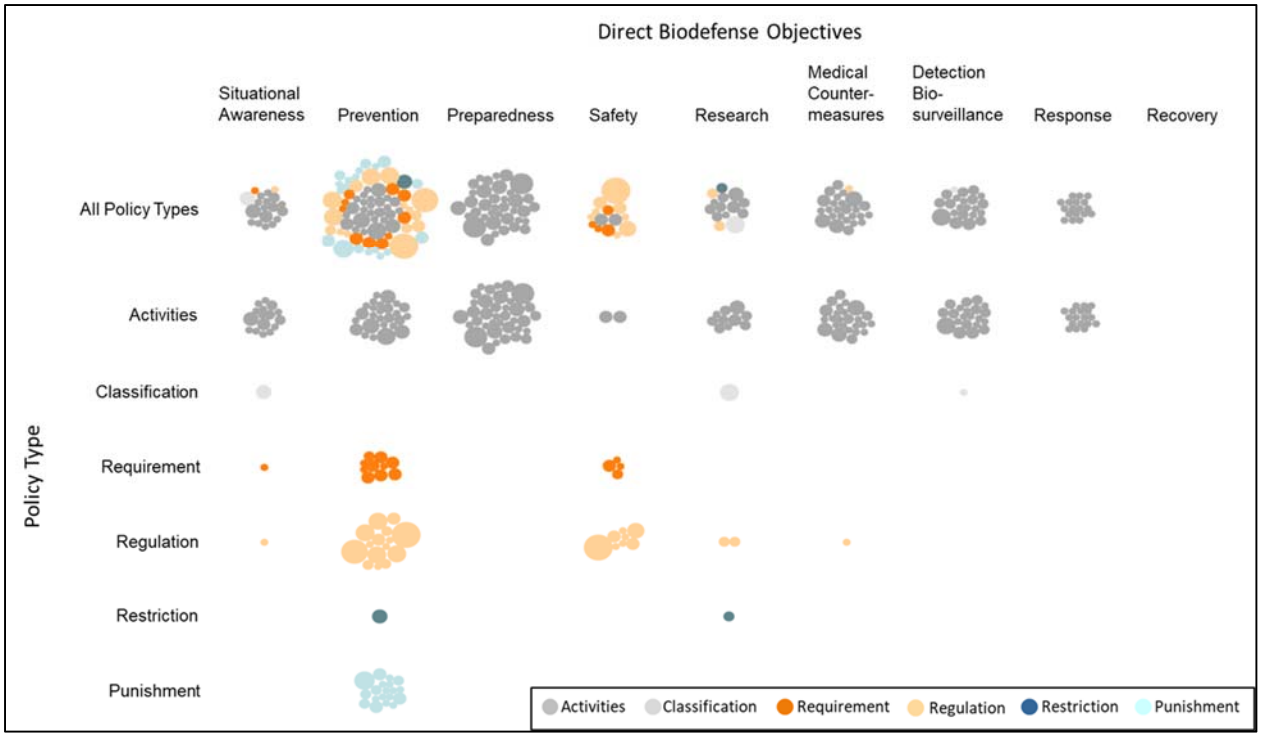


Figure 10. Breakdown of policy types by biodefense objectives. Each bubble is a unique U.S. Code, international agreement or partnership, Executive or agency-level policy, program activity (if not already associated with a U.S. Code, international partnership, or agency-level policy), guidance, and guidelines. The size of the circles reflects the number of policies that are associated with subject area and address a biodefense objective.

Implementation Stakeholders

Federal and non-federal stakeholders implement biosecurity and biodefense policies to varying degrees.(Figure 11) The primary U.S. government departments and agencies that are responsible for preventing theft, diversion, or deliberate malicious use of biological knowledge, skill, technologies, and agents include: Department of Health and Human Services (including Food and Drug Administration, Centers for Disease Control and Prevention, National Institutes of Health, Office of the Assistant Secretary for Preparedness and Response, and Office of Global Affairs), Department of Defense (including Defense Threat Reduction Agency, Defense Health Affairs, National Guard, and the Services), Department of Homeland Security (specifically, Science and Technology Directorate and the new Counter Weapons of Mass Destruction Directorate), U.S. Department of Agriculture (including Animal and Plant Health Inspection Service and Food Safety Inspection Service), Department of State (including the Bureau of International Security and Nonproliferation, Bureau of Arms Control Verification and Compliance, and Office of International Health and Biodefense), Federal Bureau of Investigation, Office of the Director of National Intelligence and associated intelligence agencies (including Central Intelligence Agency and Defense Intelligence Agency), Environmental Protection Agency, and Department of Commerce (specifically, the Bureau of Industry and Security). Many of the same agencies also are involved in implementing policies for building U.S. capabilities to prepare for and respond to biological threats. The Department of Commerce and Department of State do not appear to have formal roles in implementing preparedness and response activities.

However, the Federal Emergency Management Agency of the Department of Homeland Security and U.S. Agency for International Development do.

Non-governmental sectors involved in implementing biosecurity and biodefense policies include: the health sector (including public health laboratories, veterinary diagnostic laboratories, health care facilities, and clinical diagnostic laboratories), the research sector (including academia, non-profit research institutions, and pharmaceutical and biotechnology companies), emergency response personnel, food and agriculture industry and local farms, members of the public, and international counterparts of governmental and non-governmental entities.

This complex landscape of implementing stakeholders can create difficulties in coordination and communication between organizations with different missions, especially if one or more of the stakeholders have completing responsibilities or do not view biodefense as a primary objective of the organization. For example, universities that support basic and applied biodefense research have the primary missions of education and research. Similarly, the Occupational Health and Safety Administration (OSHA) primarily focuses on worker protection, but this function overlaps significantly with laboratory biosafety practices, which focus on preventing accidental exposures of laboratory workers to pathogens. OSHA's authorities are distinct from the agencies associated with laboratory biosafety, but they overlap conceptually and in practice. The different stakeholders and their missions either may be supportive if stakeholders are willing to work together on identical activities despite differences in missions; complement each other if stakeholder missions and activities are similar, but not identical; or counteract one another if stakeholder missions or activities oppose each other. For example, the need to communicate scientific and health information may be in direct conflict with the calls for preventing malicious actors from accessing scientific methodologies and results. The 2012 debate about publication of the H5N1 papers raised this situation as a significant problem. On the one side, the National Science Advisory Board for Biosecurity recommended redaction of information about specific sequences that could enable mammal-to-mammal transmission of the virus. On the other, the editor-in-chief of *Science* called for a mechanism or platform through which to communicate the data to key stakeholders in public health. This open communication is part of academic freedom and upheld by the National Security Decision Directive 189, which states that fundamental research intended for open publication be unclassified. Ultimately, *Science* was required to apply for an export control license for publishing the modified paper co-authored by the Dutch researchers so that other scientists, human health practitioners, and animal health practitioners were able to access the results of the study. Together, these considerations highlight the need for an overarching strategy for biosecurity and biodefense that accounts for synergistic, complementary, and counteracting stakeholder missions and activities. Furthermore, these considerations help to identify communication and coordination needs among different stakeholder communities.

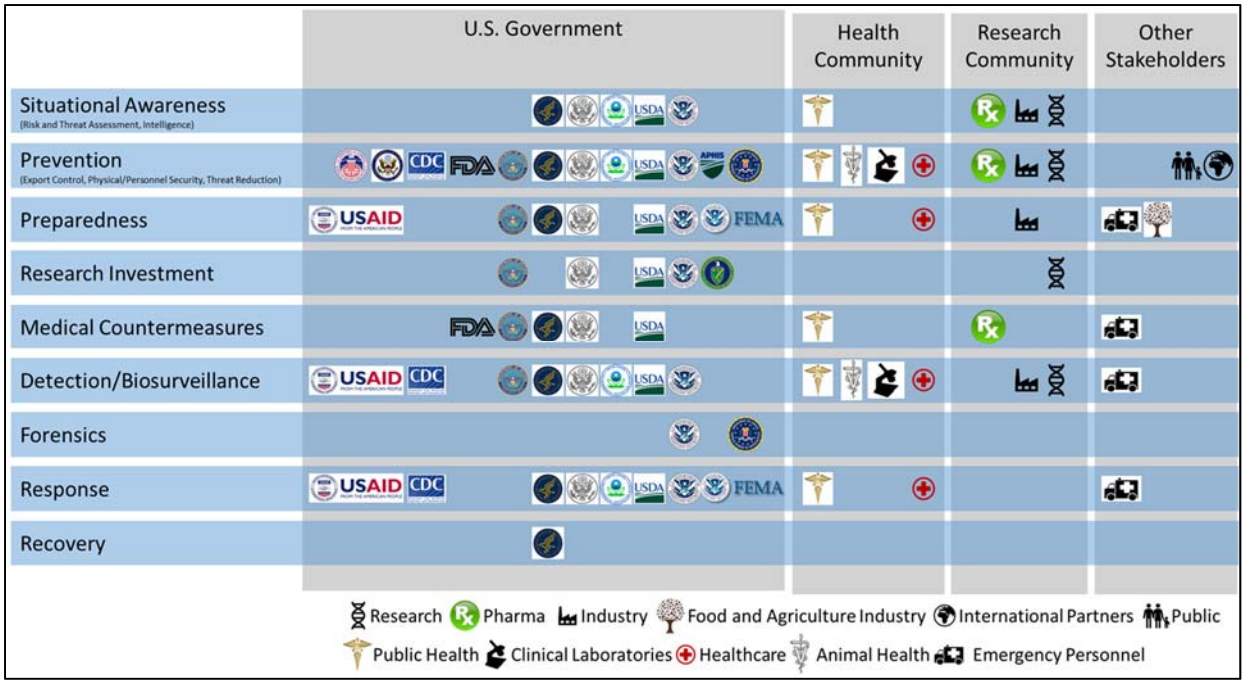


Figure 11. Federal and local stakeholders responsible for implementing policies for different biodefense objectives. Several federal and local stakeholders are responsible for implementing U.S. biosecurity and biodefense policies. Some stakeholders play a role in implementing several biosecurity and biodefense objectives, whereas some stakeholders only implement certain objectives. Understanding the roles and responsibilities of stakeholders of each objective is helpful in understanding the degree to which communication and coordination is needed.

Limitations of Current Policies

The policy analysis conducted as part of this study has revealed several limitations associated with the development and implementation of biosecurity and biodefense policies. These limitations fall into three main categories: a) breadth and relevance of policies (Table 3); b) consistency of agency-level policies promulgated to achieve government-wide objectives (Table 4); c) and stakeholder contributions in policy implementation (Table 5).

Table 3. Limitations of the Breadth and Relevance of Policies. The scope of biosecurity policies can be too expansive inadvertently including unrelated items, or too narrow, focusing on a subset of biological agents, experiments, and/or equipment.

Limitation	Examples
Expansive policies may lack clarity about what is or is not covered under the policy, which promotes variability in policy implementation at the federal and local levels and risks affecting sectors and activities in unanticipated ways.	The U.S. Code 18 Section 175C on Variola Virus (the virus that causes smallpox) initially was interpreted as including possession of any relative of the smallpox virus, which would hamper significantly research in several non-biodefense fields. The Department of Justice was asked to provide an interpretation of this statute to clarify its scope.
	The use of the Biological Weapons Anti-terrorism Act, which implements the Biological and Toxins Weapons Convention, was used to arrest an artist who was growing bacterial cultures in his home for a museum exhibit. The indictment eventually was dismissed because the artist was found not guilty of developing, producing, stockpiling or using the cultures as a weapon.
Narrow policies, especially those based	U.S. policies on review of dual use life sciences research of concern requires oversight of research involving a specified list of 15 pathogens and toxins, 14

on defined lists of restricted items, often prevent thorough analysis of research to anticipate and address risks early and to maximize benefits.	of which are already restricted by the Federal Select Agent Program, and 7 specified experiments. Although exceptions exist, most institutions either no longer review proposed experiments for dual use potential if they do not support research with any of the 15 pathogens, or do not review experiments involving pathogens other than the 15 listed agents if they do support research with any of the pathogens. The result is a lack of general awareness about potential malicious exploitation of biological information or research, of broader understanding about what constitutes as dual use potential, of a common and defensible approach to assessing benefits, and of objective analysis of risk and benefit at the institutional and national levels.
Policies that are required only at institutions that receive U.S. government funding do not necessarily cover scientific activities that are not federally funded regardless of whether they are conducted in the United States or another country, adversely affecting awareness about technological advances and of research oversight.	In 2015, the NIH director stated that no federal funds would be used to support gene editing research in human embryos, upholding the Dickey-Wicker Amendment of 1996, which states that no HHS funding could be used for "research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than allowed for research on fetuses in utero..." Individual U.S. states have passed more or less restricted policies on human embryo research; some states allow human embryo research to be conducted if privately funded. In 2017, U.S. researchers at the Oregon Health and Science University published its work on CRISPR/Cas9-mediated genome editing of viable human embryos, which was fully funded by philanthropic organizations, institutional funds, and the Shenzhen government (likely supporting BGI's collaboration in sequencing embryo genomes). In addition, six other countries, including China, the United Kingdom, and Sweden, have approved gene editing studies involving viable human embryos. These advances are significant given new requirements of the U.S. government agencies to monitor and assess advances in gene editing annually.
	In 2017, researchers at the University of Alberta synthesized horsepox virus, a previously extinct orthopoxvirus, from published sequences. This study, which was conducted and overseen in Canada, was fully funded by a private U.S.-based company. The researchers informed the World Health Organization of their achievement in 2016 after they successfully had recreated the live virus. Box 2 and Appendix 1 provides a detailed case study of this experiment and its implications to U.S. biosecurity and biodefense policy.

Box 2. Case Study Summary: Synthesis of Horsepox Virus

In 2016, Canadian researchers informed the World Health Organization Advisory Committee on Variola Virus Research that they had synthetized horsepox virus, a previously extinct orthopoxvirus, in 6 months and with only $100,000.(2) These claims elicited concern about dual use potential of the research among the WHO committee members and subsequently, among biosecurity experts in the United States. Among their concerns are the risks that publication of the methods could enable a malicious actor to replicate the research with smallpox or another harmful orthopoxvirus, and that scientists, either knowingly or unknowingly, could assist a terrorist group in creating smallpox.(3, 4) In addition, the researchers describe three reasons for conducting this research: 1) to show that synthesis of an orthopoxvirus could be done; 2) to create a viral vector that can attack cancerous cells; and 3) to be used as a potential candidate vaccine for smallpox. The researchers' claims, the biosecurity community's concerns, and the stated reasons for conducting this type of research provide a useful case study with which to examine the broader policy implications of synthesis of an orthopoxvirus. In this case study, we review the actual experiments involved in the research and the regulatory environment in which it was conducted, evaluate the policy and scientific enablers, and explore the relevance of existing U.S. policy on similar types of research if it were conducted in the U.S.

The key findings and conclusions from this case study are:

- The existing regulatory system for governing life sciences research in the United States is overlapping and if implemented well, could result in review and oversight of research involving synthesis of an extinct pathogen and an orthopoxvirus.
- If followed exactly as written, biosecurity policies would not apply to synthesis of horsepox virus. However, biosafety and ethics policies likely would trigger review and oversight of such research even though security experts did not raise these concerns.
    - The Institutional Biosafety Committee would review the research for risks of accidental exposure (i.e., biosafety risks) to comply with the NIH guidelines for recombinant and synthetic nucleic acids, and of dual use if its review processes exceed the federal policy on dual use life sciences research of concern.
    - The biosafety official would conduct a risk assessment for biosafety and biosecurity, and identify risk mitigation strategies to comply with the 5th Edition of the Biosafety in Microbiological and Biomedical Research Laboratories Manual.
- From a scientific standpoint, the synthesis of horsepox virus requires advanced knowledge and skill suggesting that well-resourced actors who have existing poxvirus research capabilities may be able to reproduce the research.
- Because vaccinia virus (the original smallpox vaccine) is 98% identical to horsepox virus and may have been derived from horsepox virus, the safety and security risks may be no greater than corresponding risks of vaccinia virus.
- From an international perspective, scientific and national differences in understanding and addressing dual use life sciences research present significant challenges in promulgating practices that could help identify and mitigate serious biosecurity risks.

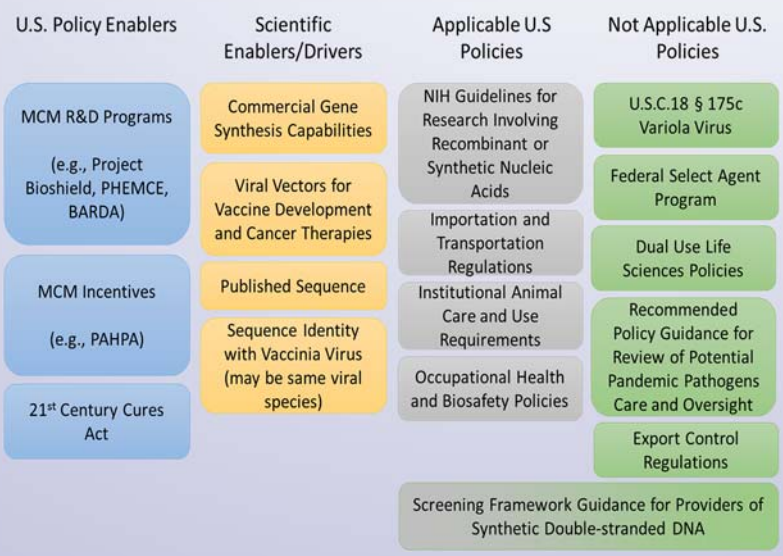


Table 4. Limitations to Consistency of Policy Development and Implementation Across the U.S. Government. Several U.S. government agencies are stakeholders of biosecurity or biodefense policies. Fourteen federal agencies fund biological research, which are expected to develop and implement policies to identify, analyze, and mitigate biosafety, biosecurity, and bioethical risks. A subset of these agencies support research, activities and initiatives to achieve biodefense objectives.

Limitation	Examples
The current policy system is not suitable to evaluate the broader consequences of investments or regulations.	In 2002, the NIH established Centers of Excellence for Emerging Infections and Biodefense, which were academic consortia designed to conduct basic and applied research to generate new scientific knowledge that would inform development of medical countermeasures, detection technologies, and biosurveillance approaches. This initiative led to an increase in researchers studying pathogens and toxins of greatest concern to the U.S. national security community and the construction of regional and national biocontainment laboratories to conduct research and support public health investigations. At the same time, concerns about malicious actors accessing and exploiting BSAT led to the strengthening of the Federal Select Agent Program and associated regulations and initiation of policy and outreach activities on dual use life sciences research of concern. The stakeholders most affected by both sets of policies – the influx of funds to conduct biodefense research and the strengthening or establishment of policies to prevent theft and exploitation BSAT knowledge, skills, and materials – are the same, specifically the research community. However, previous evaluations of U.S. biodefense capabilities did not include a systematic evaluation of policies to understand their potential relationships and potential broader implications, including the possibility of counteracting policies
Federal and local stakeholders of overlapping policies may not be the same	The Occupational Health and Safety Administration (OSHA), which is in the Department of Labor, is responsible for promoting safe practices with biological and chemical hazards in laboratories, including training for safe handling of bloodborne pathogens.(52) At the same time, the CDC and NIH are responsible for updating the Biosafety in Microbiological and Biomedical Laboratories (BMBL) guidelines and promulgating laboratory biosafety practices in the U.S. and internationally. In addition, CDC regulates BSAT facilities, using the BMBL and NIH Guidelines for Recombinant and Synthetic Nucleic Acids as a guide for inspections. Although the authorities of OSHA, CDC, and NIH are different, a single office in local facilities (the environmental health and safety office) often is responsible for implementing and overseeing activities in compliance with OSHA, CDC, and NIH requirements for biosafety. Therefore, these overlapping activities either may reinforce common practices or may result in confusion of differently-interpreted practices.
No consistent or common process for reviewing and overseeing research with potential for exploitation by malicious actors. Oversight of research is agency-specific.	The U.S. government has issued policies for review and oversight of dual use life sciences research of concern and of research involving pathogens of pandemic potential. Although these policies describe scope of the policies (i.e., including inclusion criteria for research that should be flagged), individual U.S. government agencies that fund biological research are responsible for developing their own review and oversight mechanisms. Differences in review criteria and process, suggested risk mitigation strategies, and oversight processes can cause confusion and compliance burdens on the research communities. In addition, these differences may result in inconsistent implementation among government funders.
	Over the lifetime of the Federal Select Agent Program, inconsistency in requirements, inspector training, and inspection criteria has been observed between agencies responsible for implementing the FSAP (CDC

	and USDA Animal and Plant Health Inspection Service) and the agencies that fund research (e.g., Department of Defense and Department of Homeland Security). The 2012 update of the BSAT Regulations include provisions for joint inspections and inspector competency, but agency-level requirements continue to present challenges. For example, the Department of Defense policy for biosurety (AR50-1) is more stringent than the personnel security/surety requirements of the BSAT regulation, leading institutions that receive research funds or biological agents from DoD to have a higher level of personnel security than the BSAT regulations require.

Table 5. Limitations to Stakeholder Engagement in Policy Implementation. Stakeholders from different sectors and organizations are involved in implementing U.S. biosecurity and biodefense policies. Regardless of whether developed policies are feasible or financially-supported, federal and local stakeholders may be held responsible for their implementation or if given a choice, may opt to not participate as an implementing stakeholder.

Limitation	Examples
Stakeholders do not necessarily understand their roles in achieving biosecurity and biodefense objectives.	Local and state public health department are key stakeholders in implementing preparedness and response policies. However, they rarely are involved in the early stages of policy development to ensure that their roles and responsibilities, strengths, capability gaps, and resource needs are considered. This lack of engagement during the policy development process may result in policies that are infeasible for certain stakeholders to implement or are not consistent with the roles and responsibilities of the stakeholder group. In addition, lack of early engagement may prevent local stakeholders from understanding how they play a role in implementing a given policy, particularly if the policies are vague.
	Basic and applied research contributes to the development of medical countermeasures, detection tools, biosurveillance systems, metrics and evaluation methodologies, risk assessment tools, and many other biodefense and health security capabilities. However, researchers in these fields often are not part of local, national, and international discourse on prevention, detection, and response to biological events. This lack of engagement may be self-directed particularly if scientists do not know about potential application of their work for biodefense. Alternatively, the lack of engagement may be caused by security experts, health practitioners, and/or policy-makers who may not see the role that researchers may play in preparing for and responding to biological events.
Limited or no additional funds are available to assist key stakeholder groups comply with biosecurity regulations.	Because most of the pathogens on the BSAT list of restricted agents can infect and cause disease in animals and humans (zoonotic diseases), veterinarians play a significant role in detection of pathogens and prevention of human and animal infections with these pathogens. However, the cost of initial and ongoing compliance with the BSAT regulations has become prohibitive for many veterinary diagnostic reference laboratories, leading many to choose not to maintain BSAT in their facilities. This lost resource may limit or delay detection and biosurveillance efforts.
Some tools for prioritizing biological threats result in the identification of the same agents regardless of country or situation.	The U.S. government uses a variety of information and approaches for prioritizing biodefense activities. For example, the CDC has developed a methodology for prioritizing agents of member countries of the Global Health Security Agenda.(53) This tool resulted in the identification of Brucellosis, rabies, zoonotic influenza, anthrax as the top ranked diseases of four or more of seven countries (which included five African, one

	Eastern European, and one Southeast Asian country) initially included in the analysis. Using the tool, the top ranked diseases of another African country are anthrax and zoonotic disease followed by eight other diseases, two of which are brucellosis and rabies.(54) In addition, an assessment of top ranked diseases in another African country also included zoonotic influenza virus, rabies, and anthrax.(55) Although the lists of top-ranked pathogens varies slightly, a few pathogens appear to be common to several, if not all, countries.

Significant Gaps in Biosecurity and Biodefense Policy

During the analysis of U.S. biosecurity and biodefense policy, several capability, implementation, and infrastructure gaps were identified. That is, goals which are plainly stated in biodefense legislation, presidential directives, or other policy instruments, are found to be associated with few implemented programs or actions. These gaps include:

- Capability Gaps:
  - **Microbial forensics** is an underinvested field in the United States and internationally, but could be enhanced by leveraging technologies such as bioinformatics and next generation sequencing. Two U.S. government policies highlight the need for microbial forensic capabilities: HSPD10/*Biodefense for the 21st Century* (2004) and the National Strategy to Support Research in Microbial Forensics Attribution Investigations and National Security (2009).(56, 57) These strategies, along with recent reports completed by the National Academies of Science, Engineering, and Medicine and the Government Accountability Office can help define near-term recommendations for addressing this gap. Leveraging new biotechnologies may enhance capabilities for microbial forensics at a lower overall cost and/or higher throughput than traditional forensics methods.
  - **Systems for scanning scientific advances** that could lead to new technology developments exist in offices that support or conduct research and advanced development. However, end-users often do not have access to these systems or have similar systems of their own, which limits field application and relevance to biodefense activities.
  - Despite significant investment in biosurveillance approaches and platforms, the underlying data used to develop effective **early warning** methods is highly variable and uncertain. This challenge suggests a gap in robust approaches for generating reliable, curated input data. In addition, this challenge highlights the lack of communication and interaction between scientific experts and policy-makers, which may be needed to ensure that existing, verified data is included in the decision-making process of preparedness activities and potential emergency situations.
  - The increasing convergence of scientific disciplines, changing funding paradigm, and expansion of biotechnology practitioners suggests that greater attention is needed on **evaluating the security implications of biological and biotechnological advances and applications that are not only focused on pathogens and toxins**. In 2014, the American Association for the Advancement of Science, FBI, and United

National Interregional Crime and Justice Research Institute published a report on the national and transnational security implications of Big Data in the Life Sciences. This report acknowledged the increasing production of genomic data by research, clinical, and direct-to-consumer organizations throughout the world; the continuously advancing computational and data science capabilities; and the frequency of cyber-attacks of health care and insurance databases. This combination of factors led the FBI and others to evaluate more closely the potential national security risks presented by these activities and approaches for reducing the risks while not adversely affecting commercial, research, and clinical innovation.

- Infrastructure Gap
  - Despite investment on basic research on pathogens, the academic research sector, including the biocontainment laboratories, are not considered a **critical infrastructure** and therefore, have little to no external financial or expert support to prepare for, respond to, and recover from potential events. However, the basic knowledge about pathogens are generated by this sector and the capabilities to identify newly-emerging or never-before-seen pathogens are resident within this sector.
  - Very few policies and programs exist for **promoting resiliency** in the biodefense, health, and research sector. But, resiliency is a local issue, which suggests that the federal government role may be in facilitating preparedness, planning, and recovery efforts. No policy appears to include outreach efforts to the scientific community to promote resiliency.
  - Although the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 includes a section on support for **applied biosafety**, very little, if any, funding has been appropriated for research to generate the data needed to evaluate effectiveness of biosafety measures.

- Implementation Gap
  - Several sectors and organizations do not have **sufficient funds to support compliance** with biosecurity regulations so they choose not to participate in activities involving restricted agents. The most significantly-affected sectors are public health and veterinary diagnostic laboratories, which require external funding and technical support to maintain compliance with the Biological Select Agents and Toxins (BSAT) Regulations.
  - The **continuous changes to the BSAT Regulations** have resulted in significant challenges and delays in federal implementation and local compliance. Although federal regulators previously have met with the regulated community to discuss changes to federal BSAT policies, these outreach activities seem to have ended. Instead, the Federal Select Agent Program directors have initiated new efforts that involve interaction and

engagement with local Federal Bureau of Investigation Weapons of Mass Destruction Coordinators.

- Practical resources for enabling program managers, research reviewers, and scientists to **assess the risks and benefits** of research do not exist. These resources would ensure that science and technology investments for promoting biodefense and health security objectives can be leveraged maximally while risks are addressed adequately.
- Annual and inconsistent investment **in nonproliferation activities**, specifically for cooperative threat reduction programs, limits long-term sustainability of partnerships and outcomes. Threat reduction or bioengagement programs require long-term planning, engagement, and funding to increase the likelihood of sustainability of activities (e.g., through financial support of the recipient country), enabling an exit strategy for U.S. government funding.
- Effective **measures for evaluating biosecurity policy implementation** have not been developed. Members of the scientific and security community routinely have stated that the development of measures are not feasible because measuring the absence of an event (i.e., measuring a negative result) is impossible. Conversely, measures for evaluating some biodefense investments do exist, each different from another. This variability highlights inconsistencies that may arise from the different, often ad hoc evaluation metrics used to assess biodefense investments.
- No analytic framework currently exists for **assessing opportunity costs** of biosecurity policy. Often direct costs are calculated in advance as part of regulatory impact assessments. But, indirect costs and downstream consequences, which represent opportunity costs of a policy, resulting from these direct costs are not calculated. However, many in the regulated community use arguments about opportunity cost when engaging in policy discussions, highlighting the importance of considering costs downstream of direct time and financial investments.

Key Observations

Systematic analysis of the U.S. biosecurity and biodefense policy and implementation, the authors have arrived at several key observations that form the basis for the roadmap for implementing biosecurity policy, which was described in the Roadmap chapter. These observations include:

- The current U.S. system of governance for biosecurity and biodefense is iterative, segmented, and reactive creating a patchwork of policies for countering natural and man-made biological threats.
- The U.S. biosecurity and biodefense policy landscape is a system of intersecting components, which can lead to mutually reinforcing policies or counteracting policies. Therefore, approaching U.S. policy development, analysis, and

implementation in a systematic way enables more thorough understanding of the indirect costs, trade-offs, and feasibility of policies and their implementation.

- No single strategy describes the full range of biosecurity and biodefense objectives of the U.S. To date, the 2002 Homeland Security Presidential Directive-10/Biodefense for the 21st Century and the 2009 National Strategy for Countering Biological Threats provide the greatest overarching framework for primary U.S. objectives. Therefore, the U.S. biosecurity and biodefense enterprise would benefit from the development of a comprehensive, inclusive strategy that recognizes the interconnectedness of existing policy, depth of implementing and affected stakeholders, and outstanding gaps.
- On occasion, local stakeholders voluntarily have developed and implemented policies and practices to address biosecurity and biosafety risks, and biodefense knowledge and technological gaps. Though not prescribed in federal legislation, strategies, or guidance, these voluntary actions play a major role in risk reduction and capability building for the U.S.
- Several barriers may prevent policies from being fully or adequately implemented, limiting their abilities to meet U.S. biodefense objectives. These barriers include counteracting policies, lack of support for compliance with high-burden requirements, and lack of cross-sectoral and cross-disciplinary stakeholder involvement in the policy development process. Recognizing and alleviating these potential barriers during the policy development phase may enable the development of more feasible policies and/or provide options for ensuring full implementation.

Conclusion

Overall, the U.S biodefense and biosecurity policy landscape should be treated as a dynamic system that seeks to leverage the knowledge and capabilities of the science and technology community while promulgating practices for preventing malicious development and use of biology and biotechnology. Using a systems-based approach has enabled the identification of key observations, limitations of the current policy landscape for achieving biodefense goals, and gaps in biodefense activities. These observations, limitations, and gaps led to the identification of the actions described in the Roadmap chapter, which assumes that the systems-based approach is an integral path towards improving biosecurity and biodefense in the United States.

Evaluation Metrics Framework

The question of metrics of policies, programs, and initiatives is of great interest at the local, federal, and international levels and affects stakeholders at each of these levels differently. For example, the performance and/or effectiveness of specific programs and initiatives led or sponsored by U.S. government agencies and departments regularly are evaluated within a given agency, by the White House Office of Management and Budget, and by Congress as part of the routine oversight and budget request processes. In addition, programs may be evaluated by the Government Accountability Office and interested civil society. Each internal and external group has developed different measures and criteria for evaluation of programs. For example, in 2010, the Congressional Commission on the Prevention of Weapons of Mass Destruction (WMD) Proliferation and Terrorism released its report card of U.S. government progress towards preventing WMD proliferation and terrorism.(58) More recently (2017), the Government Accountability Office released its report on the Federal Select Agent Program, which included an evaluation of oversight and regulatory guidance and identification of approaches that could enhance future oversight.(59) Finally, during the past five years, the Department of State Biosecurity Engagement Program and the Department of Defense Cooperative Biological Engagement Program have funded efforts to develop metrics for evaluating the performance of their programmatic investments.(60)

One significant challenge that these efforts, and other similar efforts, have encountered is the inability to measure intangible or unquantifiable outcomes, such as the building of trusted partnerships, promoting the development of knowledgeable leaders, and preventing deliberate incidents from occurring. So often, policy experts throw up their lands saying that metrics inherently are flawed because data for measuring these desired outcomes of biosecurity and biodefense activities does not exist. However, this conclusion can lead to the development of uninformative metrics or a misalignment of metrics with the program under evaluation, which could result in inaccurate assessments of policy and program implementation.

A key part of a forward-looking roadmap is a complementary approach(-es) for evaluating the effectiveness and progress of policy implementation. Therefore, a systematic approach was used to identify performance matrices by: a) review of policy and program matrices currently adopted for biosafety and safety programs in general; b) review of existing evaluation matrices for cross-application; and c) review of published scholarly literature in journals.(61) The goal was to draw a preliminary framework and develop options for evaluation metrics for implementation of biosecurity and biodefense policies.

Scholarly approaches for metrics and evaluation includes: a) interview, survey, or discussion-based methodologies wherein external evaluators speak to key stakeholders and interested individuals about the program or activity of interest; b) an analysis of strengths, weaknesses, opportunities, and threats (SWOT) associated with programs; and c) an analysis based on measures defined by the implementer and/or funder. The

specific measures included in these approaches depend on the goals of the analyses. Despite the different methodologies used to obtain data, an approach that has been used to evaluate existing chemical safety and security, biosecurity, and biodefense programs involves the development and analysis of activity-based measures and outcome-based measures. This approach of evaluating the successful implementation of activities and the successful achievement of outcomes led the authors to develop a single analytic framework for assessing policy implementation. The remaining chapter briefly summarizes three frameworks that have been developed by and/or for international and U.S. government organizations, and describes our proposed analytic framework for policy evaluation.

Organization for Economic Cooperation and Development (OECD) Guidance on Safety Performance Indicators for Chemical Accident Prevention, Preparedness and Response

At the institutional level, implementation of biosecurity policies and metrics to ensure compliance with biosafety, biocontainment and laboratory biosecurity regulations is an essential component of the organizational and governance structure. These indicators may provide opportunities to develop structured performance assessments of laboratory biosafety and biosecurity to enable continuous improvement through the identification and mitigation of evolving challenges, risks, and institutional needs. Although no consistent and widely-accepted performance measures for laboratory biosafety and biosecurity exists, the private sector routinely uses safety performance measures, some of which are included in the literature.(62-64) The Organization of Economic Cooperation and Development (OECD) has published what is regarded as one of the most comprehensive guidelines on safety performance indicators for preventing, preparing for, and responding to chemical accidents.(65) These industry guidelines list possible outcomes and activity indicators applicable to all stakeholder communities. The overall assumption is that the combined evaluation of activity-based indicators and outcome indicators provides a more complete picture of safety implementation at the institutional level and the contributions of industry, public authorities, and communities in promulgating and improving chemical safety.(64)

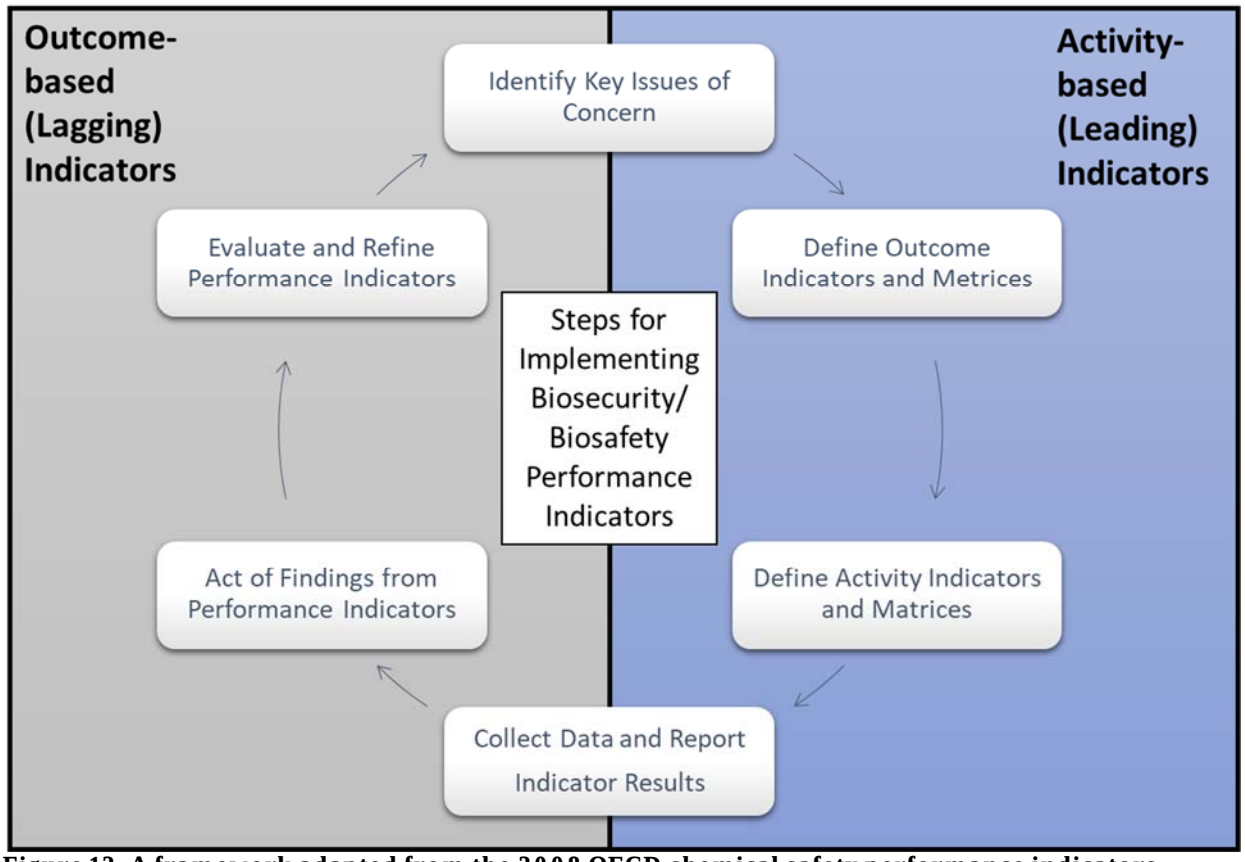


Figure 12. A framework adapted from the 2008 OECD chemical safety performance indicators guidance.(65) The leading indicators reflect activities undertaken to implement a policy or program. The lagging indicators reflect outcome-based evaluation measures.

RAND Corporation Framework for Measuring Cooperative Biological Engagement Program Performance

In 2014, the Rand Corporation published a report proposing a conceptual framework for measuring performance of investments of the U.S. Cooperative Biological Engagement Program of the Defense Threat Reduction Agency (DTRA/CBEP).(60) This conceptual framework was developed after asking the following questions:

- What programmatic activities should DTRA/CBEP measure?
- How should DTRA/CBEP identify metrics?
- What metrics should RAND recommend to DTRA/CBEP?

Based on these guiding questions, RAND identified several quantitative measures for evaluating capacity for DTRA/CBEP's identified objectives - biorisk management (management systems for preventing accidental and deliberate biological risks) programs and for biosurveillance - that could be used immediately to assess the ability of programmatic activities to build capacity. In addition, the report highlights several measures, many of which result in yes/no answers, that could be used to evaluate longer-term outcomes of programmatic activities to assess capabilities or sustainability enablers of activities. This two-part approach of measuring immediate capacity and

long-term capability served as the foundation for the conceptual framework, which included the use of logic models and functional representations (i.e., "telling the story").

Thought Experiment: Extrapolating Activity- and Outcome-based Evaluation to Biosecurity

Extrapolating these frameworks to laboratory biosafety may be possible. (Figure 12) For example, development of activity and outcome indicators for the 2010 calls to strengthen BSAT security and oversight in the U.S was explored as part of a thought experiment. The 2010 Executive Order 13546 *Optimizing the Security of Biological Select Agents and Toxins in the United States* established the Federal Experts Security Advisory Panel (FESAP), which led to the development of guiding principles for enhancing security and oversight of BSAT research.(66) Possible activity-based indicators may be:

- Articulation of the roles and responsibilities of all individuals conducting or overseeing life sciences research to ensure compliance.
- Frequency of institutional assessments of committees, officers, and departments with responsibilities for oversight to assess their function and strengthen their performance when necessary.
- Exitance of training programs delivered to all personnel working with BSAT or in BSAT laboratories at the institution.
- Frequency and level of senior leadership engagement with respect to institutional biosafety and biosecurity oversight and compliance functions.

Possible outcome-based indicators may be:

- Transparency of institutional biosafety and biosecurity oversight mechanisms
- Leadership of institutional administrators and researchers for promulgating safe and security practices within and outside their institutions.
- Trust between institutional stakeholders and law enforcement, public health, federal government, and general public stakeholders to communicate about risks and benefits of BSAT research.

Although the frameworks described above primarily are focused on risk and threat reduction programs, the concept that activity and outcome-based evaluation also may be applied to biodefense activities. For example, activity and outcome-based measures could be developed for evaluating the U.S. medical countermeasure research, development, and acquisition enterprise. This use case is included in Appendix 2.

Evaluation Metrics Framework

Based on a review of the literature, existing evaluation frameworks, and our extrapolation of these frameworks, we developed an evaluation metrics framework for analyzing implementation of biosecurity and biodefense policies.(Figure 13) This framework involves two parts, one focused on activity-based measures and one focused

on outcome-based measures. In general, the two parts of this framework would be analyzed sequentially.

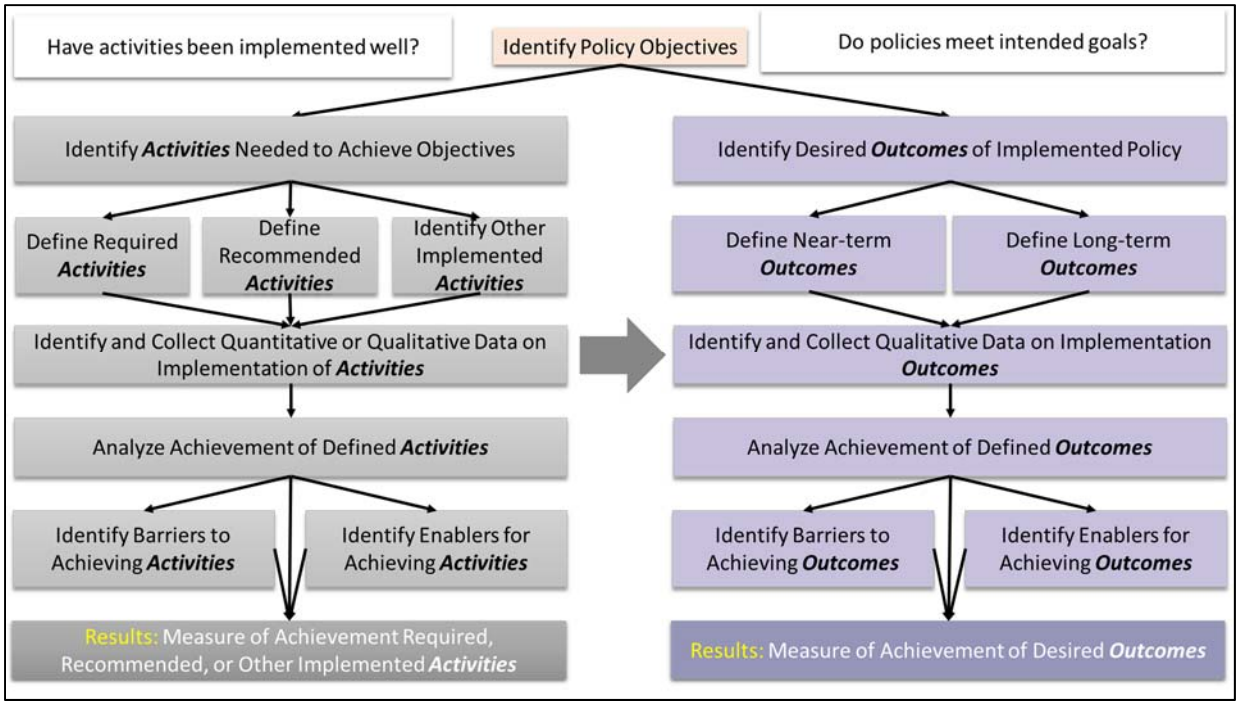


Figure 13. Evaluation Metrics Framework. This framework includes two parts: 1) quantifiable or semi-quantifiable, activity-based evaluation; and 2) qualitative, outcome-based evaluation. The specific measures used are based on required, recommended, and voluntarily implementing activities and the policy goals.

The process involved in assessing the successful achievement of activities undertaken to implement policies includes:

1) Identification of required, recommended, and voluntary activities undertaken to achieve the objectives of a given policy.
2) Identification of quantitative and qualitative data needed to assess the successful completion of the activities.
3) Solicitation and analysis of the data using any of the methodologies described in literature.
4) Identification of barriers preventing successful completion of the activities.
5) Identification of enablers aiding the successful completion of the activities.

The result of this process is a quantitative or semi-quantitative measure of the successful implementation of the specified and unspecified activities undertaken to meet policy objectives.

The process involved in assessing the successful achievement of policy goals includes:

1) Articulation of desired objectives based on policy and programmatic goals.
2) Identification of outcomes that may be observed in the near-term compared to those observed over a longer period of time.

3) Identification of qualitative data needed to assess achievement of desired outcomes. (The types of data needed to assess outcomes may not be publicly available, but may be obtainable by law enforcement, regulatory agency, or members of the intelligence community. Alternative, data may be related to the persistence of repeat, institutionalized, or diversified activities. Examples of different types of data needs are included in the use cases in Appendix 2.)
4) Solicitation and analysis of the data.
5) Identification of barriers preventing successful achievement of activities.
6) Identification of enables aiding the successful completion of activities.

The components and process of this framework were applied to three existing policies in the broader biosecurity and biodefense policy arena to understand how well the framework can be generalized to a variety of different types of policies. The use cases chosen include a voluntary or semi-voluntary policy (the NIH Guidelines for Recombinant and Synthetic Nucleic Acids), statutory or regulatory policy (the Biological Weapons Anti-terrorism Act of 1989), and a capability-building policy (the Public Health Emergency Medical Countermeasure Enterprise). These use cases, which are included in Appendix 2, highlight the generalizability of the evaluation metrics framework shown in Figure 13.

Opportunity Cost Framework

Purpose

Biosecurity policies, such as the BSAT regulations and export controls, promote national security by preventing theft, diversion, and deliberate malicious use of biological knowledge, skills, technologies, materials, and/or pathogens and toxins. At the same time, the restrictions imposed by these policies may have indirect effects on biodefense and health security activities (e.g., research, medical countermeasure development, and biosurveillance), which inadvertently could present barriers to achieving U.S. biodefense objectives.

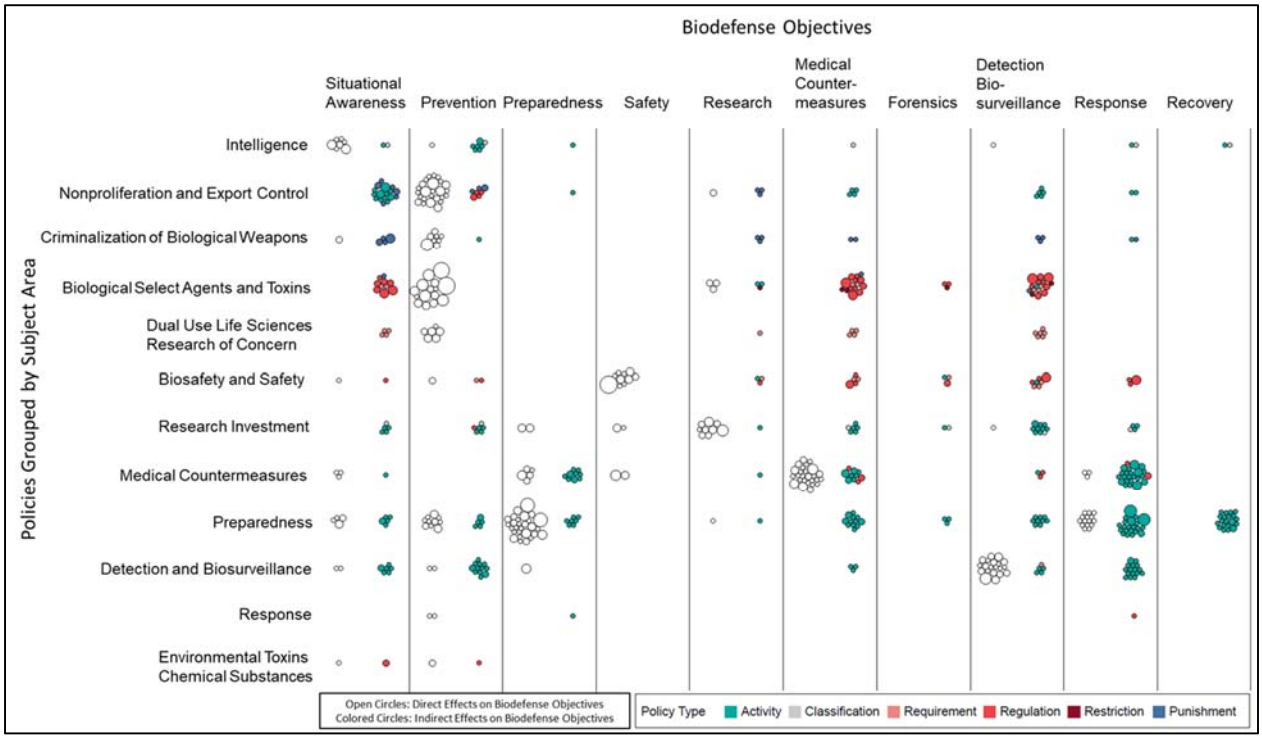


Figure 14. The potential indirect effects of U.S. biosecurity and biodefense policies on U.S. biodefense objectives. Each circle is a unique U.S. Code, international agreement or partnership, Executive or agency-level policy, program activity (if not already associated with a U.S. Code, international partnership, or agency-level policy), guidance, and guidelines. The white circles represent the biodefense objectives (columns) that policies in each of the subject area categories (rows) addresses. The colored circles indicate indirect effects of the policies in the subject area categories to biodefense objectives. The green circles indicate capability-building activities. The pink circles indicate requirements, the red circles indicate regulations, and the burgundy circles indicate restrictions, all of which seek to promote biosecurity and biosafety activities. The blue circles are policies that criminalize development and/or use of biological weapons or their delivery systems for malicious use. The graph is intended to look by row.

Figure 14 maps U.S. biosecurity and biodefense policies by subject area and biodefense objective, as described in in the Policy Analysis chapter. Each biodefense objective is associated with two columns, the first of which are policies whose direct purpose is the indicated objective and the second of which are the policies that indirectly affect the indicated objective. Looking by row, the direct and potential indirect effects of groups of

biosecurity and biodefense policies can be viewed side-by-side. Based on this analysis, policies for securing BSAT, which are a crucial part of preventing theft of high-consequence pathogens and toxins, also may have adverse effects on biodefense objectives that involve research with BSAT such as laboratory-based risk or threat assessment, development of medical countermeasures, and detection and biosurveillance. Appendix 3 includes a historical analysis of direct costs, indirect effects, and downstream consequences from the BSAT regulations, supporting this conclusion. The mapping exercise also reveals policies that may be mutually reinforcing for other biodefense policies. For example, policies enabling medical countermeasure development and detection and biosurveillance provide indirect benefit to response and recovery. Similarly, policies promoting research indirectly benefits the objectives of situational awareness, prevention (including one unfunded statute authorizing applied biosafety research and one Executive Order on promoting behavioral sciences research), medical countermeasure development, and development of detection and biosurveillance technologies. The conclusions from this analysis are embedded in the observations and actions of the Roadmap, and policy gaps included in the Policy Analysis chapter. Furthermore, this analysis provides an initial step in considering potential opportunity costs of existing and developing biosecurity and biodefense policies.

Analyzing Costs of Policies

Few processes currently exist for evaluating the costs of policy implementation or compliance. Since 1993, federal agencies have been required to conduct Regulatory Impact Assessments (RIAs) on any proposed regulations.(67, 68) The RIA involves an economic cost-benefit analysis to ensure that the regulation is compatible with economic growth, innovation, job creation, and competitiveness. In 2012, the FSAP assessed the cost of compliance with the BSAT regulations, citing an annual cost for FBI background checks as $432,000, cost for information security at a regulated entity as $5,500, the average cost for pre-access suitability assessment and occupational health programs at regulated entities as ranging from $9,600 to $15,100.(69) However, RIAs do not account for the trade-offs that institutions and individuals make to fund policy compliance activities or other direct costs experienced by affected entities, such as the effects of delays in review processes established by regulations. As a result, RIAs likely undervalue the opportunity costs of regulations. However, no policy-agnostic framework exists for analyzing the indirect effects of these direct costs and the resulting downstream consequences (or, opportunity costs) of biosecurity policies to U.S. biodefense objectives.

In addition to the RIA process, individual efforts have been made to capture the opportunity costs of specific biosecurity policies, and institutional administrators have cited costs well beyond financial and administrative burden. For example, the time involved in compliance with BSAT regulations and associated costs were assessed in 2004 and 2006, around the time of the first major change to the BSAT regulations.(70, 71) In 2009 and 2010, two academic studies evaluating the effects of BSAT regulations on publication of scientific articles were published.(72, 73) Studies examining the cost of

compliance with the financial conflict-of-interest requirements and animal research protections also were conducted.(74, 75) More recently, a study quantifying the costs of compliance with federal research regulations at 13 universities was conducted.(76) This study found that the average federal regulatory compliance cost burden ranged from 3-11% of total expenditures. Contributing the most to these costs were grant and contract administration, and compliance with human subjects protection and environmental health and safety regulations. In addition, the time research staff, research facilities, and administrative staff spent on compliance ranged from 4-15% in 2015.

Despite these and other attempts at evaluating the direct costs of regulations, no analytic methodology has been developed to assess opportunity costs, including costs to achieving U.S. biodefense objectives. Therefore, the authors sought to develop a framework for analyzing the opportunity costs of new or changing biosecurity policies, which is intended to be used to evaluate direct costs, the indirect effects resulting from these costs, and their downstream consequences. By evaluating new policies using this framework, policy-makers can evaluate potential opportunity costs than what currently exists and to identify policy strategies that could mitigate anticipated costs before they unintentionally counteract investments. This framework also can guide the collection of data for evaluating implemented policies to understand fully the effects of a given policy.

The development of the analytic framework was guided by three key questions:

- What types of data should be collected to assess the opportunity costs of biosecurity policies?
- How should direct and indirect costs be assessed?
- How should individual, institutional, and national-level mitigation measures be incorporated into the analysis?

These questions were addressed through historical case studies on the opportunity costs of existing biosecurity policies. The following sections describe the approach to the case studies and framework development, key findings from the case studies, and the analytic framework. Full results from the case studies and the application of the framework to a new biosecurity policy are presented in Appendices 3-5.

Approach

Historical case studies were developed to identify the types of data (i.e., parameters) that should be incorporated into an analysis of opportunity costs of new policies. Two historical case studies were conducted on the following topics:

1) Biological Select Agent and Toxin Regulations (SAR), with a focus on the updates to the regulations occurring in:
    a. 2012 Final Rule – in particular, the addition of SARS-CoV (SARS coronavirus, the causative agent of severe acute respiratory syndrome) to

the select agent list and the designation of enhanced biosecurity measures for Tier 1 agents;

b. 2017 guidance on pathogen inactivation – in particular, the requirement to re-validate all agent inactivation procedures and the development of more stringent guidelines for agent inactivation.

2) U.S. government dual use research of concern (DURC) policies, including the policy for federal agency review and oversight of DURC, which was released in 2012, and the policy for institutional oversight of DURC, which was released in 2014.

To enable the systematic identification of data types needed to assess opportunity costs, a variety of stakeholders affected by these policies were engaged. The stakeholders included:

- Academia and government research community, including researchers and environmental health and safety (EH&S) personnel;
- Professionals in public health laboratories and veterinary diagnostic laboratories;
- Experts from industry, including medical countermeasure (MCM) development companies and contract research organizations (CROs); and
- Public health and environmental health stakeholders at the state, local, territorial, and tribal (SLTT) levels.

The goal of these discussions was to capture the *types* of opportunity costs that *individuals* and *institutions* have experienced as a result of the SAR and federal DURC policies. Information on two types of costs was gathered:

1) Direct costs: Time, money, and other resources required to comply with the policy.
2) Indirect opportunity costs: Indirect costs (“*trade-offs”)* arising from the direct costs and the *downstream consequences* of these indirect costs. For example, indirect costs may include abandoned research and development activities, the loss of opportunities for training and career development, and the loss of institutional capabilities to conduct select agent research. These indirect costs may impair advancements in select agent research and diminish capabilities for preparedness and response of biological incidents. Collectively, the indirect costs and their downstream effects on U.S. biodefense objectives represent opportunity costs of the policy.

Opportunity Costs are indirect costs (“*trade-offs*”) arising from the direct costs and the *downstream consequences* of these trade-offs.

Members of the experts working group also provided recommendations for evaluating how the indirect costs may affect U.S. biodefense objectives.

Based on the information collected from stakeholder discussions and the experts working group, key data needs for assessing the costs of biosecurity policies were identified, including:

- The direct costs for complete and accurate policy compliance, and
- Potential trade-offs caused by resources directed to policy compliance activities and their downstream effects on U.S. biodefense objectives.

The data needs/parameters were organized into an analytic framework that involves an ordered series of questions about direct compliance costs, indirect effects, and downstream consequences, which can be evaluated quantitatively or semi-quantitatively for new or changing biosecurity policies in the future.

Because such an effort previously has not been undertaken, no attempt has been made in these case studies to conduct a quantitative or semi-quantitative assessment. Furthermore, although some quantitative data exist for administrative burden and financial cost of initial and ongoing implementation of regulations, little, if any, quantitative data exist for the indirect effects of those costs and the downstream consequences (e.g., lost workforce or scientific knowledge). However, now that an analytic framework has been developed, data on direct costs and indirect effects can be collected and analyzed.

This effort has several limitations. First, the prevalence of a particular cost or challenge across various types of institutions could not be evaluated because a limited number of stakeholders were engaged in this study. However, several individuals discussed the frequency with which their colleagues at other institutions experienced the similar costs. Therefore, the analyses are not intended to be quantitative or comprehensive, but rather illustrative of the costs incurred by various stakeholders to help develop an opportunity cost analysis framework. Second, the findings described in this report may not represent all opportunity costs associated with the 2012 and 2017 SAR updates and the federal DURC policies. Engagement with additional stakeholders affected by these policies may reveal additional costs. Third, stakeholder discussions focused on elucidating costs arising from the policies themselves (i.e., what is written explicitly in the policy), but costs also may arise from policy implementation (i.e., activities that are not mandated by the policy, but are necessary for compliance or implementation).

Despite these limitations, the case studies captured a wide range of direct and indirect costs experienced by stakeholders who were affected by the SAR and DURC policies, enabling the development of a robust framework for evaluating the opportunity costs of biosecurity policies. Opportunity costs and data needs identified through future discussions with biosecurity policy stakeholders can be incorporated into this framework.

Key Conclusions from the Historical Case Studies

The historical case studies on the SAR and federal DURC policies are described in Appendices 3 and 4, respectively. This section highlights key findings from the case studies, including: 1) the types of direct costs, indirect costs, and downstream consequences that stakeholders experienced while complying with or implementing these policies; 2) factors to consider for an accurate assessment of these costs; and 3) strategies for mitigating opportunity costs that stakeholders shared.

Direct Costs

Stakeholders described three types of direct costs associated with implementation or compliance with biosecurity policies: financial costs, time costs, and frustration of researchers and other affected stakeholders. Table 6 summarizes the key findings associated with direct costs of policy implementation.

Table 6. Key findings related to the direct costs of policy implementation or compliance.

Categories of Cost	Findings
Financial Resources and Time	The direct financial and time costs of complying with a new biosecurity policy are influenced by whether, and to what extent, the policy likely requires changes to the infrastructure or operation of affected institutions. Determining these changes requires consideration of two factors: 1) overlapping requirements of guidelines established by other policies; and 2) existing laboratory architectures, workflows, and procedures. These elements vary systematically between different types of institutions (e.g., research institutions versus diagnostic reference laboratories).
	Cost assessments of policies related to research procedures should consider whether affected entities need to conduct new experiments to satisfy the record-keeping and/or inspection requirements of the policy, even if those experiments explicitly are not required by the policy. Evaluations of the direct financial and time cost of policy compliance should account for the cost of those experiments (labor, consumables, etc.).
Financial Resources	A realistic accounting of financial costs associated with biosecurity infrastructure, including physical, cyber, and other security measures, must consider the costs of equipment maintenance and upfront purchase and installation costs.
Time	To address the direct time cost of a new biosecurity regulation, assessing both the upfront and ongoing level of personnel effort needed for compliance is critical. This assessment also should include regulations that codify practices or systems that already are being followed by regulated entities.
	Assessments of the time costs for ongoing compliance with research review policies should account for the total number of research proposals that are reviewed, not simply those projects deemed to fall within scope of the policy.
	To assess the direct time cost of a new biosecurity regulation that involves exemptions, the level of administrative effort needed for documenting exemptions should be considered.
	Delays in research or other biodefense activities can have adverse effects on research even if affected stakeholders are not engaged actively in compliance with policies. These activities include: 1) delays in review or approval processes for regulated activities; and 2) lengthy security vetting processes

	for newly-hired personnel. These delays should be considered a direct *time* cost of biosecurity policies.
Frustration	Researchers have experienced frustration arising from several different types of biosecurity policies, such as: 1) personnel security policies, because of their intrusiveness; and 2) dual use research policies, because of perceived redundancy with other research review policies and stigmatization of the research by some members of the public and biosecurity communities.

Indirect Effects

Stakeholders described three types of indirect effects arising from the direct time costs, financial costs, and frustration experienced by affected stakeholders: 1) costs to research and other biodefense activities; 2) costs to workforce, including costs to workforce development and the loss of individual capabilities; and 3) the loss of institutional capabilities. Table 7 summarizes the key findings associated with indirect effects resulting from the direct costs of policy implementation.

Table 7. Key findings related to the indirect costs of policy implementation or compliance.

Categories of Cost	Finding
Regulated Activities	The source of funding for compliance activities (e.g., direct federal funding, institutional overhead funding, or research funding) influences the indirect effects of compliance expenses on research activities at affected institutions. For example, using money dedicated for research to fund compliance activities may prevent researchers from achieving their project outcomes, potentially affecting the overall funding initiative.
Regulated Activities **Workforce (Development)**	The direct time and financial costs of complying with or implementing biosecurity policies may limit opportunities for training in regulated research areas, which can impede workforce development. For example, many institutions have limited the number of personnel in their select agent programs and reduced visiting scientist programs to minimize the costs of personnel security programs required by the SAR. Reduced training opportunities, including visiting scientist programs, also may adversely affect research collaborations.
	The time needed to comply with new biosecurity policies may stall or slow the progress of research or other biodefense activities. Additionally, research delays may have consequences for workforce development by impeding researchers' ability to advance their careers by publishing papers, obtaining grants, or achieving promotions.
	Time delays for research reviews or other compliance activities may cause researchers to re-direct their research to activities that are not regulated, which may limit research capabilities and have adverse consequences for workforce development by reducing training opportunities.
Regulated Activities, Loss of Institutional Capabilities	Hiring challenges arising from lengthy personnel vetting processes can lead to research delays and contribute to institutional decisions to not support regulated activities such as select agent research.
Workforce (Loss of Individual Capabilities)	Frustration with biosecurity policies may contribute to the decisions of some affected stakeholders to leave their fields, potentially leading to loss of subject matter expertise in a given field.
Loss of Institutional Capabilities	The financial and time costs of compliance with biosecurity policies have contributed to institutional decisions to cease supporting select agent research because of: 1) the expense for maintaining security infrastructure and personnel reliability programs; and 2) escalating administrative burdens.

	The loss of institutional biodefense capabilities leads to a loss of critical research and training activities.
Workforce (Export of Capabilities Overseas)	The loss of individual biodefense capabilities may result in the export of these capabilities and knowledge overseas, if trained individuals move from U.S. to foreign institutions to continue their research or other regulated biodefense activities.
Regulated Activities **Workforce** **Loss of Institutional Capabilities**	Costs to workforce, institutional capabilities, and/or research activities may result in the U.S. abandoning or significantly curtailing certain biodefense research and development activities, limiting the United States' ability to keep pace with scientific and technological advances and applications occurring in other countries.

Downstream Consequences (Opportunity Costs)

Stakeholders described two types of downstream consequences arising from indirect costs, which represent the opportunity costs of biosecurity policies: 1) adversely affected or lost national capabilities; and 2) shift in balance of power between the U.S. and adversary countries. Table 8 summarizes the key findings associated with downstream consequences resulting from the indirect effects of policy implementation.

Table 8. Key findings related to the downstream consequences of policy implementation or compliance. The downstream consequences of institutions ceasing to support regulated activities varies between institution types, depending on the institution's mission, and training and research activities.

Categories of Cost	Findings
Lost National capabilities	Indirect effects on workforce development, including the loss of individual and institutional biodefense capabilities, adversely affect the ability to meet U.S. biodefense objectives by *reducing the number of trained personnel* available for critical biodefense activities (e.g., basic and applied research on pathogens, biosurveillance, MCM development, and forensics).
	Indirect effects on biodefense activities, including the loss of individual or institutional biodefense capabilities, can adversely affect the ability to meet U.S. biodefense objectives by *delaying or preventing critical research activities* for detection of new zoonotic diseases, characterization of pathogens, development of new MCM, and microbial forensics.
Shift in Balance of Power	Reduced global competitiveness in biodefense fields arising from the loss of individual and institutional capabilities and the export of biodefense capabilities and knowledge could lead to a shift in the balance of power between the U.S. and adversary nations.

Mitigation Strategies

Stakeholders proposed or had implemented a variety of solutions to mitigate the direct or opportunity costs of biosecurity policies. These strategies include:

- Solutions to limit direct financial costs.
    - Provide dedicated funding for institutions to implement or comply with biosecurity policies. For example, ensuring sufficient funding from the CDC's Public Health Emergency Preparedness (PHEP) grants can be used to support SAR compliance activities at public health laboratories.

- Solutions to limit direct time costs.
    - Split administrative work between multiple senior researchers, which reduces administrative burden on any single person in the laboratory, limiting adverse effects on research productivity.
    - Centralize compliance activities in one place such as Environmental Health and Safety (EH&S) offices, provided that institutions secure sufficient funding for EH&S personnel.
    - Increase financial support to the implementing federal agency(-ies) to enhance consistency between inspections, if applicable, and shorten response times of inquiries. This support could reduce administrative burdens arising from differences in interpretation of the regulations between inspectors or between federal agencies and institutions.

- Solutions to limit frustration of affected stakeholders.
    - Improve communication between the scientific community and the public about the benefits and risks involved in research that elicit biosafety and biosecurity concerns, and strategies for risk mitigation. This outreach effort could help to alleviate the stigmatization of some life sciences research.

- Approaches for mitigating indirect effects from reduced or ceased select agent research activities.
    - Encourage researchers to conduct their research at a different facility, if their home institutions or supervisors choose to stop supporting regulated research, including research with BSAT. For this strategy to be feasible, existing challenges for visiting scientists (i.e., arising from personnel security requirements) must be addressed.
    - Serve as a contract research organization or collaborating institution for laboratories that choose not to support regulated research.

Opportunity Cost Framework

The case study findings revealed a set of data needs/parameters for assessing the opportunity costs of biosecurity policies. These data needs enable: 1) identification of the types of direct and opportunity costs arising from policy compliance and implementation activities; and 2) full and accurate determination of these costs. Relationships between parameters (e.g., how particular direct costs may lead to certain indirect effects) also were elucidated, enabling the ordering of parameters into a structured analytic framework for assessing the opportunity costs of policy. Finally, based on an analysis of suggested mitigation strategies, opportunities for mitigating policy costs were incorporated into the framework. Figure 15 presents the Opportunity Cost Framework and its application to the assessment of biosecurity regulations, guidelines, or guidance.

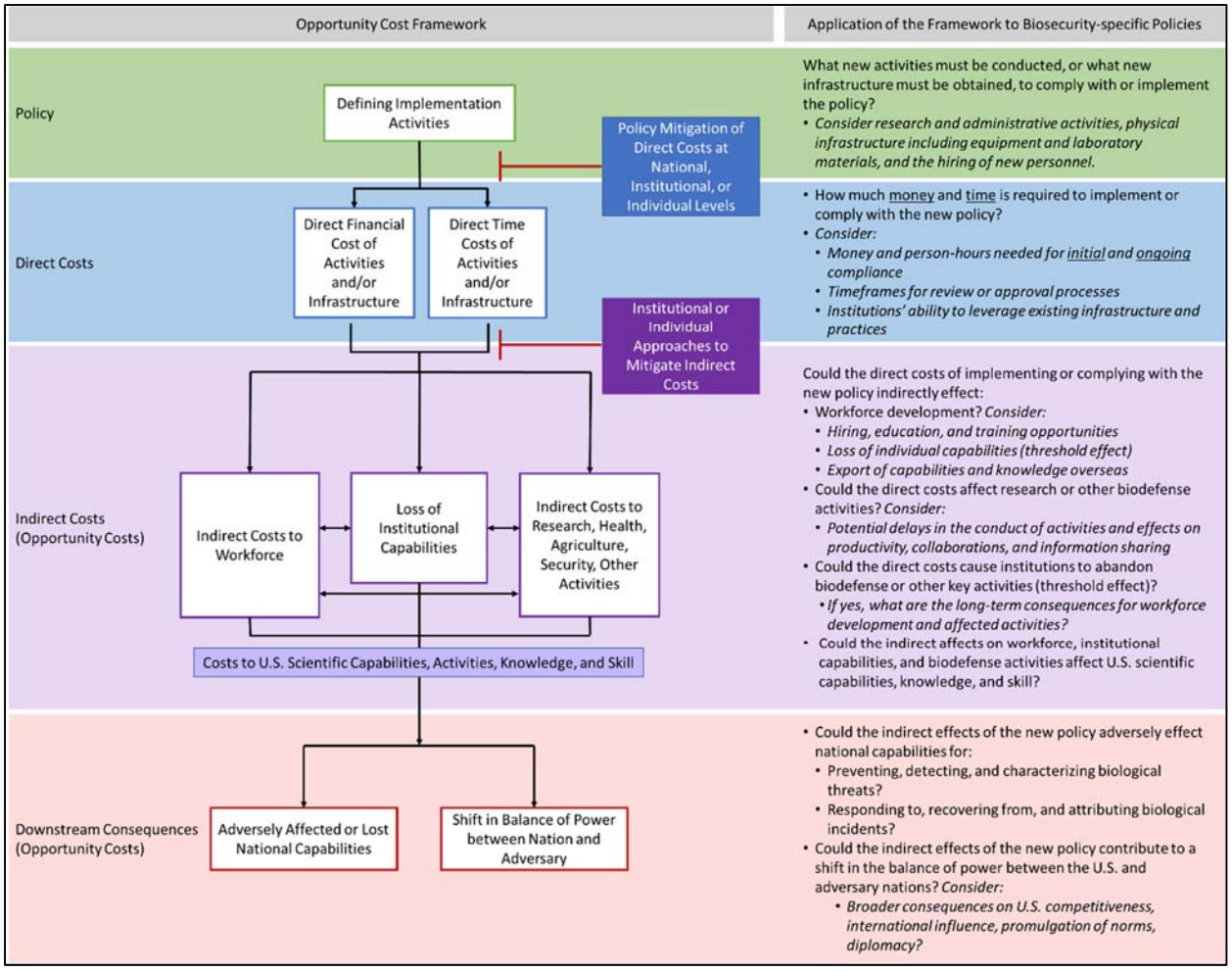


Figure 15. Opportunity Cost Framework.

A key principle underlying the framework is that the direct costs of policy implementation or compliance can lead affected stakeholders to make trade-offs that, collectively, may compromise U.S. workforce, infrastructure, capabilities, and activities in the policy area (in this case, biodefense). Seemingly small financial or time costs can limit the ability and/or desire of an individual or institution to conduct regulated work because of their mission, responsibilities, and resources. Summing up direct costs across all affected stakeholders, as is done for a regulatory impact assessment, obscures the indirect costs on individuals and institutions, thereby underestimating the potential consequences of a policy on U.S. national objectives. To address this principle, application of the framework to new or changing policies involves sequential assessment of the direct costs, indirect costs, and downstream consequences.

Although this framework was developed based on historical case studies of biosecurity policies, the authors propose it could be used broadly for the assessment of policies related to research, health, agriculture, and security. Key factors to consider when applying the framework to biosecurity policies are described in the right-hand section of the figure, and further details are provided below.

Step 1: Defining Implementation Activities

The first step involves defining the activities that must be conducted and the infrastructure that must be obtained to implement or comply with the policy. Examples of these activities include: research and administrative activities, hiring of new personnel, and purchase of equipment or laboratory materials. To determine whether and how policy implementation involves changes to the infrastructure or operation of affected institutions, two factors should be considered: 1) overlapping requirements of guidelines established by other policies, which may have led institutions to implement the changes already; and 2) existing laboratory architectures, workflows, and procedures. Additionally, the personnel responsible for conducting the activities and the source of funding for compliance activities or infrastructure needs should be identified because both can influence the indirect effects arising from the direct costs.

Consider evaluating opportunity costs separately for different types of institutions. For example, institution types that are important to consider when evaluating biosecurity policies include: academic research institutions, government research institutions, public health laboratories, veterinary diagnostic laboratories, contract research organizations, and companies developing medical countermeasures or other biodefense products. The opportunity costs of historical biosecurity policies varied between these institution types, which have different missions, levels of resources, and roles and responsibilities in biodefense.

Step 2: Assessing Direct Costs

The second step involves determining how much money and/or time is required to conduct the implementation activities. Considering the funds and person-hours that are required for upfront *and* ongoing compliance is critical for accurately assessing these costs. Direct time costs should include both 'active' time (i.e., when affected stakeholders actively are engaged in compliance activities) and 'passive' time (i.e., when affected stakeholders are waiting for compliance review or completion of approval processes).

Step 3: Assessing Indirect Costs

The third step involves determining how the funds and time that institutions dedicate to compliance activities lead to indirect effects ("trade-offs"). The 'threshold effect' may be a useful concept for evaluating the relationship between the direct costs and the trade-offs. (Figure 16) At a low level, direct time or financial costs may *limit* or cause *delays* in regulated activities. For example, the amount of administrative work required to conduct select agent research slows the pace of research by diverting researchers' time to administrative work. This administrative burden also may limit select agent research capabilities. To minimize this administrative burden, some researchers may use attenuated or surrogate strains in place of select agents, but the results of these experiments may not be translatable to the select agents. In this example, the trade-off is between level of administrative activities conducted and research relevance.

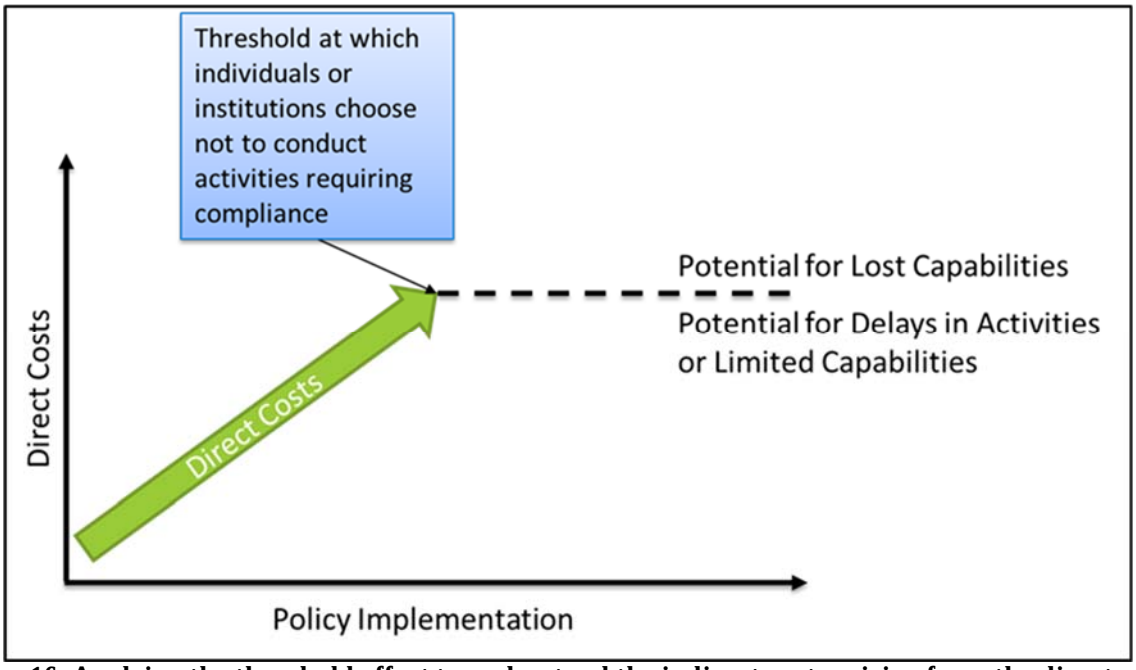


Figure 16. Applying the threshold effect to understand the indirect costs arising from the direct costs of policy compliance or implementation. Low-to-moderate direct costs may limit or cause delays in regulated activities. Above a threshold level, direct costs become high enough that individuals or institutions choose not to conduct or support the regulated activities.

Above some threshold level, the direct costs of compliance become high enough that an individual or institution chooses to cease conducting or supporting the regulated activity. For example, the financial costs of complying with physical and personnel security requirements of the SAR have contributed to the decisions of multiple diagnostic reference laboratories to relinquish their Tier 1 status or withdraw from the Federal Select Agent Program altogether. The expense and time required for personnel clearance also have caused multiple institutions to eliminate or greatly reduce their visiting scientist programs. Because these programs are valuable training opportunities, their loss hampers the development of the select agent workforce. The threshold level of direct costs is specific to and varies between individuals and institutions. The historical case studies highlighted individual and institutional stakeholders who chose to cease work with BSAT or research with dual use potential because the direct costs of compliance exceeded their threshold levels, whereas other stakeholders' threshold levels were higher resulting in their continued support of BSAT activities. The level of cost tolerance of different individual and institution stakeholders can be used to evaluate proactively indirect costs. Furthermore, this threshold concept is a bridge between direct costs and indirect effects.

Indirect effects in three key areas should be considered: research and other regulated activities, workforce, and institutional capabilities. Costs to regulated activities could arise from delays in the conduct of the activities and indirect effects on productivity, collaborations, and information-sharing. Costs to workforce could arise through several different mechanisms, including: 1) the loss of hiring, education, or training opportunities adversely affecting workforce development; and 2) individual choice to

not conduct the regulated activity. When evaluating the loss of individual capabilities, the assessment should consider whether those individuals likely would continue working in the regulated profession abroad, an outcome that could contribute to the shifting of power between the U.S. and adversary nations. The loss of institutional capabilities occurs when institutions cease to support regulated activities because of high direct costs of policy implementation or compliance. In addition to immediate effects on the regulated activities conducted at the institution, the loss of training opportunities may adversely affect workforce development and the loss of infrastructure may adversely affect research and development activities supporting national objectives.

Collectively, the indirect effects to regulated activities, workforce, and institutional capabilities may lower U.S. scientific and technical capabilities and/or cause the U.S. to abandon or significantly curtail certain lines of research and development.

Step 4: Assessing Downstream Consequences

The fourth step involves assessing the downstream consequences of the indirect costs to U.S. national objectives. Costs to U.S. scientific and technical capabilities and/or to U.S. research and development activities may adversely affect national capabilities. At the same time, the export of knowledge and capabilities abroad and the continued advancement of research in adversary nations in areas that have been abandoned or limited in the U.S. could reduce U.S. global competitiveness. These consequences could contribute to a shift in the balance of power between the U.S. and adversary nations, limiting U.S. influence within the international science and technology community.

The authors acknowledge that declines in national capabilities or global competitiveness arise from a complex interplay of scientific and technical, political, economic, and socioeconomic factors. This complexity poses challenges for forecasting or retrospectively evaluating the extent to which the indirect costs of policy implementation or compliance contribute to these consequences. Future work to characterize the workforce and institutional capabilities needed to support key national objectives could inform this process. However, this assessment is beyond the scope of the current study.

Step 5: Identifying Mitigation Strategies

The final, optional step involves identifying strategies for mitigating the opportunity costs. Mitigation measures could be applied to the direct costs to prevent or reduce the indirect costs, or to the indirect effects to minimize the downstream consequences. Solutions for alleviating direct costs could be implemented at the national, institutional, or laboratory levels. For example, policy-makers could provide funding options to off-set the direct costs of implementation and compliance, institutions could centralize administrative work to minimize individual administrative burdens, or laboratories could distribute administrative work among multiple individuals to reduce overall burden on any one individual. Solutions to mitigate indirect costs often are specific to individuals or institutions and thus, tailored approaches could be identified based on specific needs. Proactive or retrospective implementation of the mitigation measures may reduce the long-term opportunity costs of the policy.

Appendix 1: Policy Analysis Case Study: Synthesis of the Horsepox Virus

The Policy Backdrop

After the 2001 terrorist attacks, the United States (U.S.) invested billions of dollars in research and development of medical countermeasures (MCM) (specifically, vaccines and drugs) against material biological, chemical, and radiological threats. These investments provide funding for activities at all research, development, and approval steps of the MCM development pipeline.

Basic research efforts involve a variety of studies in cultured cells and animals to identify which parts of a pathogen elicit protective immune response, create and test candidate vaccines and drugs, and develop new platform technologies for MCM such as new viral vectors or synthetic organisms that produce therapeutic molecules. MCM that show promise in animals must go through a lengthy process for gaining regulatory approval that is designed to assess the products' safety and effectiveness in humans. For vaccine and drug candidates against common infectious diseases (e.g., malaria and tuberculosis), large numbers of people already are infected or at risk of infection, allowing scientific entities (academic centers, government laboratories, pharmaceutical companies) to recruit hundreds to thousands of people to test the candidate MCM. However, some material threat agents may cause disease sporadically, while others may have been eradicated in nature, making traditional clinical trials difficult or impossible in human populations. Furthermore, natural infection may result in different disease presentation and outcomes than man-made events, such as purposeful release of a material threat agent (i.e., biological, chemical, or radiological agent) or accidental release of a laboratory-made pathogen. The only way to generate the efficacy data for MCMs under the typical vaccine or drug approval process would be to expose human subjects to the agent,(77) which for many material threat agents is considered unethical.(78)

Because generating the data on how well the candidate vaccine or drug works against the material threat agents is a critical step in the approval process, the Food and Drug Administration (FDA) established the FDA Animal Efficacy Rule in 2002. This Rule applies to any candidate vaccine or drug for which human efficacy testing is either unethical or infeasible. The 2015 guidance related to MCM development is most relevant to this case study. This Rule and associated guidance allows the FDA to use data from animal studies, in lieu of human trials, to evaluate the effectiveness of the candidate MCM against the relevant material threat agent(s). The primary challenge in using this Rule for approval is the development of animal models that reflect human infection and disease with relevant material threat agents and routes of exposure. To generate the scientific data needed for this work, the FDA and U.S. National Institutes of Health formalized a partnership in 2010 to fund research in regulatory science to enable testing

of the efficacy of candidate MCMs and pharmaceutical products against other rare diseases.

In addition to these efforts, the U.S. Congress passed laws to incentivize scientific entities to develop MCMs. These incentives included the establishment of milestone-based payments for interim results of candidate products, formation of the Biomedical Advanced Research and Development Authority (BARDA) to fund advanced development of MCM, and the creation of the Emergency Use Authorization (EUA) to allow MCMs within 8 years of FDA approval to be procured by the U.S. Strategic National Stockpile (the U.S. repository of critical medicines for emergencies). Most recently, Congress passed the 21st Century Cures Act, which includes provisions for priority review vouchers for candidate MCMs. Through this program, the FDA may provide priority review vouchers for products meeting certain criteria after approval of a material threat MCM application. The priority review voucher can be used by the recipient or sold or transferred to another organization who may use the voucher for a product that would not otherwise receive priority review. This program incentivizes companies to develop MCMs against material threats (for which commercial markets do not exist) by providing opportunities to buy down the financial risks of product development for both MCM and other FDA-regulated pharmaceuticals.

In 2004, the U.S. Congress passed the Intelligence Reform and Terrorism Prevention Act, which includes a provision stating that to “knowingly produce, engineer, synthesize, acquire, transfer directly or indirectly, receive, possess, import, export, or use, or possess and threaten to use, variola virus” is unlawful.(79) This section defines variola virus as “a virus that can cause human smallpox or any derivative of the variola major virus that contains more than 85% of the gene sequence of the variola major virus or the variola minor virus.”(79) This law caused significant concern among poxvirus researchers in the U.S. about the risk of criminal charges being brought against researchers working with poxviruses because most share greater than 85% sequence similarity to variola virus (also called smallpox virus). In 2006, an international group of researchers published the genomic sequence of a 1976 isolate of horsepox virus and showed its relationship to vaccinia virus and other members of the orthopoxvirus family, including the smallpox virus.(80) The protein sequence derived from the horsepox virus genome is 98% identical to vaccinia virus, which is the historical vaccine for smallpox. The authors describe genetic sequences that are shared between the smallpox virus and horsepox, but they do not describe the overall percent identity between the viruses. Although horsepox virus is thought to be extinct, some scientists believe that vaccinia virus, the original smallpox vaccine, was derived horsepox and originally came from poxvirus infections in horses.(81, 82)

As these efforts evolved, the U.S. government examined the potential for harmful use of legitimate research involving pathogens. These efforts, which fall under the dual use research of concern umbrella, informed the development of U.S. policies on review and oversight of such research. Although the initial policy dialogues focused on pathogen research that could result in certain traits or create extinct pathogens, as described in the National Research Council Report *Biotechnology Research in an Age of Terrorism*

and documents from the National Science Advisory Board for Biosecurity, the federal policies ultimately covered research with certain traits of concern in 15 specified pathogens. One of these pathogens is smallpox and one of the traits of concern is resurrection of an extinct pathogen or toxin. In 2017, the U.S. government issued additional guidance for dual use research of concern (Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO)), which currently is being implemented by federal agencies that fund life sciences research. This new guidance adds to the current policy on dual use life sciences of concern by adding a new category of restrictions – specifically on research with pathogens that could cause a human pandemic if released from laboratories – and instructing federal agencies to develop new procedures for reviewing and overseeing such research.

The Horsepox Virus Synthesis and Regulatory Context

The Experiment

In November 2016, Dr. David Evans, a vaccinia virus researcher at the University of Alberta in Edmonton, Canada, discussed his laboratory's recent achievement in synthesizing horsepox virus with the World Health Organization (WHO) Advisory Committee on Variola Virus Research, of which he is a member.(2, 83) The horsepox virus genome is 212 kilobases, has complex structures at its ends, and was described in 2006. Dr. Evans' laboratory purchased overlapping DNA fragments, each about 30kb long, that spanned the entire genomic sequence of horsepox virus from a commercial vendor. The researchers purchased 157 base pair long DNA fragments corresponding to the vaccinia virus end segments from Integrated DNA Technologies.(83) The researchers connected the purchased end segments to the ends of the purchased DNA and introduced those DNA fragments into cells that were infected with an animal virus in the poxvirus family(84-86) (a Leporipoxvirus), which resulted in the creation of infectious horsepox virus.(87). Figure 1 shows a schematic of the horsepox synthesis experiment, based on the 2018 publication of the research.(83)

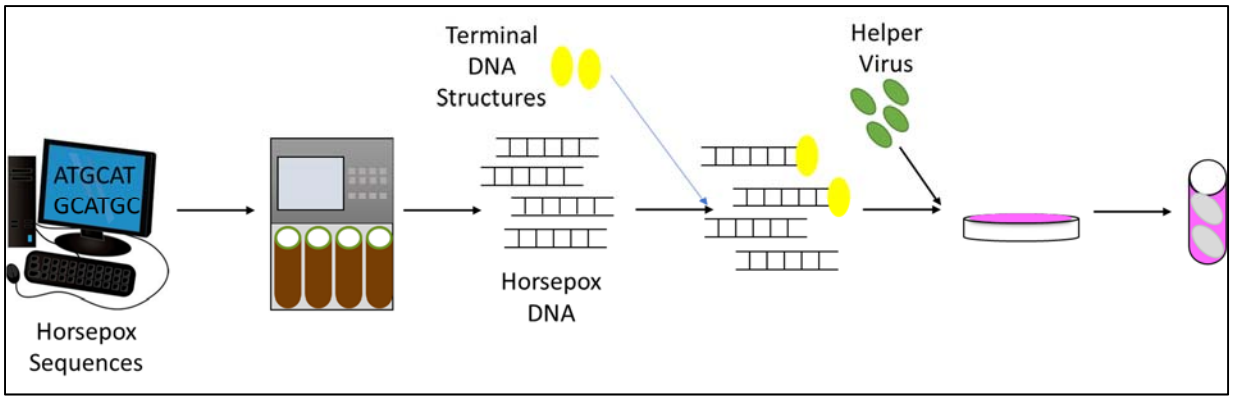


Figure 17. Schematic of the expected experimental procedure used to create horsepox virus from sequence.

The Evans laboratory claims to have spent $100,000 and 6 months synthesizing and recovering infectious horsepox virus. However, their experimental procedures appear to have been developed and optimized well before 2016. A review of Dr. Evans' publication record highlights his previous efforts in developing and optimizing the experimental procedures he used for the synthesis of horsepox virus, a conclusion supported by the discussion of the WHO advisory group. Furthermore, this timeframe does not account for the scientific knowledge, skill, materials, and poxvirus parts that previously existed in the Evans Laboratory. In addition, the stated timeframe does not include the years of research involved in defining the optimal sequence lengths and terminal pieces that were needed to gain full coverage of the genome and to add the termini to the fragments. Therefore, the level of tacit knowledge needed to create horsepox virus from published sequence was high, requiring specialized skill and knowledge which many actors do not have.

Canada's Biosafety and Biosecurity Policy Framework

According to the publication, Dr. Evans contacted the relevant Canadian regulatory authorities to seek approval for the research.(83) In 2009, Canada passed the Human Pathogens and Toxins Act (HPTA), which establishes a safety and security regime for human pathogens and toxins that pose significant risks to public health and safety.(88) On December 1, 2015, the HPTA and the *Human Pathogens and Toxins Regulations* (HPTR) were fully implemented, which allows for oversight for activities including the import, export, handling, production, permitting access to, possession, use, storage, release, disposal, or transfer of human pathogens and toxins. The scope of the HPTA includes all Risk Group 2 to 4 human pathogens and toxins, whether imported or domestically acquired, or naturally occurring or synthesized.(89)

The HPTA requires facilities to obtain a license for activities with Risk Groups 2, 3, and 4 human pathogens and toxins, (equivalent to biosafety levels 2, 3, and 4 in the United States), and reinforces institutions' internal accountability systems. The Canadian Biosafety Standard (CBS) is a national standard that sets out the physical containment, operational practice, and performance and verification testing requirements for the safe handling and storing of human and terrestrial animal pathogens and toxins in Canada.(90) The CBS is used by the Public Health Agency of Canada (PHAC) and the Canadian Food Inspection Agency (CFIA) to verify the ongoing compliance of facilities regulated under the HPTA, and the Health of Animals Act and *Health of Animals Regulations* (HAR) to support license applications and renewals for human pathogens and toxins, and animal pathogen import permits.

Under the HPTA, PHAC delivers a national program that includes individual security clearances for those with access to select high risk pathogens, laboratory incident reporting, compliance promotion, monitoring and verification, pathogen risk assessments, standards and guidance development, biosafety and biosecurity awareness and training, stakeholder engagement, and enforcement.(91)

The HPTR also require facilities conducting scientific research to develop and submit a plan for administrative oversight that describes how their facility administratively

manages and controls biosafety and biosecurity risks at the institutional level, including the identification, assessment and mitigation of risks associated with research with dual-use potential.(92) Ongoing compliance monitoring activities conducted by PHAC verify that regulated facilities are adhering to appropriate biosafety and biosecurity practices, including those described in their plans for administrative oversight. Dr. Evans' institution, the University of Alberta, submitted a plan for administrative oversight to PHAC as part of the University's HPTA license application.(91, 93, 94)

Prior to the full implementation of the HPTA and HPTR, PHAC worked with the regulated community to guide them through the implementation transition period and to provide them with resources to help them comply.

The Canadian Food Inspection Agency has regulatory authority of pathogens causing foreign animal diseases and pathogens causing emerging animal diseases that are imported into the country under the *Health of Animals Act* and the *Health of Animals Regulations*.

Relevant U.S. Policy Considerations

Dr. Evans informed the WHO that he chose to synthesize horsepox virus to show that it was feasible with publicly available information and relatively few funds and time.(2) However, all other publicly-available articles describe this re-created virus as an alternative smallpox vaccine. In March 2017, a U.S.-based company, Tonix Pharmaceuticals Holding Corp., issued a press release announcing its partnership with Dr. Evans in developing a new candidate smallpox vaccine.(95) This candidate vaccine is a "live form of horsepox virus that has been demonstrated to have protective vaccine activity in mice." The development of a potential MCM (i.e., the chimeric horsepox virus) for smallpox virus, which is a material threat in the United States, allowed Tonix to be eligible for the priority review voucher program that was established for MCMs in the 2016 21st Century Cures Act.(96) Because Tonix is a U.S. based company, the virus would need to be imported into the United States for advanced development and manufacturing. Transferring the synthesized horsepox virus to the U.S. likely would be regulated by U.S. import regulations for infectious biological agents, infectious substances, and vectors (42 §71.54). However, horsepox virus is not a listed agent on the U.S. Export Administration Regulations Commerce Control List, and if used as a vaccine, the synthesized virus may be excluded from export control regulations if it were listed (ECCN 1C351). The horsepox virus is not listed as a controlled agent by the Australia Group, of which the United States and Canada are members.

An Assessment of U.S. Policy Relevance if the Horsepox Virus was Synthesized in the U.S.

If a research group in the United States attempted to synthesize horsepox virus, the research would not necessarily be restricted within current regulatory and policy frameworks.

- The National Institutes of Health Guidelines for Research Involving Recombinant or Synthetic Nucleic Acids would hold U.S. universities responsible for reviewing the proposed research for biosafety. At this stage of review, the Institutional Biosafety Committee (IBC) and/or biosafety official would assess the biosafety risks of the research (including risks associated with animal studies), recommending research conditions under which the research could be conducted safely. If risks cannot be addressed adequately, they may not approve the research to continue. Adherence to the NIH Guidelines is mandatory for federally-funded research and institutions receiving federal funds, but voluntary for research institutions that do not receive U.S. government research funding.
- The IBCs and biosafety officials would review the research for potential biosecurity risks, per the 5th Edition of the Manual on Biosafety in Microbiological and Biomedical Laboratories (BMBL). Although not required by federal law, most research institutions would comply with the biosafety and biosecurity guidance in the BMBL to promote good practice, comply with funding award requirements, and/or prevent reputational harm, financial penalties, or removal of funding if an accidental release occurs. Furthermore, if the research was regulated by the Federal Select Agent Program (i.e., involving synthesis of a regulated poxvirus), the institution would be required to comply with the BMBL and NIH Guidelines.
- The Animal Welfare Act and Animal Welfare Regulations require institutions to review and oversee research involving animals. According to the Tonix Pharmaceutical press release, the synthesized horsepox virus was studied in mice. Although mice used in research laboratories are explicitly excluded in the Regulations, animals that may be used in advanced development of MCM likely are covered. Furthermore, the NIH Public Health Service Policy requires institutional review and oversight of NIH-funded research involving mice. Therefore, testing of the synthesized virus likely would be reviewed by the Institutional Animal Care and Use Committee if the research was funded by NIH and if studies involved animals covered in the Animal Welfare Regulations. At this stage, questions about the source of the virus may have been raised by the responsible veterinarian and committee members.
- In 2010, the U.S. government released its Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA. This framework is voluntary for industry and resembles industry guidance for sequence and customer screening, which is promulgated by the International Gene Synthesis Consortium (IGSC). The U.S. government's and the IGSC screening frameworks are based largely based on the Biological Select Agents and Toxins list, on which smallpox is listed. If a researcher orders the synthetic DNA from a company that follows this guidance, the company may inquire further, decline to fulfill the order, or contact the Federal Bureau of Investigation or similar governmental authorities given the high degree of similarity between horsepox virus genes and smallpox virus genes. Because smallpox is a restricted agent in the United States and by the World Health Organization, the IGSC companies would treat any orders containing any sequences identical to the smallpox genome differently than other sequences. The company's scrutiny of the order may delay or prevent the research from

continuing. However, if the customer has demonstrated its legitimacy, the order may be fulfilled. According to the WHO report, obtaining the synthetic DNA fragments was the longest step in the synthesis process, but no additional details are provided.

- The horsepox virus is not listed as a Biological Select Agent and Toxin and consequently, does not fall under oversight of the Federal Select Agent Programs. (42 §73 and 9§121)
- The horsepox virus is not one the biological agents listed in the United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern and the United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern. However, institutions that use an approach for reviewing dual use potential of life science research that is broader than the current federal policy may recognize the potential security risks of the research, recommend risk reduction strategies for the research, and/or oversee the research.
- The 2017 Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO) likely would not enable review and oversight of the horsepox virus synthesis research. U.S. government funders of life sciences research currently are developing their review and oversight processes for implementing this federal guidance document. The guidance states that potential pandemic pathogens are highly transmissible in human populations and highly likely to cause significant illness and/or death. The guidance goes on to describe enhanced potential pandemic pathogen as the modification of natural pathogens to increase their ability to spread between people and to cause increased illness and/or death. At the same time, the guidance excludes modifications that are “associated with developing and producing vaccines.” If the security concern about horsepox virus is that information about how to synthesize a poxvirus may aid adversaries, the research would not be covered by the processes developed from this guidance. If the concern is that an adversary can use the synthesized horsepox virus to cause harm to individuals, the research likely would not fall under oversight processes because horsepox virus is thought to only infect and cause disease in animals and Tonix claims this virus was developed as a candidate MCM for smallpox.
- Although a high degree of sequence identity exists between horsepox virus and other orthopoxviruses, the virus may or may not be covered under 18 USC §175c. The definition of variola virus included in the U.S. Code is highly ambiguous, resulting in its clarification by the Department of Justice (DoJ). In 2008, the DoJ defined the term variola virus, within the context of 18 USC §175c, as not including “other naturally occurring orthopoxviruses, such as cowpox and vaccinia, but is rather limited to viruses that cause smallpox or are engineered, synthetized, or otherwise produced by human manipulation from the variola major virus or its components.”(97) By this definition, horsepox virus would not be included in this statute, which may be supported by recent publications stating that vaccinia virus is derived from horsepox virus. However, some horsepox genes are identical to smallpox and horsepox previously was considered an extinct virus, raising questions about whether horsepox may be included. Despite

this ambiguity, horsepox probably would not be included in this statute because it was not derived from variola virus.

If the research resulted in a virus that was used to harm humans or animals deliberately, the perpetrator could be prosecuted under the Biological Weapons Anti-Terrorism Act of 1989, which is the United States' implementing legislation for the Biological and Toxins Weapons Convention.

The primary policy findings from this case study are:

1) The U.S. biosecurity policies do not apply to the synthesis of horsepox virus. Detection, regulation, and oversight of research involving synthesis of horsepox virus would not occur through biosecurity policies, including the DNA screening framework guidance, because it is not listed as a Biological Select Agent and Toxin and it is being marketed as a candidate smallpox vaccine.
2) The U.S. biodefense program may provide an incentive and rationale for synthesis of the horsepox virus (i.e., to create a MCM for smallpox). In this situation, the potential benefit of horsepox as a smallpox vaccine has to be compared to the potential risk that knowledge about the methods for synthesizing horsepox virus, especially because MCMs already exist for smallpox virus and vaccinia virus (the original smallpox vaccine) was derived from horsepox virus. Therefore, the publicly-stated benefits *and* risks may be overestimated.
3) The U.S. biosafety guidance and animal care and use requirements, which addresses an ethical risk (protection of research animals), likely would trigger review and oversight of the horsepox virus research.
4) Based on the current regulatory requirements for biosafety and ethics, the system under which life sciences research is conducted, if implemented well, is able to detect, review, oversee, and manage moderate and high-risk research. However, reliance only on biosecurity policies to detect, review, and oversee research is restricted to a defined list of agents. This difference is exacerbated at institutions that precisely comply with relevant policies, which may result in quick policy "fixes" that may adversely affect some, but not necessarily the most relevant research. However, institutions that implement review and oversight procedures that exceed federal policies may be well-situated to detect and mitigate risk proactively, without preventing the research from being conducted and without eliciting exaggerated policy responses based on alarmist sentiments or scientifically unfounded fears.
5) The synthesis of horsepox virus highlights the international nature of the science and technology landscape. The assessment of relevant U.S. policy actions in response to the synthesis of horsepox virus is a thought exercise designed to identify gaps in policy and policy implementation. However, the actual research was conducted outside the U.S. and the researchers are attempting to publish their work, which would be shared with scientists around the world to enable scientific progress and advancement on beneficial research (e.g., viral platforms for creating vaccines against infectious disease or cancerous cells, both of which are possible uses of horsepox virus). Internationally, the International Health

Regulations and Global Health Security Agenda set competencies for biosafety and biosecurity of diagnostic laboratories, but only the World Health Organization's published guidelines for biosafety, biosecurity, and responsible science applies to research laboratories. International scientific organizations have engaged scientists and other organizations on dual use life sciences research. However, scientific and national differences in understanding and addressing dual use life sciences research present significant challenges in promulgating practices that could help identify and mitigate serious biosecurity risks.

Appendix 2: Evaluation Metrics Use Cases

Application of the Evaluation Metrics Framework developed for this project to three use cases is presented in this appendix. The use cases included in this appendix are:

- NIH Guidelines for Recombinant and Synthetic Nucleic Acids, which is a voluntary guidance that is contractually required for all research institutions that receive U.S. government funding
- Biological Weapons Anti-Terrorism Act, which is a legally-binding criminal statute
- Public Health Medical Countermeasures Enterprise (PHEMCE), which is a U.S. government-wide biodefense program

These use cases illustrate how the framework can be applied and enabled the authors to revise the initial framework to ensure its relevance to different types of policies.

Policy	**NIH Guidelines on Recombinant and Synthetic Nucleic Acids**	
Policy Goals	Reduce the potential safety risks that may result from research involving genetic engineering Reduce the potential safety risks that may result from research involving use of synthesized DNA	
Policy Objectives	Implement a system for reviewing and overseeing genetic engineering research Establish a process for identifying, analyzing, and mitigating potential safety risks genetic engineering research	
Policy Type	Policy Guidance, contractually required in grant awards	
	Activities	**Sample Evaluation Questions**
Required Activities	• Institutional biosafety committee at research institutions receiving federal funding that: o Reviews and oversees genetic engineering research o Recommends conditions under which genetic engineering research can be conducted safely o Recommends alternative approaches for high-risk research o Approve or reject genetic engineering based on the biosafety risks posed o Report outcomes of reviews to the National Institutes of Health Recombinant DNA Advisory Committee (RAC) o Has required diversity of expertise o Is trained to review and oversee recombinant and	<u>Institutional Questions</u> • Has the institution established an institutional biosafety that: o Has knowledgeable scientists, institutional biosafety administrators, and public representatives serving? o Has a biosafety officer, who is involved in the IBC review and oversight process? o Keeps well-documented records of the meetings and reports to NIH on time and as required? o Meets on a regular schedule? • How often are committee members trained? • How often are the training materials updated with new policy-relevant information and scientific advances? • What is the turn-around time for the reviews? • How many protocols are evaluated each year?

	synthetic nucleic acid research o Participates in review of human subjects research, if appropriate o Ensures PI compliance with the Guidelines o Determine health surveillance needs of researchers • PI responsibility: o Submit registration documentation to the IBC for research that must be reviewed o Submit information about certification of new host-vector systems o Seek approval of NIH conduct covered experiments and request exemptions o Seek determination from NIH about containment requirements, especially if not included in the Guidelines o Seek approval by IBC for clinical trials added after the research has been registered with NIH o Communicate with IBC throughout the entire research effort o Maintain and promote safe laboratory practices • Institution Responsibilities: o Allow members of the public to observe IBC discussions o Adopt emergency plans for spills o Establish procedures for safe conduct of recombinant or synthetic nucleic acid research o Comply with shipping requirements o Have a biological safety officer o Inspect laboratories to ensure appropriate safety measures are being used o Review research conducted at institutions to ensure compliance with Guidelines o Report violations of the Guidelines, accidents, or problems	• How many protocols have received recommendations for experimental alteration based on biosafety risks? • How often have study principal investigators been involved in discussing the risks, experimental conditions, and alternative approaches? • How many protocols are rejected each year? • How many protocols are approved each year? • How many times has the IBC consulted with non-member, subject matter experts each year? • How often does the IBC allow members of the public to observe the reviews? • Do IBC member recuse themselves from review of their own research or research from which they could benefit? • How many protocols receive detailed review each year? • Does the institution have plans for addressing accidents or violations? • How often is research conducted at the institution reviewed to ensure compliance? • How many research activities that have not undergone review are identified each year? • Do procedures exist for seeking research approval and determination of containment from the NIH? • How many laboratory staff are aware of the safety risks of their research? <u>NIH Questions</u> • RAC o How many protocols has the RAC reviewed? o What recommendations has the RAC made for addressing risks? o How often does the RAC convene to review protocols? o How many IBC members have received training by the NIH? o How often do the Gene Therapy Policy Conferences occur? o How many people attend the Gene Therapy Policy Conferences?

	• federal advisory committee (RAC): o Review proposed studies that may present significant biosafety risk o Provide recommendations to the research institution and NIH about mitigation of biosafety risks of genetic engineering research o Provide recommendations to the research institution and NIH about mitigation of ethical, legal and biosafety risks of human gene transfer studies o Provide training in laboratory safety to IBC members o Convene Gene Therapy Policy Conferences	• What methods has the NIH used to certify or decertify new host-vector systems?
Recommended Activities	• The RAC evaluates emerging biotechnologies and recommends modifications to the guidance to address new biosafety risks posed by emerging biotechnologies	• How often does the RAC convene to discuss emerging biosafety considerations of biotechnologies? • How often does the RAC engage with scientists, technologists, and other stakeholders when it evaluates emerging technologies? • What information does the RAC review when analyzing emerging technologies? • What types of biosafety risks have been identified by emerging biotechnology? • What suggestions have been made to address these risks?
Other Activities	• Institutions promulgate adherence to Guidelines even if research is not covered	• Does the institution have a process for interacting with researchers who are not immediately covered by the Guidelines? • How many institutions that are not required to comply with the Guidelines, nonetheless have established procedures for adhering to the Guidelines?
	Outcomes	**Sample Evaluation Questions**
Near-Term Outcomes	• Institutions have the requisite guidance and resources to evaluate the biosafety risks of unfamiliar research methodologies. • Institutions and researchers work together to identify, analyze, and mitigate risk.	• Across institutions, how uniformly do institutions review and adjudicate concerns? • How well do the reviews of protocols by institutions and the RAC align? • What processes exist to share best practices in review and oversight of genetic engineering research?

	• Best practices in biosafety risk identification, analysis, and mitigation are shared to institutions, researchers, and RAC members, which promotes consistency of review. • Institutional review procedures that meet the intent of the Guidelines.	• Are institutional review committees involving principal investigators in the review, analysis, and identification of risk mitigation strategies? • Have challenges in review and oversight of research involving genetic engineering been identified and addressed? • Have institutions and the RAC established common practices in evaluating research involving emerging biotechnologies and new research stakeholders? • Are scientists of all levels aware of best practices for their research?
Long-term Outcomes	• Biosafety risks of research are anticipated and reduced consistently across institutions and the RAC.	• Has the frequency of accidental or unintended exposures or releases decreased since the guidance was issued? • Have risks of purposeful release of engineered or synthesized organisms (e.g., gene drives in mosquitoes and synthetic organisms for remediation or environmental clean-up) been anticipated and addressed? • What tangible benefits have resulted from implementation of the policy?

Policy	**Biological Weapons Anti-Terrorism Act**	
Policy Goals	Implement the Biological Weapons Convention Protect the United States against biological terrorism	
Policy Objectives	Punish individuals who develop, possess, produce, stockpile, transfer, acquire, retain, or possess pathogens, toxins, or delivery systems for use as weapons Punish individuals who knowingly assists an organization or foreign government to develop, possess, produce, stockpile, transfer, acquire, retain, or possess pathogens, toxins, or delivery systems for use as weapons	
Policy Type	Criminal statute	
	Activities	**Sample Evaluation Questions**
Required Activities	• The Federal Bureau of Investigation has an established process for prosecuting individuals who develop, possess, or use pathogens as weapons • The FBI seizes pathogens, toxins, or delivery systems not	• Does the FBI have standard operating procedures for assessing whether an event is covered by the statute? • How often have suspects been prosecuted under this law? • How often have suspects been falsely prosecuted under this law? • How many FBI agents know about this statute?

	intended for peaceful or prophylactic purposes • Federal law enforcement has a process for destroying or disposing of seized pathogens, toxins, or delivery systems	• How many local police know about this law? • Does FBI have standard operating procedures for interacting with local partners?
Recommended Activities		
Other Activities		
	Outcomes	**Sample Evaluation Questions**
Near-Term Outcomes	• Uniform operating procedures for assessing events for its relevance to the statute • Established partnerships and open lines of communication with local police, FBI, emergency response personnel • Common definition of 'biological threat' • Seizure and destruction of confiscated pathogens, toxins, and delivery systems not intended for peaceful or prophylactic purposes	• Are operating procedures implemented uniformly by local and federal law enforcement? • Do communication platforms or systems exist to promote information-sharing? • Do platforms or forums exist to promote sharing difficulties in assessing potential events? • Do local and federal law enforcement have the same understanding of biological threat? • Does federal law enforcement have the same threshold for evaluating relevance of and applying the statute? • Do local and federal stakeholders conduct table top exercises?
Long-term Outcomes	• Prevent biological weapons attacks in the United States • Prevent malicious individuals from possessing biological agents	• How many potential incidents have been prevented because of this statute? • What evidence exists to suggest long-term outcome is achieved?

Policy	**Public Health Emergency Medical Countermeasure Enterprise**	
Policy Goals	Improve the U.S. capability for medical countermeasure research, development, and acquisition	
Policy Objectives	Establish a coordinated system for research, development, and acquisition of medical countermeasures against material threat agents Define the roles and responsibility of federal, industry, and research stakeholders in the system Define the priorities for MCM against material threat agents	
Policy Type	Program strategy based on statutes	
	Activities	**Sample Evaluation Questions**
Required Activities	• Create and communicate clear regulatory pathways for MCM development • Promote dialogue with FDA	• Have lines of communication for regulatory issues been created? • How many academic stakeholders access these communication pathways each year?

	• Identify scientific and regulatory challenges in MCM development • Develop operational plans for maintaining the MCM inventory • Develop operational plans for communicating guidance to end-users • Develop and provide training and education of MCM stakeholders • Develop and implement strategies for assessing and monitoring MCM safety and performance in an emergency • Set requirements to MCM research, development, acquisition • Support Development of MCM • Maintain and manage MCM stockpile • Facilitate deployment of MCM • Provide guidance and support for distribution, dispensing, and administration of MCM • Support research and development of MCM (NIH, DoD, ASPR) • Support advanced development of MCM (BARDA) • Develop a Regulatory Management Plan for MCM • Describe CBRN agents that present threats to the U.S. (DHS) • Evaluate progress of MCM research, development, procurement, and use • Report available funds for procurement of MCM through the Special Reserve Fund	• How many industry stakeholders access these communication pathways each year? • How many U.S. government stakeholders access these communication pathways each year? • How many international stakeholders access these communication pathways each year? • How often does FDA speak to MCM developers? • How many unique MCM developers does FDA speak with each year? • What standard operating procedures exist for MCM inventory management? • Do these procedures withstand or adapt to changes in inventory needs? • What standard operating procedures exist for communicating needs with end-users? • How many end-users think they adequate and sufficient information to answer their questions? • What strategies have been developed to assess MCM safety in an emergency? • What strategies have been developed to monitor MCM performance in an emergency? • What educational materials exist for MCM stakeholders? • How many the trainings are required? • How many unique stakeholders take each training each year? • How often is training provided? • How often are training materials updated? • How are stakeholders notified about new or updated training materials? • How often are MCM priorities and requirements set? • Are interagency partners involved in MCM-priority and requirement setting? • Are requirements communicated to regulatory bodies? • Are requirements communicated to MCM developers? • What percentage of federally-funded MCM research and development is driven by specific product requirements? • What percentage of federally-funded MCM research and development results from exploratory efforts?

		• What percentage of privately-funded research and development is eligible for MCM advanced development and procurement? • Does the U.S. government provide guidance to local emergency response stakeholders about MCM distribution, dispensing, and administration? • Does the U.S. government provide technical and financial support for MCM distribution, dispensing, and administration in an emergency? • How often are policies for MCM distribution, dispensing, and administration reviewed and updated? • Are local emergency response stakeholders involved in the development of MCM distribution, dispensing, and administration plans? • What is the cost-breakdown of basic research funding for MCM and related research? • What is the cost-breakdown of advanced development funding for MCM? • Does the process for assessing MCM needs improve as new information or risks are identified? • How often do stakeholder agencies communicate and coordinate activities with each other? • How many times have agencies leveraged MCM research and development investments of other agencies? • How often do stakeholder agencies report on MCM research and development achievements? • How often do stakeholder agencies report on procurement and use of Special Reserve Fund?
Recommended Activities	• Cooperate with DoD research and development of MCM for force protection • Support research on regulatory science • Implement infectious disease risk assessments that require MCMs (HHS) • Assess economic consequences of terrorism threats (DHS) • Engage intelligence community to conduct terrorism risk assessments (DHS)	• To what degree has HHS and DoD cooperated on basic and applied research and development of candidate MCM? • Are there procedures in place to identify advantageous knowledge or technologies for MCM development from published literature? • How often are infectious disease risk assessments conducted? • How adaptive are the risk assessment inputs to new threat and risk information?

	• Evaluate cross-threat considerations for MCM development and use (ASPR, CDC) • Develop (CDC) and review (FDA) pre-Emergency Use Authorization (EUA) packages for qualified MCM	• Do economic consequences get assessed? • How often is the intelligence community engaged in threat assessment? • How often are cross-threat considerations evaluated? • What procedures exist to address potential cross-threat issues? • How many pre-EUAs have been developed? • What criteria are used to determine the need for a pre-EUA? • How are pre-EUA packages communicated to MCM stakeholders?
Other Activities	• BARDA monitor emerging technologies for their potential application to MCM platform or product development • Research institutions work with private industry to conduct advanced development and manufacture MCM • CDC provide training to stakeholders about the MCM stockpiles • Conduct preparedness assessments to identify MCM needs • Evaluate suitability of current MCM to meet preparedness needs • Develop clinical practice guidelines for MCM use • Assess policy implications of MCM use • Develop procedures for communicating risk and information to the public in a pandemic • Support construction of MCM development and manufacturing capabilities (BARDA) • Develop an Innovation Modeling Hub to provide analytic decision-support and access real-time modeling capabilities (ASPR)	• How often does BARDA monitor and evaluate emerging technologies? • How often does BARDA monitor scientific literature for beneficial technologies? • How often does BARDA attend conferences to identify beneficial technologies? • What percentage of MCM companies are start-ups, emerging from the MCM market? • What percentage of large pharmaceutical or biotechnology companies are involved in MCM research and development? • What percentage of large companies have partnerships with academic or government scientists who conduct MCM research? • What percentage of start-up companies have partnerships with academic or government scientists who conduct MCM research? • How often does CDC train stakeholders about the MCM stockpile? • How often are training materials reviewed and updated? • How do stakeholders learn about new or revised training materials? • How often are preparedness assessments conducted? • How adaptable are preparedness assessments to societal, demographic, and other population-based changes? • How often is the MCM stockpiled evaluated for suitability? • What methods or considerations are used to assess suitability of the MCM stockpiles?

		• For how many different products have clinical practice guidelines been developed? • How are these guidelines communicated to end-users? • What procedures are in place to communicate information to the public during emergencies? • Have centers of MCM development and manufacturing been designed? • Have centers of MCM development and manufacturing been established and/or constructed? • How many of these centers leverage existing consortia and research hubs? • Has an Innovation Modeling Hub been developed? • To what degree are past investments in modeling, biosurveillance, and decision-support leveraged for the Innovation Modeling Hub? • Which stakeholders access the Hub? • Do the results from modeling efforts inform preparedness assessments?
	Outcomes	**Sample Evaluation Questions**
Near-Term Outcomes	• An integrated process for identifying, developing, producing, and acquiring high-priority MCM • MCM platforms that enable rapid development and acquisition of MCM products • Processes that enable rapid scale-up and manufacturing of MCM in emergencies or outbreak conditions • Improved investments in MCM development and maintenance • Incorporation of new knowledge, technologies, and equipment in the development of MCM products and platforms • Policies on support of civilian use of MCMs in an emergency • International collaborations for developing MCMs	• Does a single process for defining, identifying, developing, and acquiring high-priority been developed? • Are all stakeholders aware of this process? • To what extent have emerging technologies improved MCM platform and product development? • To what degree are regulators able to evaluate successfully new products, especially those based on new technologies? • To what degree are MCM producers willing to incorporate new approaches for MCM development and production? • Has the PHEMCE strategy and implementation plan provided sufficient guidance for MCM investments? • Do policies for supporting civilian use of MCM in an emergency exist? • Are stakeholders knowledgeable about these policies? • How many international collaborations for MCM development are initiated each year? • How many foreign governments have provided a market for developed MCMs?

		• How many foreign governments have provided a market for developed MCMs? • Has the risk from high priority threat agents decreased?
Long-term Outcomes	• Rapid development and deployment of MCM in an outbreak or emergency • Strong communication and coordination among enterprise stakeholders, including domestic and international stakeholders • Stockpile needed MCM • Seamless, sustained process for reviewing and approving MCM • Acquisition of MCM for at-risk individuals • Ongoing interagency coordination for development of MCM • Ready capability to develop and manufacture MCM • Capability to model threats to enable decision-support	• How well-protected (medically) are U.S. citizens in an emergency? o How quickly have MCMs been developed in an emergency? o How quickly have MCMs been deployed in an emergency? o Do MCM developers understand the process for development, review, and approval of MCM? o What high-priority threat agents are at-risk individuals protected against? o Do stakeholder agencies leverage each other's investments? o Do stakeholder agencies leverage new scientific and technology advances? • Are stakeholder agencies able to evaluate information and assess uncertainty of incomplete information to enable decision-making in an emergency?

Appendix 3: Opportunity Cost Historical Analysis: Biological Select Agents and Toxins Regulations

The Federal Select Agent Program (FSAP) regulates the possession, use, and transfer of biological select agents and toxins (BSAT), which are pathogens and toxins that could cause significant damage to public health and safety if accidentally or deliberately released. The U.S. Centers for Disease Control and Prevention and the U.S. Animal and Plant Health Inspection Service jointly oversee and administer the program. The program derives its legal authorities from the BSAT Regulations (a.k.a., Select Agent Regulations or SAR), authority for which was created by the Antiterrorism and Effective Death Penalty Act of 1996. This law was passed after Larry Wayne Harris (a member of the Aryan Nations) illegally acquired the bacteria that causes plague from a U.S.-based culture collection. The initial regulations focused on the transfer of BSAT between approved entities. The regulations were enhanced significantly after the events of 2001. The USA PATRIOT Act of 2001 defined restricted persons and illegitimate uses of BSAT. The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 expanded the BSAT list to include agricultural pathogens, established a security risk assessment process for vetting individuals seeking access to BSAT, and required registration of individuals and facilities possessing, using, and transferring BSAT. The changes included in these laws were finalized in 2005. Shortly thereafter, two significant events occurred that precipitated additional changes to the SAR: 1) the identification by the Federal Bureau of Investigation (FBI) of Dr. Bruce Ivins, a 30-year researcher at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), as the perpetrator of the 2001 anthrax letters; and 2) the revelation that a researcher, who was not registered as a select agent-approved researcher, at Texas A&M contracted brucellosis after coming into contact with a contaminated animal infection chamber in a select agent-approved laboratory. These events resulted in a flurry of policy debate on personnel reliability of BSAT researchers and support staff, and security in BSAT facilities. The White House established an interagency working group to review existing laws, regulations, and policies related to the FSAP, oversight and security of high-containment laboratories, and personnel security measures as directed by Executive Order 13486, Strengthening Laboratory Biosecurity in the United States. Following this review, the White House established the Federal Experts Security Advisory Panel (FESAP), to evaluate and provide recommendations on the tiering of BSAT, removal or additions of BSAT, personnel reliability practices, physical and cyber security measures, and other relevant policy issues as directed in Executive Order 13546, Optimizing the Security of Biological Select Agents and Toxins in the United States. The recommendations were considered and incorporated into the 2012 final rule of the SAR.

Table 9 summarizes key regulatory changes included in the 2012 and 2017 updates to the SAR.

Table 9. Selected Regulatory Changes in the 2012 Updated BSAT Regulations.		
Requirement Category	**Prior Requirements**	**New requirements**
	2012 Updates	
Physical security	Two physical barriers protecting select agent storage units	*Tier 1 agents*: Three physical barriers protecting select agent storage units; all registered space must be protected by an intrusion detection system
Personnel reliability	Security risk assessments: electronic records check to determine whether individual meets any of the statutory restrictions that prohibit access to select agents	*Tier 1 agents*: initial and ongoing suitability assessments, including more thorough investigation of individuals and the establishment of a system for self and peer reporting of incidents that might compromise suitability
Occupational Health	No requirement	*Tier 1 agents*: occupational health monitoring for individuals with access to Tier 1 agents
Training	Standard biosecurity training	*Tier 1 agents*: additional insider threat awareness training
Coordination with local law enforcement	No requirement	*Tier 1 agents*: 15-minute response time for security forces or local police following a security breach
Listed agents	-	Addition of SARS-Coronavirus, Chapare virus, and Lujo virus to the list
	2017 Updates	
Agent inactivation	Non-viable select agents are excluded from SAR, but no requirements regarding inactivation procedures for rendering agents non-viable	New requirement that inactivated select agents or regulated nucleic acids intended for future use must be subjected to an in-house validated inactivation procedure that is confirmed through a viability testing protocol

Note: This table does not include all changes issued in the 2012 and 2017 updates to the SAR but rather highlights those changes that led to opportunity costs for affected stakeholders.

Findings

The findings of these case studies are organized around the following policy elements:

- Enhanced security requirements for Tier 1 agents, issued in 2012;
- Baseline security requirements for non-Tier 1 agents, as required after the 2012 Final Rule and which apply to laboratories that conduct SARS-CoV work;
- Policy elements that apply to both Tier 1 and non-Tier 1 agents, such as the new inactivation guidelines issued in the 2017 SAR Final Rule.

Although our discussions focused on the 2012 and 2017 updates to the SAR, some of the costs described dated back to the 2005 Final Rule, including institutions that relinquished select agent status following the 2005 updates. Analytic parameters reflecting these costs were identified and wherever possible effects associated with the 2005 Final Rule were indicated.

Information from stakeholder discussions was supplemented with data described in published literature, including data from published surveys and articles on the costs associated with the SAR. However, most of these studies were conducted prior to 2012, and so evaluated a select agent regime that looks quite different from that of today.(70, 72, 73, 98) Further, most do not distinguish between the direct effects of the SAR and effects arising from other scientific or political issues, such as fluctuation in research funding levels and changes in publication priorities and standards.

Within each policy element, the direct costs of compliance with the policy are first discussed, followed by the trade-offs for individuals and institutions and the downstream consequences for select agent research and preparedness.

Enhanced physical security measures

This category includes costs incurred by select agent-registered institutions to upgrade the physical security systems of their Tier 1 labs to meet the enhanced requirements issued in the 2012 SAR final rule and the cost to retrofit or move laboratories when new agents are added to the select agent list. The direct costs and financial burden associated with physical security infrastructure varied systematically between different types of institutions, in part depending on whether the institution supported its own physical security expenses or had outside sources of funding.

Direct Financial Costs

Research institutions generally incurred the direct financial costs of establishing or upgrading physical security barriers, as opposed to the federal government. At some research institutions, upgrading the physical security systems of Tier 1 laboratories required significant upfront investments. For example, one academic institution highlighted the expense of the intrusion-detection system. In contrast, some research institutions previously implemented stringent security measures that met the enhanced requirements issued in 2012 and therefore incurred minimal (or no) new expenses. Research institutions receiving DoD funding had to establish stringent physical security systems prior to 2012 to comply with DoD regulations, whereas some academic institutions implemented these measures voluntarily.

Multiple public health and veterinary diagnostic laboratory stakeholders indicated that the financial costs of installing the physical security measures outlined in the SAR, in particular the enhanced security requirements for Tier 1 agents, represent a significant financial burden for this cohort of laboratories. In part, this burden reflects the older age of many of these laboratories – the average age of a veterinary diagnostic laboratory is about 40 years old – such that significant infrastructure upgrades would be required to make the facility SAR-compliant. Further, public health and veterinary diagnostic labs support most of their laboratory infrastructure expenses themselves, and budgets are already stretched thin.

Small and mid-sized companies that support medical countermeasure (MCM) development generally engage contract research organizations (CROs) to perform select agent studies (e.g., challenge testing) to reduce the high costs of establishing and

maintaining a select agent laboratory and to leverage an experienced CRO workforce. Some large MCM development companies have their own select agent laboratories, but at least one pharmaceutical company recently has closed some of its select agent laboratories in favor of outsourcing their select agent studies, in large part because of the high costs of physical security maintenance and upgrades. In contrast, the financial costs associated with maintaining physical security infrastructure at CROs is offset by the fees of their select agent research services. Because the development of MCM for select agents is funded primarily by the government, through contracts from agencies such as NIAID, BARDA and various DoD components, these expenses are passed on to the government (i.e., in the form of higher overhead fees on contracts). Because government agencies have been willing to pay industry for the escalating costs of select agent research as physical security and other BSAT requirements have increased, the expenses associated with physical security infrastructure for select agent research have been minimally borne by industry. However, absent increases in government biodefense funding, these increases in the security costs effectively decrease government funding for biodefense research.

For all types of select agent laboratories, the costs of maintaining physical security infrastructure are significant. The maintenance costs are on par with upfront equipment costs at their institutions. At institutions that support their own laboratory infrastructure, which includes most academic institutions and public health and veterinary diagnostic laboratories, securing funding for maintenance of security equipment poses significant challenges. No federal grants for this purpose are available to academic institutions or veterinary diagnostic laboratories, and minimal federal money is available to public health laboratories through the Public Health Emergency Preparedness (PHEP) grants distributed by the CDC. In contrast, at other institutions (e.g., National Biocontainment Laboratories, USG research institutions), maintenance of physical security is directly or indirectly supported by the USG.

Trade-offs of Financial Costs

The cost of maintaining and upgrading physical security infrastructure to remain compliant with the SAR was a major factor in the decisions of many academic institutions, public health laboratories, veterinary diagnostic laboratories, and MCM development companies to shut down their select agent programs. Many labs let their select agent registration lapse after the 2005 SAR updates. Additional laboratories working on Tier 1 agents or SARS-CoV relinquished their status following the 2012 updates. Moreover, this cost has deterred non-registered institutions from joining (or re-joining) the FSAP. The implications of a reduction in the number of select agent laboratories for research and preparedness against biothreats are discussed further below.

Take-aways

- The direct financial costs of maintaining physical security equipment are on par with the upfront purchase and installation costs.
- The direct financial costs and financial burden of policies involving laboratory infrastructure vary systematically between different types of institutions. In part,

the financial burden depended on the source of funding for compliance activities (e.g., direct federal funding versus institutional funding).

- The costs of maintaining and upgrading physical security infrastructure to remain compliant with the SAR has deterred non-registered labs from joining the Federal Select Agent Program and was a major factor in the decisions of many registered institutions to withdraw from the program.

Personnel reliability

This category includes requirements for personnel security risk assessments (SRAs), required for all individuals with access to select agents, and personnel suitability programs, required for individuals with access to Tier 1 agents only. SRAs, which are conducted by the FBI Criminal Justice Information Services (CJIS), comprise an electronic records check to determine whether an individual meets one of the statutory restrictions that prohibits access. Beginning in 2005, individuals were required to undergo an SRA to gain approval for accessing select agents, which was valid for five years. In 2012, the duration of approvals was shortened to three years, and institutions were required to assess suitability of personnel working with Tier 1 agents. Personnel suitability programs comprise a more thorough pre-suitability assessment of an individual's background and behavior history than the SRA alone, as well as ongoing monitoring to identify behaviors of concern.

Direct Financial and Time Costs

Personnel reliability requirements have not prevented the institutions consulted for this project from hiring skilled individuals, but the long timeframes for clearance investigations pose significant logistical challenges for hiring. Clearance investigations for SRAs may take one to a few months for U.S. citizens, but can be much longer for foreign nationals, in large part because information required to conduct a thorough background check often is not available or hard to obtain.

Institutions with Tier 1 labs spent significant amounts of time and money developing and maintaining new personnel suitability programs for personnel with access to Tier 1 agents following the 2012 updates to the SAR. In part, the costs of program development arose from the need to engage a diverse set of institutional and community stakeholders in the program, including the research community, environmental health and safety, university health services, the institution's legal department, human resources, and the local police department. Many of these stakeholder groups continued to be involved in personnel assessment, and some institutions also incorporate annual psychiatrist reviews into their programs, which can be a significant expense. Based on comments from stakeholders, the cost of background checks and suitability assessments for Tier 1 personnel can be over $2,000 per individual. Most institutions fund their personnel suitability programs through institutional funding mechanisms rather than drawing from the research grants of select agent principal investigators.

In contrast, most companies developing select agent MCM have not incurred direct costs from the SAR personnel reliability requirements because they outsource their select agent studies to CROs, which are required to comply with personnel security

requirements. As discussed above, ultimately this cost is borne by government contracts for biodefense MCM, in the form of higher overhead fees. Although quality assurance/quality control (QA/QC) personnel from the MCM development companies audit CROs through on-site visits to ensure that CRO practices meet company standards, their audit activities do not require accessing laboratory spaces where select agents are stored. As a result, the QA/QC personnel do not need to obtain clearance.

Trade-offs of Financial and Time Costs

The direct time and financial costs associated with personnel reliability requirements have led many institutions to limit the number and type of personnel conducting research with select agents at their institutions.

The time burden of the SRAs poses challenges for hiring and can lead to research delays. Because non-registered individuals must be escorted continuously by a registered individual in areas with access to select agents, the non-registered individuals can contribute minimally, or not at all, to select agent research activities while waiting for clearance. (During this waiting period, these individuals are often trained in standard operating procedures (SOPs) in non-registered, BSL-2 spaces.) Some select agent labs have ceased hiring foreign individuals because supporting their salaries during this long waiting period poses a financial burden. Alternatively, for one large, university-associated veterinary diagnostic lab, this situation has contributed to the lab's decision to not obtain select agent status, because the hiring of the spouses of foreign students as laboratory technicians is a common practice in the laboratory (and some other university-associated diagnostic laboratories). The concern that lengthy clearance investigations may delay research was previously identified in a 2004/2005 survey of select agent researchers; this survey queried U.S. researchers about direct and indirect costs associated with the 2003 interim rule for the SAR, which were nearly identical to the Final Rule released in 2005.(71) These delays are problematic for research laboratories and institutions because grants are time-sensitive, grantees cannot carry over more than 25% of costs in any given year of a grant, and no cost extensions are only automatic for one year. Therefore, an inability to hire new staff quickly may compromise a grantee's ability to achieve the research milestones in their grant.

Multiple academic institutions deliberately limit the number of personnel in their select agent programs to minimize the *time* and *expense* of maintaining the personnel reliability components of the program. For example, many institutions re-configured lab spaces to limit the number of personnel with access to Tier 1 select agents following the 2012 SAR updates. However, this strategy is not possible in many public health laboratories (PHLs) and veterinary diagnostic laboratories because of the open, shared structure of these labs and the need for high-containment lab spaces to be available for testing many different agents. As a result, these laboratories would need to enroll all (or nearly all) of their staff in their personnel security programs to comply with the regulations, which would be expensive and time-consuming. The time and financial burdens of developing and maintaining these programs were a major factor in the decisions of multiple PHLs and veterinary diagnostic laboratories to relinquish their Tier 1 status or their select agent registration altogether. Similarly, the costs of

personnel reliability programs contributed to the decision of at least one large MCM development company to shut down their own select agent labs and shift to outsourcing their select agent studies to CROs. Although CROs must incur these costs, the costs minimally affect their business because they are passed on to their clients in the form of higher fees, as described in the previous section. Alternatively, laboratories that retain their select agent registration but control costs by limiting the number of registered personnel may need to curtail training of non-registered students, fellows, and postdocs that would otherwise occur in the registered space.

Multiple research institutions have eliminated or greatly reduced visiting scientist programs for their select agent laboratories (including Tier 1 and non-Tier 1 laboratories) because of the *expense* and *time* required to clear personnel through the institution's select agent program. Most institutions require that visitors to select agent laboratories participate in the host institution's select agent program even if those individuals are enrolled in their home institution's program to minimize safety, security, and liability concerns for the host institution. When participation in these programs becomes significantly difficult (or impossible), the lost training opportunities impede development of a sufficient and qualified select agent workforce. Visiting scientist programs provide important training opportunities in select agent research techniques, including informal opportunities through research sabbaticals, formal training opportunities such as the BSL-4 training course offered by the International Biosafety Training Center at the Galveston National Laboratory, and other arrangements. Visiting scientist programs also foster research collaborations that are critical to technology and scientific advances that help to push forward scientific research. For example, these programs allow select agent researchers to host visiting scientists with specialized skills to apply new techniques that could enhance their research. Without this capability, the research may be delayed (i.e., if the select agent researchers have to learn the new technique themselves rather than leverage their colleagues' expertise), or a particular line of research may be discontinued. Previous surveys of select agent researchers, conducted in 2004/2005 (described above) and 2009 found that the SAR had hampered researchers' ability to collaborate both domestically and internationally, in part by making visits to select agent laboratories slower and more tedious.(70, 72, 73, 98)

Researcher Frustration: Direct Costs and Trade-offs

Responsible officials from several academic institutions shared that their Tier 1 select agent researchers were frustrated by the intrusiveness of the suitability program and/or by the time needed for participation in the suitability program (for example, for annual psychological assessments). Although these stakeholders had not observed any of their researchers drop out of the select agent program to avoid participating in these programs, they suggested that researcher frustration contributes to the overall resentment of the "big brother" nature of the select agent program that plays a role in some researchers' decisions to leave the field.

Take-aways

- Laboratory architectures and workflows influence the direct costs of policies related to agent access, in particular the ability of laboratories to re-configure their space or processes to limit the number of personnel with access to restricted agents. An inability to control the costs of personnel reliability programs by limiting the number of personnel enrolled may lead institutions to relinquish their select agent registration.
- Hiring challenges arising from lengthy personnel vetting processes can lead to research delays and contribute to institutions' decisions not to participate in the FSAP.
- The time and expense of personnel reliability programs may limit the number of personnel participating in an institution's select agent program, including visitors and individuals at the home institution. This effect may lead to the loss of training opportunities and impede research collaborations, which could have broader consequences for the research community's ability to conduct basic research for characterizing pathogens and developing early-stage countermeasures, both critical aspects of U.S. biodefense objectives.
- Frustration with the perceived intrusiveness of personnel reliability programs may contribute to some researchers' decisions to leave select agent research, thereby impeding the development and maintenance of the select agent workforce.

New regulatory requirements for the inactivation of select agents

In January 2017, the Federal Select Agent Program issued a new provision stating that inactivated select agents or regulated nucleic acids that can produce infectious forms of any select agent virus must be subjected to an *in-house validated* inactivation procedure that is confirmed through a viability testing protocol. Previously, the regulations provided that non-viable select agents and genetic material were excluded from the requirements of the SAR but did not include any requirements regarding the procedures for rendering agents non-viable. This new provision was introduced in response to the 2015 discovery that failures to fully inactivate *B. anthracis* spore samples by Department of Defense laboratories led to the inadvertent transfer of potential live *B. anthracis* samples.

The new regulations also established requirements for record-keeping of validation data for inactivation procedures. Registered institutions are responsible for evaluating their own inactivation protocols; this review is conducted by the local Institutional Biosafety Committee (IBC). During inspections, inspectors may verify that institutions have validated their inactivation protocols and review validation data. Although the new regulation does not explicitly require registered entities to re-validate their agent inactivation procedures, in practice entities had to do so to generate *in-house* validation data and satisfy the record-keeping requirement.

The regulations do not set specific performance standards, but accompanying guidance encourages institutions to demonstrate that the risk of live agent remaining in an inactivated sample is "as low as realistically possible." Local IBCs have sought clarity

from the FSAP on their interpretation of the performance standard, to ensure that the standards they apply when evaluating inactivation procedures will be approved by FSAP inspectors. However, multiple institutional stakeholders have stated that the FSAP has not provided sufficient clarity on this issue. Consequently, multiple IBCs have been reluctant to approve inactivation procedures or have applied extremely stringent performance standards, to avoid the perception that their institution does not take biosafety seriously. This approach is problematic for viruses because of technical challenges for validating the efficacy of virus inactivation procedures.[2] Nearly one year after the issuance of the new regulation, multiple select agent virus laboratories had not yet had their virus inactivation procedures approved.

Direct Financial Costs and Trade-offs

Institutions have dedicated significant time and money to re-validating all of their select agent inactivation procedures. The costs of validating inactivation procedures, including labor and consumables costs, can range from ~$100,000 to validate procedures for two BSL-2 agents to several millions of dollars to validate multiple procedures for each of several different agents. Institutions receive no funding to comply with this new requirement. Because the regulation involves experimental procedures, funding for compliance was drawn from research grants or budgets rather than institutional overhead funding, which is typically used to fund compliance with requirements that do not directly involve the process of research, such as physical security. The diversion of research funds to validate inactivation procedures may prevent researchers from achieving the outcomes of their research projects because they have less money available for planned experiments. This effect may impede researchers' career advancement and undermine the ability of research funders to meet their missions.

Direct Time Burden and Trade-offs

Institutions consulted for this study spent weeks re-validating their inactivation protocols for bacteria. However, technical challenges for validating the efficacy of virus inactivation procedures have taken many months to resolve, as described above.[3] During this time, researchers were diverted from their normal research activities to generate the validation data, and inactivated samples could not be taken out of the BSL-3 suite for follow-up experiments until the inactivation procedures were approved by an institution's Institutional Biosafety Committee. This led to delays in research. Even though delays of weeks to months may be considered short given the long timescales of research (including basic and applied research), these delays can have significant consequences for individual researchers, laboratories, or institutions. Academic training and hiring cycles, grant deadlines, and the tenure process are not adjusted to account for unexpected research delays that may be caused by changes in research policies. The

[2] Thorough inactivation of virus-containing samples is typically established by infecting cells with the inactivated sample to confirm that no infectious virus remains. However, the chemical agents used for inactivation are toxic to cells, so that inactivated samples must be diluted prior to infection of cells. This need for dilution practically affects assessments of the limit of detection of the inactivation assay.

[3] Thorough inactivation of virus-containing samples is typically established by infecting cells with the inactivated sample to confirm that no infectious virus remains. However, the chemical agents used for inactivation are toxic to cells, so that inactivated samples must be diluted prior to infection of cells. This practical need for dilution affects assessments of the limit of detection of the inactivation assay.

delays can stall the career development of researchers at all levels.[4] Consequently, some researchers likely are to leave the field; some voluntarily, out of frustration, and some involuntarily, because of an inability to secure funding or progress their career. Additionally, research delays could impede an emergency response to a biological incident that requires a flexible and rapid scientific capability, which researchers often support.

Take-aways

- FSAP-registered institutions dedicated significant time and money to re-validating their agent inactivation procedures to satisfy the record-keeping requirement of the 2017 provision on select agent inactivation, even though the policy did not explicitly require the conduct of new experiments.
- Institutions diverted research funds for re-validation of their inactivation procedures, which may have limited researchers' abilities to meet their project outcomes.
- The time needed for re-validation of select agent inactivation procedures delayed research projects involving select agents. These delays can have consequences for workforce development by impeding researchers' ability to advance their careers by publishing papers, obtaining grants, or achieving promotions, and by compromising emergency response capabilities.

Administrative aspects of compliance

All aspects of the SAR require accompanying compliance documentation, including experimental procedures, incident response plans, and records for occupational health, personnel clearance and suitability, and training for all individuals in the select agent program. This administrative work is carried out primarily by principal investigators (PIs) of select agent laboratories (and/or their researchers) and responsible officials, depending on the type of documentation.

Direct time burden

Documenting compliance with the SAR requires significant time investments from principal investigators, researchers, responsible officials, or select agent program managers. The upfront time needed to document compliance with new security measures is substantial, particularly when new agents are added to the select agent list and compliance documents for all elements of the SAR must be prepared. Even if a new regulation codifies a practice or system that already is in place, formally documenting compliance with that regulation requires significant time.

[4] At academic institutions, research professors are hired on a probationary basis and evaluated after a set number of years (typically four to eight years) to determine whether they should be granted a permanent position or leave the institution; this evaluation is called the tenure process. At most institutions, tenure decisions primarily consider the researcher's grant and publication records, while service to the university and community are given less weight. Therefore, any reduction in the number of grants and papers a researcher can obtain during their probationary period could negatively impact their tenure prospects. Although the public health and national security relevance of select agent research may be considered a positive service to the community, this is not likely to off-set any deficiencies in grants or publications.

The administrative burden associated with ongoing compliance activities is as severe as documenting initial compliance. For example, one select agent researcher estimated that as much as 20-25% of his time is dedicated to administrative work. One contributing factor is that inspectors sometimes interpret regulations differently from year to year, which can result in administrative effort to revise experimental protocols, response plans, and other documentation to comply with new or different interpretations of the regulations. Underscoring the administrative burden of ongoing compliance, EH&S personnel at multiple institutions with research on SARS-CoV and Tier 1 agents stated that their departments hired new personnel to help comply with the additional requirements issued in the 2012 SAR updates, who have since stayed busy with ongoing administrative compliance duties.

Indirect Costs

The amount of administrative work required to conduct select agent research slows the pace of research. This effect arises from two factors: (1) the diversion of researchers' time from experiments to administrative activities; and (2) delays in initiating experiments caused by the approval processes at the institutional (i.e., approval by Responsible Officials and Institutional Biosafety Committees) and federal (i.e., FSAP) levels for SAR research. These delays may diminish the productivity of select agent researchers at all levels. For example, the length of a graduate degree involving select agent research is one to two years longer than average. Junior faculty spend significant time on upfront administrative work in setting up their new select agent laboratories rather than conducting research, which can adversely affect their research progress and career advancement.

The administrative burden of select agent compliance also contributes to senior researchers' decisions to re-direct their efforts toward research on non-select pathogens. Many SARS-CoV researchers shut down their SARS-CoV research programs when the virus was added to the select agent list in 2012 to pursue research with non-select agents. One researcher, who chose to redirect her research efforts primarily to avoid the administrative burden of select agent research, had previously conducted select agent research on a different pathogen and therefore, had a realistic understanding of the regulatory challenges associated with this type of research. Alternatively, researchers may maintain their select agent research portfolio but use non-select pathogens (e.g., to use surrogate or attenuated strains) for some experiments, the results from which may not be translatable to the select agent.

Several stakeholders described concerns about receiving penalties for mistakes on documentation. The risk of fines for compliance mistakes can drive some researchers to abandon their select agent research or redirect certain experiments to non-restricted pathogens. Additionally, the potential to incur penalties for administrative mistakes has contributed to the decisions of multiple veterinary diagnostic laboratories to relinquish their select agent status.

Non-registered diagnostic laboratories, which may identify a select agent in the course of testing unknown samples, are exempted from the SAR, but must document any

detection of a select agent within seven days. Several stakeholders affiliated with non-registered veterinary diagnostic laboratories also raised concerns about the time burden, penalties for mistakes in documentation, and liability associated with select agent requirements, especially during an animal outbreak of a disease caused by a select agent. These concerns have led some veterinary diagnostic laboratories to stop offering diagnostic services for select agents, potentially impeding early detection and biosurveillance of pathogens.

Take-aways

- The direct time costs of administrative effort needed for compliance varies by stakeholder and responsibility, resulting in different types and levels of lost opportunities.
- Institutions may spend significant time documenting compliance with systems or practices that are already in place at the institution.
- The administrative burden associated with ongoing compliance activities is significant and has caused some researchers to re-direct their research to non-regulated pathogens.
- The administrative burden of documenting exempt activities (e.g., detection of select agents in clinical samples by diagnostic reference laboratories) has deterred some institutions from engaging in those activities.
- Penalties for documentation mistakes, including documentation of compliance with regulated or exempted activities, have deterred some institutions from engaging in those activities.

Loss of institutional select agent capabilities: Downstream consequences

Direct financial and time costs of compliance with the SAR may contribute to an institution's decision to relinquish or not obtain their select agent registration. These costs include: 1) expense for maintaining physical security infrastructure and personnel reliability programs; 2) hiring challenges imposed by personnel reliability requirements; and 3) escalating administrative burdens. Recent Annual Reports of the Federal Select Agent Program indicated that 27 institutions withdrew their registrations in 2015 and 16 institutions withdrew in 2016, because their research focus changed, select agent research was transferred to another institution, or a desire to reduce administrative burden.(99, 100)[5] These institutions included academic, commercial, federal government, and non-federal government entities. The sections below describe the consequences of a loss of institutional select agent capabilities.

Research institutions. Research institutions provide research and training opportunities for researchers at all levels, from students to experienced scientists. Through grants, cooperative agreements, and contracts, academic and government researchers help to address knowledge and capability gaps in a variety of sectors, including biodefense. Furthermore, research institutions provide a setting to educate and train scientists in various fields, techniques, and biosafety and biosecurity practices.

[5] At the end of 2015, 291 institutions were select-agent registered, and at the end of 2016, 276 institutions were registered.

Stakeholders from institutions that no longer have active select agent programs stated that their institutions are unlikely to re-start these programs to accommodate new hires (or existing researchers) who would like to conduct research with select agents, resulting in limited job opportunities for select agent researchers. The competitive market may drive some researchers out of the field. As the field shrinks, so do training opportunities for junior researchers, further hampering workforce development. Although quantitative data on the number of new select agent faculty members or senior research staff hired by U.S. government or academic research institutions over the past several years are lacking, multiple academic stakeholders noted that their institutions had hired few or no select agent researchers in recent years. **These institutions had continued to hire researchers to study non-select, BSL-3 organisms such as *M. tuberculosis*, indicating that this trend is specific to select agents, not high-containment research in general.** Ultimately, the decreases in select agent researchers and training opportunities could curtail basic research on select agents in the U.S. This consequence will limit the knowledge base needed for developing new medical countermeasures, detecting and characterizing emerging pathogens, and transferring best practices for biosafety and biosecurity, which are critical to U.S. biodefense objectives.

Industry. Biotechnology companies lead the development and commercialization of medical countermeasures, including vaccines, therapeutics, and diagnostics, a primary contribution of industry to the biodefense sector. Companies also develop other technologies used for biodefense (e.g., sensors for environmental detection of biothreat agents) and may conduct applied research to inform the development of biodefense products.

Take-aways

- The downstream consequences of institutions withdrawing from the select agent program varies for different institutions, depending on their mission and training and research activities.
- The loss of institutional select agent research capabilities adversely affects the ability to meet the U.S. biodefense objectives in the near- and long-terms: (1) in the near-term, the loss of critical research activities and training opportunities; and (2) in the longer-term, inability to detect new zoonotic diseases, characterize pathogens, develop new MCM, and conduct microbial forensics.
- The ability to outsource select agent research is a workaround for the loss of in-house capabilities that has been employed successfully by the MCM development industry.

Appendix 4: Opportunity Cost Historical Analysis: United States Government Policy on Review and Oversight of Dual Use Life Sciences Research of Concern

The U.S. government released two policies for oversight of dual use research of concern (DURC) in 2012 and 2014: 1) USG Policy for Oversight of Life Sciences DURC (2012); and 2) USG Policy for Institutional Oversight of Life Sciences DURC (2014). These policies define DURC broadly as "life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security." However, the scope of the polices is limited to research involving fifteen listed agents and seven experiments of concern. All listed agents are subject to the Biological Select Agents and Toxins Regulations (SAR) with one exception: research involving small quantities of botulinum neurotoxin (BoNT) is exempt from the SAR at quantities lower than one milligram, but included in the DURC policies.(101) The DURC policies apply to USG-funded research only.

The 2012 policy describes DURC oversight responsibilities for federal departments and agencies that conduct or fund life sciences research, while the 2014 process describes institutional responsibilities for identification, assessment, and management of life sciences DURC. Because stakeholders from funding departments and agencies were not consulted in preparation of this case study, it focuses on opportunity costs experienced by institutional stakeholders only and arising from implementation of and compliance with the 2014 Institutional Oversight Policy. However, the authors did engage federal policy-makers during the project, informing them of this case study.

The 2014 Institutional Oversight Policy outlines a process for institutional identification and assessment of life sciences DURC by a dedicated committee (the institutional review entity, or IRE) in collaboration with the principal researcher. This process includes a risk assessment that underpins the identification of DURC and the development of a risk mitigation plan for conducting the research that preserves the benefits of the research while minimizing risks. Institutions must report the outcomes of all DURC reviews to the relevant USG funding agency, and the USG funding agencies must approve the risk mitigation plan prior to the conduct of research that is designated as having dual use potential.

When the policy first was released, research institutions undertook the following activities to become compliant with it:

- Establish an IRE and develop processes for institutional identification, review, and oversight of life sciences DURC.
- Develop DURC training materials and train IRE members and researchers.

- Review ongoing life sciences research projects to identify, assess, and report life sciences DURC to funding agencies.

Subsequently, newly proposed research projects or experiments have been reviewed for potential DURC according to the institution's established review process. Some institutions limit their DURC oversight to the fifteen agents and seven experiments outlined in the policy, while others evaluate DURC more broadly.

Findings

The financial costs of complying with the 2014 Institutional Oversight Policy, beyond personnel time, were found to be minor for most institutions. Therefore, this section focuses on two types of direct costs associated with this policy and their indirect effects: time and frustration. These costs may influence researchers' interest in pursuing research with dual use potential.

Time: Opportunity Costs

Direct time costs associated with *initial* compliance activities

The development of DURC review processes following the release of the 2014 Institutional Oversight Policy did not place a significant time burden on regulatory compliance officials at most institutions. These institutions already were reviewing experimental protocols to identify and mitigate DURC, typically through the Institutional Biosafety Committee (IBC), and adapted their existing practices to comply with the 2014 policy. For example, one institution shifted from using a rotating sub-group of IBC members to a permanent group for DURC reviews to satisfy the IRE requirement in the policy, but their review process remained the same otherwise.

The main costs of initial compliance with the 2014 policy arose from institutional review of ongoing life sciences research to identify, assess, and report projects involving DURC to the relevant funding agencies. One key challenge was in harmonizing institutions' and funding agencies' interpretations of DURC. One academic institution's initial DURC reviews for ongoing projects was delayed because the National Institutes of Health (NIH) did not agree fully with their determinations of which projects fell within the scope of the policy, requiring several rounds of discussion to clarify the definition of DURC and resolve the disagreement. This effort helped to define the research considered in scope of the policy, which promoted agreement between the NIH and the institution on its DURC assessments of newly-proposed experiments.

Institutions also spent time developing DURC training materials and training researchers and IRE members.

Direct time costs associated with *ongoing* compliance activities

Ongoing review of DURC requires a minimal-to-moderate time investment by members of the IRE, depending on the nature of research occurring at the institution and the institution's review process. Some institutions enroll all investigators working with listed agents in their DURC programs and subject *all* of their proposed research to a DURC review, even though only a small fraction of the reviewed research is determined to constitute DURC. For example, one academic institution estimated that fewer than

half of the projects reviewed by their IRE are elevated to the IBC and Biosecurity Task Force (larger committees) for further discussion, and only some of the referred projects are determined to be DURC. This encompassing approach to DURC review places a time burden on IRE members because of the high volume of proposed experiments that need to be reviewed, particularly at institutions with extensive research programs involving the listed agents. To accommodate the dual use reviews, some institutions have hired dedicated professionals to conduct initial research reviews to identify potential DURC, which subsequently is elevated to the IRE to limit the burden on IRE members.[6] Stakeholders also noted that reviewing research at the pre-proposal or proposal stage is inherently inefficient because some of the research is not funded because of scientific merit or research priority considerations that are independent of DURC.

From the perspective of researchers conducting dual use research, the direct time cost of policy compliance reflects the time needed for the DURC review and approval process. If a researcher would like to conduct a new experiment that may constitute DURC in between scheduled IRE meetings, that research will be delayed unless an emergency meeting can be convened. At one academic institution, this situation has arisen multiple times over the past several years; emergency IRE meetings could not be held in all cases because of the busy schedules of the committee members. For research that is deemed to be DURC, the processes of developing the risk mitigation plan and securing approval from the U.S. government funding agency have a significant time cost. The duration can be up to five months from the IRE's determination that the research is DURC according to the time frames detailed in the 2014 Institutional Oversight Policy.

Indirect Effects and Downstream Consequences Arising from Direct Time Costs

The direct time costs of *initial* and *ongoing* compliance affected stakeholders differently. Affected individuals and institutions experienced few indirect effects from the time needed to *establish* DURC review programs to comply with the 2014 Institutional Oversight Policy because most institutions could leverage their existing DURC review processes and experiences. Additionally, institutions did not experience significant costs associated with the time needed to develop DURC training materials and train researchers. Some ongoing research projects may have been paused while institutions clarified the funding agencies' interpretation of DURC (i.e., what research falls within scope of the policy), which could have adverse effects on the ability of researchers at all levels to meet career milestones (see below).

In contrast, researchers, reviewers (i.e., IRE members), and institutions have experienced indirect costs arising from the time required for *ongoing* oversight of DURC. Because IRE members have other professional responsibilities in addition to their service on the IRE, the time dedicated to IRE reviews may stress their ability to complete their other work. Institutions that hired new personnel to conduct initial DURC reviews used overhead or research funds originally marked for other purposes because outside sources of funding for compliance with the DURC policies are

[6] IRE members are drawn from a variety of positions within an institution and the community and typically have other professional responsibilities in addition to their work on the IRE, for example, other biosafety and biosecurity activities, training, and/or research.

unavailable. This diversion of funds may challenge the institution's ability to meet its research mission.

For researchers conducting dual use research, delays arising from the DURC review process may stall the career advancement of researchers at all levels. Even though delays of weeks-to-months may be considered short given the long timescales of research, these delays can have significant consequences for individual researchers, laboratories, or institutions if the delays occur around deadlines for academic training, hiring, tenure decisions, and grant award. Research delays that cause researches to miss important career milestones may cause some researchers to leave the field – some voluntarily, out of frustration, and some involuntarily, because of an inability to secure funding or progress their career.

Researcher Frustration: Opportunity Costs

Some researchers were frustrated by the need to dedicate time and effort to "yet another review" because they felt their research already was subject to a more rigorous level of review than that of their peers who study non-listed agents. Research subject to DURC review is reviewed by the IBC (i.e., to assess biosafety and other biosecurity considerations), the Institutional Animal Care and Use Committee (IACUC), and/or the Environmental Health and Safety (EH&S) Department, depending on the nature of the research.

Another source of researcher frustration is a perception that DURC is stigmatized by some members of the public, research, and policy communities as having outsize risks without significant benefit, suggesting that the researchers, institutions, and funding agencies involved in the research are irresponsible.(83, 102-106) EH&S personnel leading their institutions' DURC programs shared examples of researchers who were offended that their research was considered potential DURC or frustrated by the need to "defend" the value of their research to the IRE (despite assurances that the process would not be antagonistic). A few of these researchers chose to not conduct experiments with listed agents to avoid the DURC review.

Researcher frustration arising from the perceived redundancy in institutional review processes for life sciences research and the stigma associated with DURC caused some researchers to redirect their research to non-listed agents. This effect was most pronounced for researchers working with small quantities of BoNT, which are exempt from the SAR. For example, at two academic institutions, 5-of-10 and 9-of-10 investigators working with exempt quantities of BoNT withdrew from the institutions' exempt toxins programs because of the DURC policies.[7] These investigators, who were using BoNT as a research tool, either sought out other biological reagents that could serve a similar experimental purpose or adjusted their research if suitable alternatives were unavailable. EH&S personnel from these institutions speculated that so many researchers withdrew from their exempt toxins programs because this group of

[7] These programs were established voluntarily by institutions to track research involving exempt quantities of select agent toxins at their institutions.

researchers was less accustomed to biosecurity regulations than select agent researchers.

Take-aways

The key findings from this care study are:

- The ability of institutions to leverage existing research review practices reduced the time burden of developing formal DURC review processes to comply with the 2014 Institutional Oversight Policy.
- Several IREs review all research proposals involving *potential* DURC, a fraction of which are deemed to constitute DURC as defined in the 2012 and 2014 federal DURC policies.
- Time spent on DURC reviews and delays arising from the scheduling of research review meetings at the institutional and federal levels contributed to the time burden of compliance with the 2014 Institutional Oversight Policy. This time burden caused some researchers to re-direct their research to non-regulated activities.
- Researcher frustration arising from perceived inefficiencies because of redundancy in research reviews and/or stigma associated with DURC contributed to some researchers' decisions to re-direct their research to non-regulated activities.

Appendix 5: Opportunity Cost Use Case

		Department of Health and Human Services Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens
Policy Scope (included to provide familiarity to policy)		• Initial identification of research involving enhanced PPPs carried out at funding agency (e.g., CDC, NIH, FDA, ASPR) • Research that meets the following criteria are referred to HHS departmental-level review • Research that is subject to review: o Is scientifically meritorious as scored in the proposal review system o Involves creating, transferring, or using pathogens "judged to be a credible source of that a potential future human pandemic" o Is assessed to have greater potential risks are justified given the potential benefits to society o Has no feasible alternative approaches to reduce the risk o Is conducted in an institution that has safe and secure facilities and practices, and can manage and mitigate potential risks quickly o Can be communicated responsibly and in compliance with existing laws, funding requirements, and policies o Is ethically justifiable • Potential Pandemic Pathogens (PPP) are highly transmissible and capable of uncontrolled spread in people, and highly virulent and likely to cause significant illness and/or death in people o An Enhanced PPP is a "PPP resulting from the enhancement of the transmissibility and/or virulence of a pathogen." o Pathogens collected through surveillance activities or through the development and production of vaccines are not considered enhanced PPPs o PPP includes pathogens previously considered to have pandemic potential (i.e., SARS Co-V, MERS-CoV, and H5N1) • Policy applies only to research funded by HHS, not other U.S. government agencies or private funders (e.g., companies, venture capital, institutions, crowdsourcing, philanthropic organization, other)
Policy	**Implementation Activities**	• Overarching goal: "preserve the benefits of life sciences research involving enhanced PPPs while minimizing potential biosafety and biosecurity risks" • Affected stakeholders and responsibilities: o Funding agency: ▪ Identifies and refers for department-level review scientifically-meritorious research that they anticipate creates, transfers, or uses an enhanced PPP

		▪ Participates in departmental-level review of research ▪ Makes funding decision based on the recommendations of the departmental-level review and with stipulations or conditions for reducing risk, as appropriate ▪ Report funding decisions to HHS and OSTP ▪ Ensure compliance with risk mitigation procedures and terms and conditions of funding o HHS: ▪ Convene multi-disciplinary group for departmental-level review ▪ Evaluate risks and benefits and propose a risk mitigation plan ▪ Provide recommendations for "acceptability" of HHS funding, including specific terms and conditions of the award and risk mitigation measures suggested o Researchers/research institutions: ▪ Conduct HHS-funded research in under specified award conditions, including recommended risk mitigation plan • Re-evaluation of risks and risk mitigation strategies after research is initiated (unspecified stakeholder)
Direct Costs	**Financial Cost**	• Research institution: infrastructure and other biosecurity-related costs associated with conducting funded research according to the risk mitigation plan
	Time Cost	• Funding agency: o Personnel time to develop a process for identifying, managing, and documenting research involving enhanced PPPs, and to develop training materials for program managers about each of these activities o Personnel time required for training on assessment and comparison of potential risks and benefits o Personnel time involved in training program managers about biosafety and biosecurity practices. o Personnel time for participation in departmental review of research and oversight of funded research. o Personnel time involved in training scientific reviewers about PPP • HHS: o Personnel time required to develop a process for evaluating and comparing the potential risks and potential benefits of referred research. o Personnel time required for training on assessment and comparison of potential risks and benefits o Personnel time in training program managers about biosafety and biosecurity practices. o Personnel time for participation in departmental review of research. • Research institutions: o Personnel time in reviewing and complying with award conditions and risk mitigation plan of funded PPP research • Personnel time for trainers.

Indirect Costs	**Research and Health Costs**	• Potential delays in research arising from time needed for departmental research review process (may depend on whether the research has been initiated) • Potential stoppage of research if the research is not funded and alternative funding sources are not obtained • Potential redirection of research.
	Workforce Costs	• No significant costs anticipated
	Individual or Institutional Capability Costs	• Significant delays in research may stall the career advancement of researchers, depending on the timing and length of the delay. This effect may cause some researchers to leave the field.
Downstream Consequences	**Adversely Affected or Lost Capabilities**	• If research is stopped and/or researchers leave the field, basic research informing medical countermeasure development (e.g., antigen characterization studies), surveillance indicators, and laboratory-based risk/threat assessment

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