NTI Paper

NOVEMBER 2021

Strengthening Global Systems to Prevent and Respond to High-Consequence Biological Threats

Results from the 2021 Tabletop Exercise Conducted in Partnership with the Munich Security Conference

SUMMARY

In March 2021, NTI partnered with the Munich Security Conference to conduct a tabletop exercise on reducing high-consequence biological threats. The exercise examined gaps in national and international biosecurity and pandemic preparedness architectures—exploring opportunities to improve prevention and response capabilities for high-consequence biological events. This report summarizes the exercise scenario, key findings from the discussion, and actionable recommendations for the international community.

Jaime M. Yassif, Ph.D.
Kevin P. O'Prey, Ph.D.
Christopher R. Isaac, M.Sc.

NTI:bio

We are grateful to Open Philanthropy. The exercise and report would not have been possible without their generous support.

Copyright © 2021 Nuclear Threat Initiative

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

The views expressed in this publication do not necessarily reflect those of the NTI Board of Directors or the institutions with which they are associated.

Contents

Acknowledgments 3
Foreword 4
Executive Summary 6
About the Exercise 8
Summary of Exercise Discussion and Findings 14
Recommendations 22
Appendix A. Expert Contributors to Scenario Development 27
Appendix B. Epidemiological Model Summary 28
About the Authors 32

Acknowledgments

The authors gratefully acknowledge the support of those who were instrumental in the development and execution of this senior-level tabletop exercise. First, we would like to thank our partners at the Munich Security Conference, who jointly hosted this exercise with NTI. We are also grateful to the exercise participants whose valuable insights, expertise, and engagement were crucial to the success of this project. We also thank Talus Analytics for developing the epidemiological model underpinning this exercise, our expert advisors who informed the design of the exercise scenario early in the process, and Long Story Short for producing the exercise videos.

At the Nuclear Threat Initiative (NTI), we would like to thank members of the project team, who were instrumental to the success of this project. Dr. Andrew Hebbeler, who is now serving in government at the White House Office of Science and Technology Policy, jointly led the development and planning of this exercise with Dr. Jaime M. Yassif. Dr. Kevin P. O'Prey facilitated the scenario-based exercise, in addition to advising on exercise planning and jointly authoring this report. Christopher R. Isaac provided valuable research assistance for this project, and Amanda Cogan was instrumental in organizing the exercise event. From NTI's Communications team, Rachel Staley Grant led the development of video production for this exercise, and along with Mimi Hall, provided valuable comments on this manuscript and led the report publication process.

We are grateful to Open Philanthropy for their support for this project as part of their ongoing support of our work to reduce Global Catastrophic Biological Risks.

Jaime M. Yassif, Ph.D.
Senior Fellow, Global Biological Policy and Programs, NTI

Kevin P. O'Prey, Ph.D.
Managing Partner, The Palisades Group, LLC

Christopher R. Isaac, M.Sc.
Program Assistant, Global Biological Policy and Programs, NTI

Foreword

Over the past two years, the world has faced the devastating impact that a biological event can have on human health, economies, and political stability. As of this writing, the SARS-CoV-2 virus has infected more than 250 million people, killed more than five million, and caused trillions of dollars in economic losses. COVID-19 has revealed that national governments and the international community are woefully unprepared to respond to pandemics—underscoring our shared vulnerability to future catastrophic biological threats that could meet or exceed the severe consequences of the current pandemic.

Although national and global leaders are appropriately focused on the immediate demands of the COVID-19 response, the international community cannot postpone implementing the steps necessary to protect against future biological threats. This must include the recognition that while naturally emerging pandemics continue to pose a significant threat, the next global catastrophe could be caused by the deliberate misuse of the tools of modern biology or by a laboratory accident. Fundamentally, strengthening the preparedness of every nation to meet these challenges is a humanitarian imperative in the collective self-interest of the international community. Even the most prepared nations will remain vulnerable as long as significant biosecurity and pandemic preparedness gaps remain in countries around the world. We are only as safe as our weakest link.

Scientific and political leaders must take bold action to safeguard the global bioscience and biotechnology research and development enterprise to ensure that catastrophic accidents or deliberate misuse do not lead to the next global pandemic.

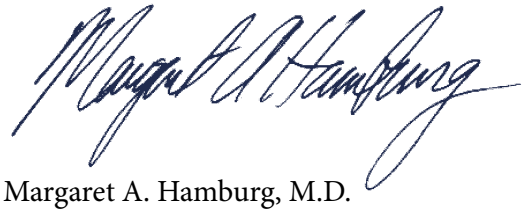
The world has witnessed how global travel, trade, urbanization, and environmental degradation can fuel the emergence and spread of infectious disease threats. However, the serious risks embedded in the very bioscience research and technology advances that offer vital opportunities to counter these risks remain less understood. Bioscience and biotechnology advances, while offering tremendous potential benefits, also present opportunities for accidental release or deliberate abuse of biological agents that could cause as much or more harm than COVID-19. Scientific and political leaders must take bold action to safeguard the global bioscience and biotechnology research and development enterprise to ensure that catastrophic accidents or deliberate misuse do not lead to the next global pandemic.

To strengthen international capabilities to respond to the next pandemic, national and global leaders must build stronger public health and medical response capabilities that can scale to address very high-consequence biological events—potentially orders of magnitude more severe than what we have experienced during the past two years. We cannot afford to be reactive. We must build our public health and medical systems to be anticipatory, responding energetically and proactively in the face of uncertainty—taking what humanitarian and crisis response communities describe as a "no regrets" approach.

NTI recognizes the critical importance of strengthening the global biosecurity and pandemic preparedness architecture. To that end, NTI is focused on catalyzing the development of stronger international biosecurity and pandemic preparedness capabilities so the world is better able to prevent and respond to future biological risks. To address important gaps in key areas, NTI is working with international partners:

- To establish a new global biosecurity entity dedicated to reducing emerging biological risks that can accompany certain technology advances. Its mission will be to reduce the risks of catastrophic consequences due to accidents, inadvertent misuse, or deliberate abuse of bioscience and biotechnology by promoting stronger global biosecurity norms and developing tools and incentives to uphold them.
- To explore the possibility of establishing a new Joint Assessment Mechanism to investigate high-consequence biological events of unknown origin. This new mechanism would operate at the "seam" between existing mechanisms—including World Health Organization (WHO) outbreak investigation capabilities and the United Nations Secretary-General's Mechanism for investigating alleged deliberate bioweapons use—thereby strengthening UN system capabilities to investigate pandemic origins.
- To advocate for establishing a catalytic, multilateral financing mechanism for global health security and pandemic preparedness. The goal is to accelerate sustainable biosecurity and pandemic preparedness capacity-building in countries where resources are most needed.

To further examine these issues, NTI has partnered with the Munich Security Conference (MSC) over the past three years to host annual tabletop exercises focused on reducing high-consequence biological threats. NTI and MSC have jointly convened international leaders and experts to explore gaps in the global biosecurity and pandemic preparedness architecture, and to identify opportunities to address urgent needs. This report shares the lessons of our 2021 exercise.



Margaret A. Hamburg, M.D.
Interim Vice President, Global Biological Policy and Programs
Nuclear Threat Initiative

Executive Summary

In March 2021, the Nuclear Threat Initiative (NTI) partnered with the Munich Security Conference (MSC) to conduct a tabletop exercise on reducing high-consequence biological threats. Conducted virtually, the exercise examined gaps in national and international biosecurity and pandemic preparedness architectures and explored opportunities to improve capabilities to prevent and respond to high-consequence biological events. Participants included 19 senior leaders and experts from across Africa, the Americas, Asia, and Europe with decades of combined experience in public health, biotechnology industry, international security, and philanthropy.

The exercise scenario portrayed a deadly, global pandemic involving an unusual strain of monkeypox virus that emerged in the fictional nation of Brinia and spread globally over 18 months. Ultimately, the exercise scenario revealed that the initial outbreak was caused by a terrorist attack using a pathogen engineered in a laboratory with inadequate biosafety and biosecurity provisions and weak oversight. By the end of the exercise, the fictional pandemic resulted in more than three billion cases and 270 million fatalities worldwide.

Discussion among exercise participants led to the following key findings:

- **Weak global detection, assessment, and warning of pandemic risks.** The international community needs a more robust, transparent detection, evaluation, and early warning system that can rapidly communicate actionable information about pandemic risks.
- **Gaps in national-level preparedness.** National governments should improve preparedness by developing national-level pandemic response plans built upon a coherent system of "triggers" that prompt anticipatory action, despite uncertainty and near-term costs—in other words, on a "no-regrets" basis.
- **Gaps in biological research governance.** The international system for governing dual-use biological research is neither prepared to meet today's security requirements, nor is it ready for significantly expanded challenges in the future. There are risk reduction needs throughout the bioscience research and development life cycle.
- **Insufficient financing of international preparedness for pandemics.** Many countries around the world lack financing to make essential national investments in pandemic preparedness.

To address these findings, the authors developed the following recommendations.

1 Bolster international systems for pandemic risk assessment, warning, and investigating outbreak origins

- The WHO should establish a graded, transparent, international public health alert system.
- The United Nations (UN) system should establish a new mechanism for investigating high-consequence biological events of unknown origin, which we refer to as a "Joint Assessment Mechanism." (More about the Joint Assessment Mechanism is found on page 22.)

2 Develop and institute national-level triggers for early, proactive pandemic response

- National governments must adopt a "no-regrets" approach to pandemic response, taking anticipatory action—as opposed to reacting to mounting case counts and fatalities, which are lagging indicators.
- To facilitate anticipatory action on a no-regrets basis, national governments should develop national-level plans that define and incorporate "triggers" for responding to high-consequence biological events. (More about "triggers" is found on page 17.)

3 Establish an international entity dedicated to reducing emerging biological risks associated with rapid technology advances

- The international community should establish an entity dedicated to reducing the risk of catastrophic events due to accidents or deliberate abuse of bioscience and biotechnology.
- To meaningfully reduce risk, the entity should support interventions throughout the bioscience and biotechnology research and development life cycle—from funding, through execution, and on to publication or commercialization.

4 Develop a catalytic global health security fund to accelerate pandemic preparedness capacity building in countries around the world

- National leaders, development banks, philanthropic donors, and the private sector should establish and resource a new financing mechanism to bolster global health security and pandemic preparedness.
- The design and operations of the fund should be catalytic—incentivizing national governments to invest in their own preparedness over the long term.

5 Establish a robust international process to tackle the challenge of supply chain resilience

- The UN Secretary-General should convene a high-level panel to develop recommendations for critical measures to bolster global supply chain resilience for medical and public health supplies.

This report is organized into three parts: the first is a description of the exercise design and scenario; the second is a summary of the exercise discussions and related findings; and the third is a set of recommendations developed by the authors to address the identified gaps and requirements. NTI developed these recommendations after the event concluded; participants were not involved in their development and have not been asked to endorse them. The appendices provide a list of the experts who supported the exercise development process (Appendix A) as well as technical details about the epidemiological model (Appendix B) used to inform this fictional monkeypox pandemic scenario.

About the Exercise

In March 2021, NTI conducted a Tabletop Exercise on Reducing High-Consequence Biological Threats, the third in a series of annual collaborations between NTI and the Munich Security Conference. The exercise examined gaps in national and international biosecurity and pandemic preparedness architectures and explored opportunities to improve capabilities to prevent and respond to high-consequence biological events. The exercise included 19 senior leaders and experts from across Africa, the Americas, Asia, and Europe with decades of combined experience in public health, biotechnology industry, international security, and philanthropy. (See the box on page 9 for the list of exercise participants.)

Exercise Scenario

Developed in consultation with technical and policy experts, the exercise scenario portrayed a deadly, global pandemic involving an unusual strain of monkeypox virus that first emerges in the fictional country of Brinia and eventually spreads globally. Later in the exercise, the scenario reveals that the initial outbreak was caused by a terrorist attack using a pathogen engineered in a laboratory with inadequate biosafety and biosecurity provisions and weak oversight. The exercise scenario concludes with more than three billion cases and 270 million fatalities globally. As part of the scenario development process, NTI conducted a virtual consultation with experts in December 2020. (See Appendix A for the list of participating experts.)

The fictional exercise scenario unfolded in a series of short news videos that participants reacted to.

The exercise was designed for participants to:

- Discuss requirements for international architectures related to science-based, early assessment of emerging pandemic risks and timely international warning and alerts for potential pandemics.
- Explore conditions that should trigger national pandemic response actions and discuss strategies and challenges for scaling public health interventions.
- Consider options to reduce biotechnology risks and strengthen oversight of dual-use bioscience research.
- Explore opportunities to strengthen international financing mechanisms to bolster global health security preparedness.

2021 NTI-MUNICH SECURITY CONFERENCE TABLETOP EXERCISE PARTICIPANTS

EXERCISE CO-CHAIRS

Dr. Ernest J. Moniz
Co-Chair and CEO
Nuclear Threat Initiative
Former U.S. Secretary of Energy

Ambassador Wolfgang Ischinger
Chairman
Munich Security Conference

PARTICIPANTS

Mr. Arnaud Bernaert
Head, Health Security Solutions
SICPA

Dr. Beth Cameron
Senior Director, Office of Global Health Security and Biodefense
U.S. National Security Council

Mr. Luc Debruyne
Strategic Advisor to the CEO
Coalition for Epidemic Preparedness

Dr. Ruxandra Draghia-Akli
Global Head
Johnson & Johnson Global Public Health R&D
Janssen Research & Development

Dr. Chris Elias
President, Global Development Division
Bill & Melinda Gates Foundation

Sir Jeremy Farrar
Director
Wellcome Trust

Dr. George Gao
Director-General, Chinese Center for Disease Control and Prevention (China CDC)
Vice President, the National Natural Science Foundation of China (NSFC)
Director and Professor, CAS Key Laboratory of Pathogenic Microbiology and Immunology, Institute of Microbiology, Chinese Academy of Sciences
Dean, Medical School, University of Chinese Academy of Sciences

Dr. Margaret (Peggy) A. Hamburg
Interim Vice President
Global Biological Policy and Programs, Nuclear Threat Initiative
Former Commissioner of the U.S. Food and Drug Administration

Ms. Angela Kane
Visiting Professor
Paris School of International Affairs (SciencesPo), and Tsinghua University

Dr. Emily Leproust
CEO and Co-Founder
Twist Biosciences

Dr. Elisabeth Leiss
Deputy Director of the Governance and Conflict Division
German Corporation for International Cooperation (GIZ)

Ms. Izumi Nakamitsu
Under-Secretary-General and High Representative for Disarmament Affairs
United Nations Office for Disarmament Affairs

Dr. John Nkengasong
Director
Africa Centres for Disease Control and Prevention

Sam Nunn
Founder and Co-Chair
Nuclear Threat Initiative
Former U.S. Senator

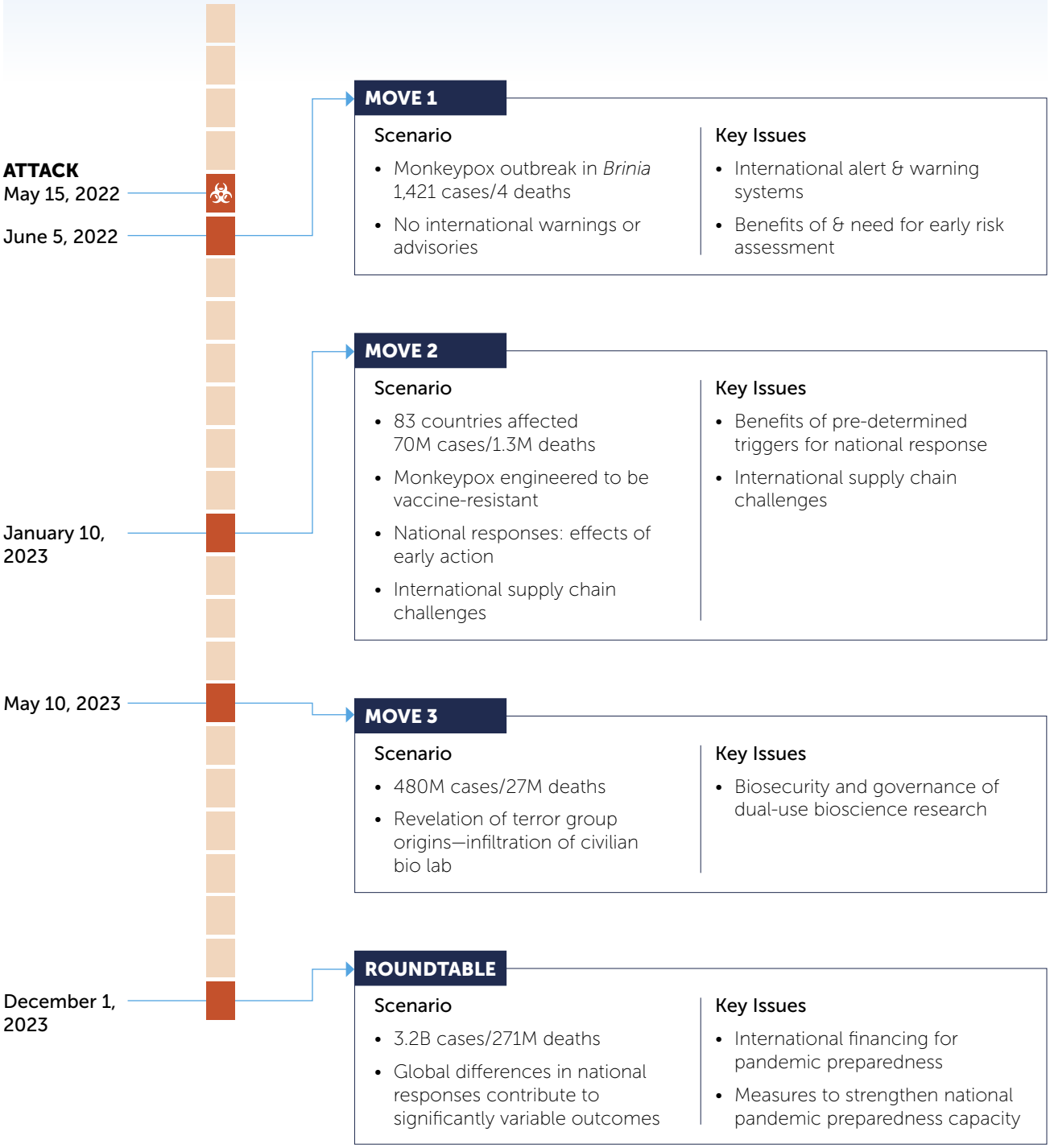
Dr. Michael Ryan
Executive Director
WHO Health Emergencies Programme

Dr. Joy St. John
Executive Director
CARPHA

Dr. Petra Wicklandt
Head of Corporate Affairs
Merck KGaA

The discussion was organized into three sequential "moves" corresponding with scenario developments, followed by a roundtable discussion of broader biosecurity and pandemic preparedness issues. The step-by-step approach to revealing scenario developments reflected the limitations of information available to real-world decision makers, as well as the resulting uncertainty associated with a pandemic of unknown origin (see Figure 1).

Figure 1. Scenario Design Summary



Move 1 (occurring on June 5, 2022, in scenario time) starts with an unusual outbreak of monkeypox in Brinia (population 250 million), with reports of 1,421 cases and four fatalities. There is no immediate evidence of international spread, but the outbreak takes place during a national holiday with extensive domestic and international travel by Brinians. Because monkeypox is not naturally found in Brinia, local and international experts consider this outbreak to be unusual. The Brinian government welcomes international outbreak investigations and requests medical support from the WHO. Genome sequencing of monkeypox patient samples reveals that the strain in Brinia contains mutations that make it resistant to existing vaccines.

The discussion that followed considered how the international system is postured to analyze initial indicators of pandemic risk and to communicate appropriate warnings.

Move 2 (January 10, 2023) occurs six months later, at which point the virus has spread to 83 countries with 70 million reported cases, causing more than 1.3 million fatalities. With no known effective therapies or vaccines, countries have had to rely principally on non-pharmaceutical interventions (NPIs) to mitigate the impacts of the pandemic. Highlighting significantly different national outcomes in managing the pandemic, some governments, including the fictional Republic of Dranma, promptly adopted aggressive measures to slow virus transmission by shutting down mass gatherings, imposing social-distancing measures, and implementing mask mandates. These countries have also established large-scale testing and contact-tracing operations and scaled-up their health care systems to support anticipated growing case numbers. By contrast, the scenario depicts another group of countries, including fictional Cardus, that have prioritized keeping their economies open, undertaking little-to-no NPIs, and downplaying the virus and its potential impacts. These countries have experienced much worse outcomes in terms of illness and mortality (Figure 2) than those that responded early and energetically. As Figure 3 shows, Dranma experienced far fewer cases and fatalities than Cardus.

Participant discussion in Move 2 focused on exploring the conditions that should trigger national pandemic response actions and discussing strategies and challenges for scaling public health interventions.

Figure 2. Cardus vs. Dranma: Cumulative Deaths

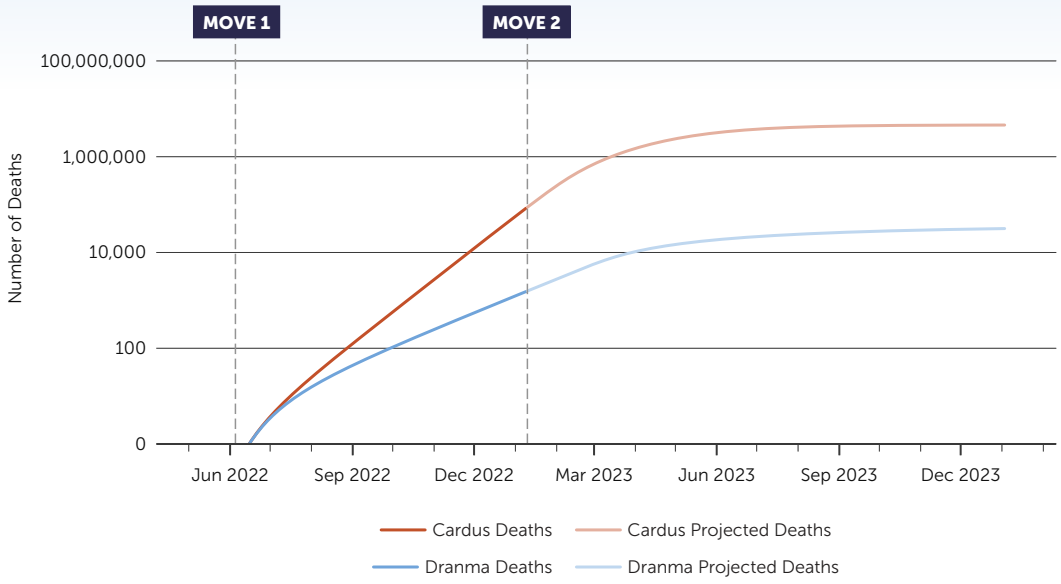
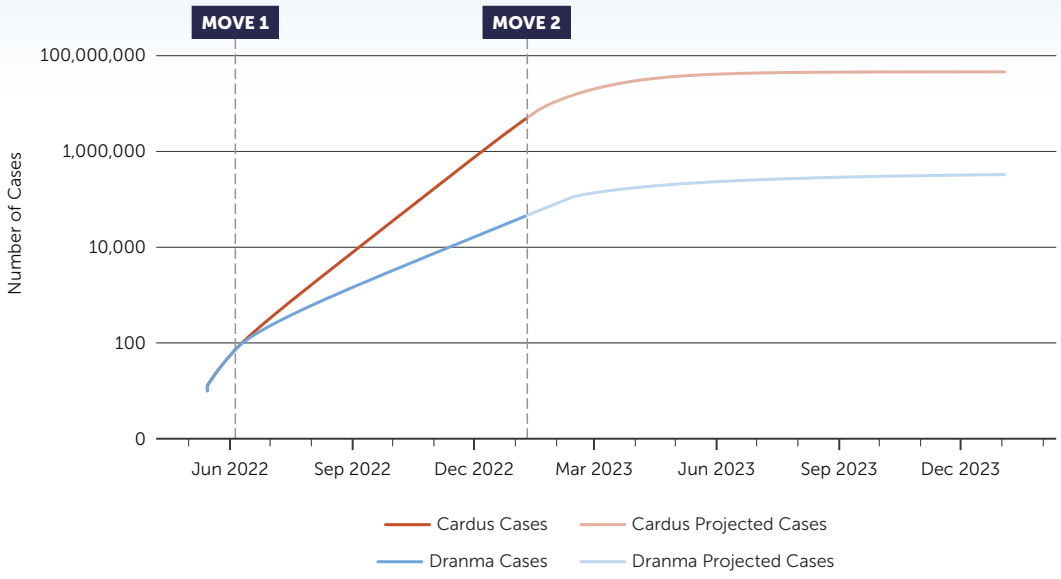
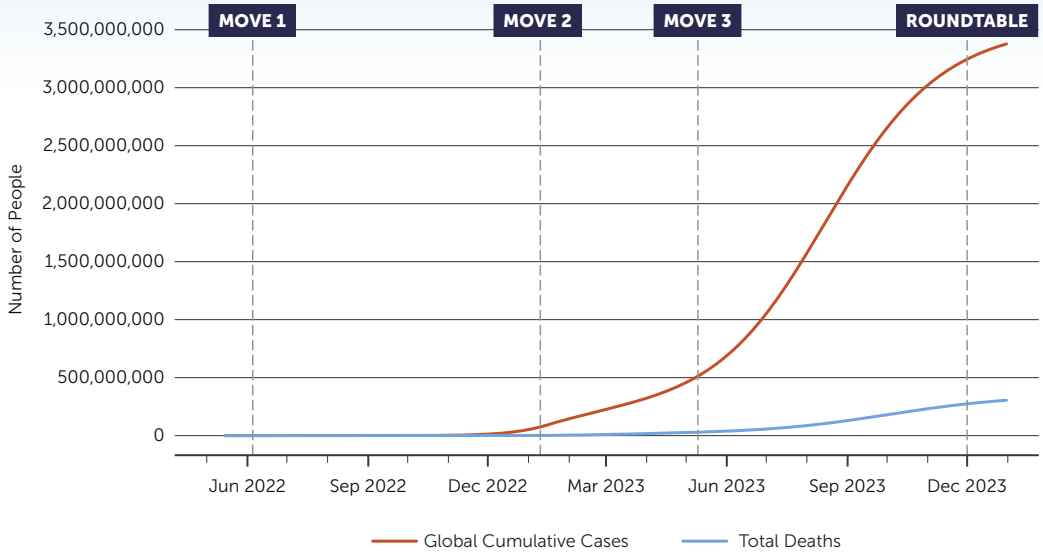


Figure 3. Cardus vs. Dranma: Cumulative Cases



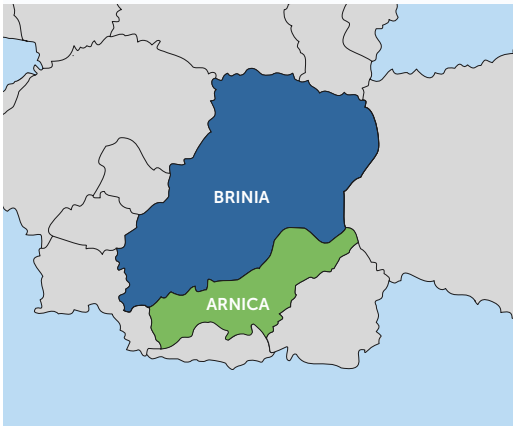
Move 3 (May 10, 2023) occurred 12 months after the initial outbreak, with more than 480 million cases and 27 million fatalities globally (Figure 4). At this stage, participants learn that the pandemic was caused by a regional bio-terror attack that far exceeded the perpetrators' goals.

Figure 4. Global Cumulative Cases and Deaths



Specifically, Brinian intelligence reveals that the engineered monkeypox virus was developed illicitly at the fictional country of Arnica's leading institute for virology. Arnica (population 75 million) has a history of conflict with neighboring Brinia (see map in Figure 5). An independent Arnican terrorist group—the SPA—had worked with sympathetic laboratory scientists to engineer a highly contagious, deadly pathogen and disperse it at crowded train stations in Brinia during the national holiday, when much of the population was travelling domestically and internationally.

Figure 5. Map of the Fictional Country of Brinia, the Geographic Origin of the Outbreak



The SPA had exploited the Arnican government's weak oversight of its bioscience research laboratories. SPA sympathizers working in Arnica's leading virology institute used publicly available scientific publications to guide their work to modify the monkeypox virus to make it more transmissible and resistant to currently available vaccines.

The discussion in Move 3 focused on governance of dual-use bioscience research as well as current weaknesses in biosafety and biosecurity systems that exacerbate biological risks.

The final phase of the exercise was a **roundtable discussion** that considered disparities in public health preparedness around the globe and the resulting need for more effective financing mechanisms to accelerate pandemic preparedness capacity building. Recognizing that pandemic preparedness requires costly investments that lower- and lower-middle income countries cannot afford to make, participants were asked to discuss strategies to catalyze these investments in sustainable ways.

Summary of Exercise Discussion and Findings

The discussions throughout the tabletop exercise generated a wide range of valuable insights and key findings. Most significantly, exercise participants agreed that, notwithstanding improvements following the global response to COVID-19, the international system of pandemic detection, analysis, warning, and response is woefully inadequate to address current and anticipated future challenges.

Exercise participants agreed that gaps in the international biosecurity and pandemic preparedness architecture are extensive and fundamental, undermining the ability of the international community to mount effective responses to future biological events—and they noted that robust preparedness will require fundamental transformation across a number of fronts. Given the inherent latency in acquisition of definitive data on pandemic threats—e.g., geographic distribution, transmission rates, and lethality—and the very serious consequences of delay in pandemic response, participants observed that the international system and national governments must be transformed to emphasize pre-determined "no-regrets" anticipatory actions. Such a system requires significant improvements in the international community's ability to detect, assess, and warn about pandemic threats as well as to develop proactive, national-level response plans and decision-making bodies. They agreed that the international community also must bolster its system of governance for dual-use life-science research, and they concluded that governments globally are severely underinvesting in pandemic preparedness—especially in low- and lower-middle income countries. These consensus findings frame the more detailed conclusions discussed below.

FINDING 1

The international community needs a more robust, transparent detection, evaluation, and early warning system that can rapidly communicate actionable warnings about pandemic risks.

Exercise participants found that the world continues to lack a coherent system for pandemic detection and assessment that would be effective across the full range of plausible scenarios. In this exercise, the scenario arguably depicted a "best case" where the country of origin reported what it knew to the WHO in a timely manner and welcomed international investigation. Yet even in this case, exercise participants expressed concern that it would be extremely challenging to discern warning signals early enough to contain or at least mitigate the effects of the initial outbreak.

Consequently, several participants stressed that the international community requires a more coordinated international biosurveillance network, which also incorporates pathogen genome sequencing. In scrutinizing disease outbreaks for pandemic potential, exercise participants identified a number of key indicators for an effective risk assessment system based on biosurveillance data.

Participants stressed that the most important indicators for analyzing the pandemic potential of an outbreak are its epidemiology and the geographic distribution of cases. A novel virus that is assessed to be

highly virulent and transmissible—either based on direct epidemiological observations or other evidence-based predictions—will warrant significant attention. Analyzing additional virus characteristics will also be important. For example, is the virus changing and/or is it different from previously detected variants? One participant observed that the number of fatalities would not be a good measure to track in the early period of a pandemic because it is a lagging indicator at a time of exponential growth in cases.

Participants also suggested that considering the social, political, and economic context of the country of origin or initial detection could be valuable for risk assessment. Key factors include the degree of societal openness of the country and the extent of international travel across its borders—both features that could contribute to faster spread. Another consideration is the strength of the country's public health system and whether the population is reducing the risk of spread by using NPIs and avoiding mass gatherings.

"We face the simultaneous challenge of responding to this pandemic and preparing for the next one. The international community has an opportunity, if not an obligation, to improve the situation."

—Exercise Participant

In the sequence of events after detection and analysis, the next step is warning. All participants agreed that the principal means of international pandemic risk warning now in place—the WHO Director General's declaration of a Public Health Emergency of International Concern (PHEIC)—requires significant reform. Among the shortfalls they identified in the current PHEIC approach is that it is a binary tool for a world where pandemic risks are characterized by different levels of risk that evolve over time. The current PHEIC approach potentially lumps risks like a limited regional Ebola outbreak with a globally catastrophic biological event. Both are concerning, but to very different degrees, and they warrant different responses. The binary nature of the PHEIC also unintentionally creates incentives to delay warnings. In effect, if analysts and decision makers only have two choices, they are likely to err on the side of certainty before activating an international alert system.

Participants stressed that a graded pandemic warning system—analogous to graded systems used for hurricanes and other natural disasters—would arguably provide a more flexible, informative, and actionable system for communicating risk. Under the current International Health Regulations (IHR 2005), the WHO could be empowered to provide more detailed risk assessments to member states. One participant noted that formally shifting the WHO PHEIC to a graded system might require a change to the IHR, which could pose significant political challenges.

Exercise participants observed that regardless of the particular institutional arrangements chosen for international systems of pandemic detection, analysis, and warning, these systems must be transparent. In particular, deliberations that currently occur behind closed doors—the WHO Emergency Committee, for example—would benefit if, at a minimum, an outside expert group could analyze the data and reach conclusions in parallel. Arguably, this would help validate and lend independent weight to official findings, or could challenge findings if they are inconsistent with available evidence.[1]

[1] For an excellent discussion of reported politicization of PHEIC deliberations and decisions, see Clare Wenham, Alexandra Phelan, Mark Eccleston-Turner, and Sam Halabi, "Reforming the Declaration Power for Global Health Emergencies," International Law Impact and Infectious Disease (ILIAID) Consortium IHR Reform White Paper Series (1), (November 2020): 8.

Evaluating Outbreak Origins

Participants noted that biological incidents of unknown original fall into a gap in the UN system. The WHO, as one participant highlighted, is the outbreak equivalent of a firefighter, not a police officer; the organization is best suited to public health and medical response, not security investigations. In cases where an outbreak is deliberately caused, a security investigation by the UN Secretary-General's Mechanism (UNSGM) would be appropriate. However, the means by which the WHO and the UN Secretary-General operate in parallel, if not in coordination, are still unclear. More problematic still are those cases where the origin of an incident is unclear or suspicious. In these cases, the respective roles of the UN Secretary-General and WHO must be clearly defined.[2]

Participants discussed additional international political challenges that could pose obstacles to effective investigation of an outbreak. First, the international community requires cooperation and transparency from the putative country of origin. Second, although the Secretary-General has the authority to use its investigative mechanism in response to a request from any member state, the mechanism has never been used to investigate a biological incident, and tensions among UN member states could cause delays. Similarly, objections by any of the WHO principal member state donors could hamper the organization's effectiveness in coordinating prompt detection and assessment.

FINDING 2

Governments should improve preparedness by developing national-level pandemic response plans built upon a coherent system of "triggers" that prompt anticipatory action on a "no-regrets" basis.

"It will be chaotic and frightening, but you can't wait until you have certainty. You have to act with no regrets."

—Exercise Participant

Tabletop exercise participants agreed that the exercise scenario and the larger lessons from the global COVID-19 response highlight the need to establish national response plans with a series of planning "triggers," or threshold conditions, that ensure anticipatory steps early in a potential pandemic. Both the exercise scenario and the COVID-19 response demonstrate that early actions by national governments have significant, positive impacts in managing the impact of the disease. Because the nature of exponential disease transmission severely punishes even modest delays, slow responses by national governments lead to higher caseloads, worse mortality rates, and potentially even the collapse of the public health and medical system.

The Benefits of Early Action

One participant observed that the exercise outcomes were consistent with national performance during the COVID-19 response; governments that

[2] The UN Secretary-General's Mechanism and the need for a Joint Assessment Mechanism were key discussion points in the 2019 and 2020 NTI-MSC tabletop exercises. Reports from these exercises are available at nti.org.

responded early and energetically to pandemic warnings were much more successful in protecting their populations. As is widely recognized, a number of wealthier countries with strong public health systems were not proactive and timely in their responses and therefore experienced significantly worse outcomes than those nations that are less wealthy but responded more proactively.

What Is a Trigger?

In national pandemic response plans, specific readiness measures would be "triggered" based on factors related to the potential severity of the outbreak, expected delays in situational awareness, and the time it would take to implement response measures and see results.

Participants stressed that national-level decision makers must build trigger-based plans that emphasize a "no-regrets" bias toward early action. Although there is inevitably a risk of false-alarm responses, participants deemed the risk of delay as far more consequential. Action, one participant argued, must be the "default pathway" because "you will not have the luxury of waiting for certainty."

Although triggered actions would vary depending upon the particular needs of the country, in most cases the goals are the same: slow the spread of disease to buy time and flatten the epidemiological curve, while using that time to scale up public health and medical systems to keep up with growing caseloads and save lives. NPIs such as mask mandates and ceasing mass gatherings were deemed to be critical for blocking chains of disease transmission. Participants generally did not endorse travel restrictions such as border closures, but travel health screening measures were viewed as valuable.

"We want to focus the triggers on a large health response so we can find the disease, understand it, slow the spread, and eventually understand what it is and how to stop it from moving."

—Exercise Participant

With the time bought by NPIs, participants argued for scaling up various capacities. The highest priority is implementing testing at scale and increasing health system capacity in terms of facilities and personnel. In addition, nations should ramp up production of the range of critical supplies that could otherwise cause bottlenecks in response operations, including masks, personal protective equipment (PPE) for health workers, testing reagents, oxygen tanks, and ventilators.

The triggers should not be limited just to actions; they should address institutional relationships as well. Indeed, a number of participants stressed that the whole-of-government decision-making process for national-level pandemic response must be planned and exercised as soon as possible, before the next pandemic. Several participants argued that most national governments have too many "silos" of decision making that must be swiftly integrated for a successful pandemic response. An effective, "no-regrets" national response will demand that the whole-of-government engage early, so internal bureaucratic hurdles do not cause critical delays.

Bolstering Pandemic Supply Chain Resilience

All participants agreed that bolstering supply-chain resilience would be critical in future pandemic responses, but they differed on how to address the challenge. In particular, a debate ensued about whether the right approach for ensuring the availability of critical items is stockpiling or maintaining "warm" production capacity,[3] or a mixture of both. For those items with long shelf lives—such as masks and other PPE—some participants argued that it is prudent for national governments and international institutions to stockpile.

Others argued that governments and/or international organizations should provide incentives to keep dual-use supply lines open or at least, "warm"—which could, for example, assist with large-scale ventilator production during an international public health emergency. An even more advanced scientific and engineering solution, where possible, would be to develop platform technologies—tools to rapidly develop diagnostics, vaccines, and other medical countermeasures for the wide range of pathogens with pandemic potential.

One participant offered a related vaccine supply recommendation that strikes a balance between national stockpiling and global coordination: selecting and empowering leading governments in each of the globe's regions. In particular, this participant argued for the creation of a global network of small-population countries that would be charged with manufacturing at scale for their respective regions.[4] Such an approach would require regional agreement and cooperative financing to build the capabilities in the selected countries.

FINDING 3

The international system for governing dual-use biological research is neither prepared to meet today's security requirements, nor is it ready for significantly expanded challenges in the future. There are risk reduction needs throughout the bioscience research and development life cycle.

Exercise participants discussed the importance of strengthening biosecurity for bioscience research and development. Emerging biological risks associated with rapid technology advances are not new, but participants recognized that the COVID-19 pandemic has exacerbated these risks. They pointed out that the international community should expect to see a rapid expansion of high-containment laboratories (biosafety level 3 and 4 labs) as a number of countries expand their bioscience research capabilities and engage in more dual-use research on SARS-CoV-2 and other pathogens with pandemic potential.

Participants agreed that, although it is essential to avoid restricting legitimate biological research, it also is critically important to incorporate stronger biosafety and biosecurity measures into bioscience research

[3] A warm production capacity would involve maintaining the production line, human expertise, and supply lines for a product even if there is no current market demand.

[4] In the case of vaccines, for example, these countries would be expected to provide for their own populations first. But because their populations are small relative to their production capacity, they would be able to turn to support the needs of their region in short order.

and development processes—from project design and funding, through research execution, and on to publication or technology commercialization.

Funders

At the beginning of the research and development life cycle, government, philanthropic, and industry funders can play a role in early review of proposed research projects, thereby creating a stronger framework for biosecurity and responsible research. Participants argued that these activities will need to encompass both public and private funders, while recognizing that incorporating the latter may be particularly challenging. During this discussion, several participants argued that the funders cannot be the only arbiter and that implementing a biosecurity review as part of the evaluation process for funding new projects will need to be part of a more comprehensive solution.

"Responsible stewardship of biotechnology and biomedical research is not going to be solved at any one institution. It will require a multifaceted approach that includes norms and standards, national regulations, and regional strategies. Companies, professional societies, funders, and publishers can all play an important role."

—Exercise Participant

Institutional Oversight

Institutional oversight—addressing both academic and industrial research institutions—is an important step in the middle of the research and development life cycle. Some participants argued that in the industry context, boards of directors should take responsibility for biosecurity much as they are increasingly addressing cybersecurity as a corporate governance issue. Participants acknowledged that biosecurity measures would likely add costs to operations—which may be considered high or even prohibitive for small biotechnology companies. However, at least one participant argued that the downside risk for a company involved in a biosecurity incident warrants this kind of executive-level attention and investment.

Some participants also argued that education can play an important role in bolstering private sector biosecurity, observing that many in the sector are ignorant of the security risks.

Providers of Goods and Services

The middle of the bioscience research and development life cycle also involves numerous private-sector entities, including providers of goods and services. For example, a number of companies provide DNA synthesis services to research laboratories. Exercise participants noted that approximately 80 percent of DNA providers are members of the International Gene Synthesis Consortium, which screens customers and DNA order sequences to prevent the building blocks of dangerous pathogens from falling into the hands of malicious actors.[5] However, screening is costly, time-consuming, and requires human expertise, so non-

[5] Formed in 2009, International Gene Synthesis Consortium (IGSC) members screen synthetic gene orders to identify regulated pathogen sequences and other potentially dangerous sequences. By screening the sequences of ordered DNA fragments and vetting customers, IGSC members help to ensure that researchers and the synthetic biology community realize the many benefits of gene synthesis technology while minimizing risk. See genesynthesisconsortium.org.

participants have an economic advantage over Consortium members. A sustainable system must include either incentives to participate or other ways to drive toward 100 percent participation.

Benchtop synthesis devices—smaller machines that individual research facilities can use to print DNA locally, as opposed to ordering from centralized DNA providers—create additional challenges. Participants observed that the entrance of benchtop DNA synthesis machines into the market poses greater risks of dangerous research with no traceability if effective biosecurity provisions are not incorporated.

International Efforts

All participants agreed that at the international level, the system for biosecurity and biosafety in bioscience research is fragmented, although they offered a range of possible remedies.

Recognizing that no comprehensive international solution exists, several participants argued for establishing a new entity that would work with a wide range of international stakeholders to develop biosecurity norms and standards and develop tools to promote compliance. It could provide both general biosecurity education as well as targeted technical assistance to companies, governments, and/or regional organizations. Several participants pointed to an example of a successful normative entity in the World Institute for Nuclear Security,[6] which performs similar functions in the nuclear security field. At least one participant stressed the importance of bolstering existing mechanisms and institutions, as opposed to creating new ones.

Participants also discussed various biosecurity approaches at national and regional levels. Short of unified international guidelines, one participant argued that opportunities exist for international approaches to encourage national-level biosecurity regulation. In particular, this participant observed that existing international agreements or frameworks—such as the Biological Weapons Convention (BWC)—might facilitate or even require member nation adoption of biosecurity legislation. Others pointed to the promise of progress at the regional level. Described by one participant as a "sea change," Africa, the Caribbean, and Europe all have developed or are developing regional biosecurity frameworks. For example, the Africa Centers for Disease Control (CDC) is developing a continent-wide biosafety and biosecurity framework. For dual-use research, Africa CDC is proposing a legal framework to establish a requirement for all institutions handling high-risk materials to conduct risk assessment and install mitigation measures and a requirement for all institutions and labs to report their cases of Dual-Use Research of Concern (DURC) to the government. The European Union has a dual-use research framework that is designed to facilitate information exchange. The Caribbean Public Health Agency has developed and implemented an ethical framework through a network of research ethics committees and is working to strengthen standards for bioscience labs.

[6] See https://wins.org/.

FINDING 4

Many countries around the world currently lack financing to make essential national investments in pandemic preparedness.

Exercise participants discussed the need for substantially increased international financing for pandemic preparedness. Although they agreed that faulty policy choices and leadership failures had contributed profoundly to poor national outcomes in the COVID-19 response, they also agreed that pre-pandemic investments in preparedness are essential. Surveying the global landscape of public health spending, one participant stressed that "we have been trying to stop a tsunami with a teaspoon." Participants noted that the challenge of financing is aggravated by significant problems of international inequity, recognizing that not all countries have the resources to make these investments. Because pandemics do not respect borders, participants agreed that a failure to bolster preparedness across all countries would inevitably pose significant risks for even the best prepared nations.[7]

"We have been trying to stop a tsunami with a teaspoon."

—Exercise Participant

Participants highlighted the need to create a sustainable financing mechanism for improving pandemic preparedness. The new mechanism should incentivize recipient governments to develop priorities and plans for domestic pandemic preparedness capacity building and to budget for these activities on an ongoing basis.

Participants argued for creating a single pot of funding with real executive authority over its disposition. At least one participant stressed that the funding should come from a larger cross-section of the global community than the limited number of countries that currently contribute. Another participant highlighted the role of the private sector as a contributor, noting that the COVID vaccine market will exceed $150 billion in 2021. A small fraction of returns reinvested by industry would make a difference.

[7] According to the UN, approximately 70 countries worldwide have been identified as "aid-dependent." Countries like Liberia, South Sudan, and Tuvalu depend upon external financing for more than 50 percent of their GDP. See "Are Developing Countries Getting the COVID-19 Funding They Need?" World Economic Forum, weforum.org.

Recommendations

NTI developed the following recommendations based on key findings from the exercise, discussed above. These recommendations were developed after the exercise and do not necessarily reflect the views of participants.

1 Bolster International Systems for Assessing Pandemic Risk, Issuing Warnings, and Investigating Outbreak Origins

The NTI-MSC tabletop exercise and other studies have made a compelling case that a radically strengthened global biosurveillance system is needed. However, data gathering and analytical elements are only part of the task of prompt and effective pandemic response; risk evaluation, warning, and assessment of pandemic origins also are critical for success.

The WHO must establish a graded, transparent, international public-health alert system.

- The WHO must upgrade the PHEIC system to provide more actionable alerts and warnings. The system should include graded or incremental thresholds with clear specification of different levels of risk supported by data, to allow for prompt decisions at the national level. Risk gradations should be built explicitly on thresholds of pandemic potential—i.e., the potential of a disease outbreak to spread globally and yield high case counts—as well as estimated severity, such as case fatality rate.
- If reforming the PHEIC system proves too difficult, given the politics of changing the IHRs, the WHO should establish a graded alert system to complement its current PHEIC tool.
- Either way, the criteria for the graded alert system should be public and fully transparent, along with any epidemiological data used to make a determination. Transparency of data and criteria will allow independent assessment and vetting by other experts and organizations.

The UN system should establish a new Joint Assessment Mechanism to investigate high-consequence biological events of unknown origin.

- The experience of SARS-CoV-2's emergence demonstrates the importance of early international investigation to aid the public health and medical response, to minimize unproductive finger-pointing, and to clearly establish an outbreak's origin so that future outbreaks might be better mitigated or even prevented.
- In addition to bolstering existing capabilities to conduct international public health investigations, a new Joint Assessment Mechanism is needed. This mechanism would use transparent, evidence-based approaches to investigate events of unknown, or even suspicious, origin. It would address gaps between existing mechanisms—specifically the WHO outbreak investigation capabilities and the United Nations Secretary-General's Mechanism—while also incorporating and building upon these existing systems.

- To ensure its legitimacy and effectiveness, UN member states should establish the authority for the new mechanism through a vote at the UN General Assembly, with support from a broad international coalition of member states.
- The mechanism should be based within the UN Secretary-General's office and under its authority.
- The Joint Assessment Mechanism must possess significant analytical and investigatory capabilities and expertise, and make use of advanced biotechnology and bioinformatics tools.

2 Develop and Institute National-Level Triggers for Early, Proactive Pandemic Response

Success in preventing or mitigating the effects of future pandemics will depend fundamentally on actions at the national level. Although international institutions can provide timely warnings, advice, and coordination, the power of national sovereignty means that the choices made by individual nations may have the most decisive impacts—both positive and negative. Moreover, the significant variability in effectiveness of national responses to COVID-19 demonstrates that public health and medical capacity alone is not a good predictor of pandemic response performance. Rather, early decisive action has been the main determinant by which countries have managed their COVID-19 outbreaks most effectively.

National governments must adopt a "no-regrets" approach to pandemic response, taking anticipatory action—as opposed to reacting to mounting case counts and fatalities, which are lagging indicators.

- Simply put, national governments and their leaders must err on the side of taking early action. Recognizing that situational awareness of pandemic threats lags behind on-the-ground reality, national leaders cannot wait for cases or fatalities to accumulate before responding. If there is a significant chance that the outbreak could turn into a pandemic, national leaders should lean forward to scale up response efforts and capabilities.

To facilitate anticipatory action on a "no regrets" basis, national governments should develop national-level plans that incorporate "triggers" for responding to high-consequence biological events.

- Triggered national-level pandemic response actions should support the strategy of flattening the epidemiological curve while rapidly scaling up health system capacity to prevent collapse in the face of growing caseloads. Triggered actions should serve three major goals: slowing pathogen transmission, saving lives, and improving situational awareness about the pathogen's spread to enable effective targeting of resources. Triggered actions should include a range of NPIs, including proactive social distancing and mask-wearing guidelines; large-scale testing and contact tracing; large-scale production of PPE and medical equipment; expansion of the pool of deployable medical personnel and space to treat patients; and comprehensive risk communication.
- National-level triggers should include adjustments to institutional relationships and decision making processes to facilitate rapid, whole-of-government response to emerging pandemic threats. Decision making bodies with whole-of-government authorities and information should be stood-up early,

and bureaucratic stovepipes that hamper information-sharing should be eliminated. Additionally, relevant waivers, emergency declarations, clarifications of authorities, and legal determinations should be identified for each phase of these triggers.

- National governments should codify triggers in plans that are routinely exercised, and the results should be systematically evaluated to identify and implement corrective actions.
- The WHO should issue guidance that encourages or requires national governments to develop national-level pandemic response triggers that are pathogen-agnostic and that scale up across multiple levels with escalating pandemic risk.

3 Establish an International Entity Dedicated to Reducing Emerging Biological Risks Associated with Rapid Technology Advances

Bioscience advances offer significant promise for the future, but they also pose risks of accidents or deliberate misuse. Despite this concern, no international entity has a specific mandate to strengthen biosecurity and bioscience governance and to reduce emerging biological risks associated with technology advances.

The international community should establish an entity dedicated to reducing the risk of catastrophic events due to accidents or deliberate abuse of bioscience and biotechnology.

- A UN agency or credible non-governmental institution should partner with experts from the scientific, philanthropic, security, and public health communities to create an international entity dedicated to identifying and reducing emerging biological risks associated with technology advances.
- The mission of this entity should be to strengthen global biosecurity norms and to develop tools and incentives to support adherence.
- The entity should be agile, innovative, and free to engage with a diverse range of stakeholders—including industry, academia, and governments—to keep up with rapid bioscience advances and quickly develop effective approaches to address emerging risks. It should work in close coordination with the Biological Weapons Convention, the WHO, and other international institutions.

To meaningfully reduce risk, the entity should support interventions throughout the bioscience and biotechnology research and development life cycle—from funding, through execution, and on to publication or commercialization. It should:

- Support comprehensive and systematic DNA synthesis screening to prevent the building-blocks of dangerous pathogens from falling into the hands of malicious actors. The new entity should support more effective and comprehensive screening internationally, while also reducing risks associated with benchtop synthesis.
- Support the development of biosecurity standards for use by bioscience funders, who are uniquely positioned to incentivize incorporation of biosecurity measures in grant or investment proposals. This could include developing more rigorous prefunding review processes to reduce the risk that

funders will support work that lacks important safeguards or is otherwise risky from a biosecurity perspective.

- Guide universities and industry in developing effective approaches to strengthen oversight of dual-use bioscience research conducted within their laboratories.
- Support effective pre-publication biosecurity review. The entity could collaborate with editors and publishers to improve biosecurity review of manuscripts and reduce the risks of public release of information hazards (i.e., information that may increase risks of intentional misuse of bioscience knowledge and biotechnology capabilities).

4 Develop a Catalytic Global Health Security Fund to Accelerate Pandemic Preparedness Capacity Building in Countries around the World

The COVID-19 pandemic has exacerbated inequalities in international pandemic preparedness.[8] Before the pandemic, experts assessed the gap in preparedness financing for low- and lower-middle income countries to be approximately US$4.5 billion per year; a gap that has only grown since that time.[9] The G20 High Level Panel concluded that governments must dedicate at least US$75 billion over the next five years to finance pandemic prevention and preparedness. A new, catalytic financing mechanism that is able to draw together resources from a wide variety of sources would transform the global system, driving resources and attention to the countries that need it most, and addressing critical gaps in the global health security architecture. [10]

National leaders, development banks, philanthropic donors and the private sector should establish and resource a new financing mechanism to bolster global health security and pandemic preparedness.

- This mechanism must mobilize at least US$10 billion annually over the next 10 years. The mechanism should be oriented toward countries with the greatest need and be based on clear metrics through rigorous assessment, such as the Joint External Evaluation and other resources like the Global Health Security Index.
- This new financing mechanism should catalyze investments across sectors, drawing in funding from governments, multilateral organizations, non-governmental organizations, private sector donors, philanthropies, and individual donors.
- The funds should be disbursed transparently, driving resources to eligible countries to accelerate progress toward specific, measurable pandemic preparedness benchmarks.

[8] See, for example, Second Report on Progress, Prepared by the Independent Panel for Pandemic Preparedness and Response for the WHO Executive Board, January 2021, pp. 5–6.

[9] *Financing Pandemic Preparedness and Response*, Background Paper 14, Independent Panel for Pandemic Preparedness and Response, May 2021, p. 16.

[10] See Pandemic Action Network Policy Brief, *A New Multilateral Financing Mechanism for Global Health Security and Pandemic Preparedness*, August 2021, https://pandemicactionnetwork.org/wp-content/uploads/2021/08/A-New-Multilateral-Financing-Mechanism-for-Global-Health-Security-and-Pandemic-Preparedness.pdf. NTI strongly supports the additional recommendations and priorities laid out in this brief, which align with and support recommendations made in this paper.

The design and operations of the fund should be catalytic, incentivizing national governments to invest in their own preparedness over the long term.

- Loans and grants through the mechanism should be managed within a country's national budget to increase accountability, incentivize domestic resource mobilization, and promote a sustainable way to shift accounting lines away from donor balance sheets to national budgets.
- To overcome the problem of dependence upon assistance, the mechanism should set various match levels by recipients, adjusted for their unique needs and means.
- The mechanism should complement existing mechanisms, such as the WHO Contingency Fund for Emergencies and other funding available through the UN and the World Bank.
- Funds disbursed should prioritize preparedness activities, strengthening countries' long-term capacity and ensuring that preparedness remains a political and budget priority.

5 Establish a Robust International Process to Tackle the Challenge of Supply Chain Resilience

As highlighted by exercise participants, the COVID pandemic has revealed significant weaknesses in global supply chains for critical medical and public health supplies. Robust systems for ensuring availability of PPE, testing supplies, and biomedical equipment are an international public good, which will be critical for responding to future pandemics. Achieving this goal will require energetic, focused planning and coordination, which must take place before the urgent need arises. To be effective, such an initiative should build upon lessons learned from the efforts of the UN COVID-19 Supply Chain Task Force and the Access to COVID-19 Tools Accelerator.

The UN Secretary-General should convene a high-level panel to develop recommendations for critical measures to bolster global supply chain resilience for medical and public health supplies, including:

- Developing more robust distributed production capabilities, which can provide needed supplies across the globe,
- Facilitating supply distribution, with a focus on transportation resources and pre-designated supplier-distributor-recipient relationships,
- Focused support on improving capabilities to deliver supplies over the "last mile" in developing countries.

Appendix A. Expert Contributors to Scenario Development

NTI convened a diverse group of experts in December 2020 to advise on the tabletop exercise scenario. These experts participated as individuals—not as representatives of their respective organizations—and they do not necessarily endorse the recommendations in this report.

Dr. Hillary Carter
Senior Advisor in the Countering Weapons of Mass Destruction Office
Department of Homeland Security

Dr. Sarah Carter
Principal
Science Policy Consulting, LLC

Dr. Bradley Dickerson
Senior Manager, Global Chemical and Biological Security
Sandia National Laboratories

Dr. Diane DiEuliis
Senior Fellow
National Defense University

Dr. James Diggans
Director, Data Science and Biosecurity
Twist Biosciences

Dr. Jessica Dymond
Assistant Program Area Manager, Health Protection and Assurance, National Health
John Hopkins Applied Physics Laboratory

Dr. Dylan George
Vice President
Ginkgo Bioworks
Former Vice President, Technical Staff
In-Q-Tel

Dr. John Glass
Professor and Leader, JCVI Synthetic Biology Group
J. Craig Venter Institute

Amanda Glassman
Executive Vice President and Senior Fellow
Center for Global Development

Dr. William Hanage
Associate Professor of Epidemiology
Harvard T.H. Chan School of Public Health

Dr. Lawrence Kerr
Director, Office of Pandemic and Emerging Threats
Department of Health and Human Services

Jeremy Konyndyk
Executive Director of the COVID-19 Task Force and Senior Advisor
United States Agency for International Development (USAID)

Amb. (ret.) Bob Mikulak
Expert Advisor on Chemical and Biological Weapons Issues
U.S. Department of State

Ryan Morhard
Director, Policy and Partnerships, Concentric
Ginkgo Bioworks

Dr. Jennifer Nuzzo
Senior Scholar and Visiting Faculty, Center for Health Security
John Hopkins Bloomberg School of Public Health

Dr. Megan Palmer
Executive Director of Bio Policy & Leadership Initiatives, Department of Bioengineering
Stanford University

Chris Park
Senior Advisor, International Security and Nonproliferation
Office of the Under Secretary for Arms Control and International Security
U.S. Department of State

Carolyn Reynolds
Co-Founder
Pandemic Action Network

Deborah Rosenblum
Executive Vice President
Nuclear Threat Initiative

Jonas Sandbrink
Biosecurity Researcher
Future of Humanity Institute

Appendix B. Epidemiological Model Summary

Developed by Dr. Ellie Graeden Trae Wallace, Talus Analytics

The epidemiological elements of the exercise scenario were developed using a standard Susceptible–Exposed–Infectious–Recovered (SEIR) compartmentalized model. The model assumes no asymptomatic spread. The structure of the model is summarized in Figure B-1. A lab-modified version of monkeypox was intentionally released via aerosols in train stations in the fictional country of Brinia (population 250 million) by agents of a terrorist group operating in neighboring Arnica (population 75 million).

Through intentional modifications made by Arnican virology lab scientists sympathetic with the Arnican terrorists, this monkeypox strain is assumed to be more contagious than naturally occurring monkeypox—with a basic reproductive number (R0) for the modified strain of 3, as compared to 2.13 for the wildtype strain.[11] The lab-modified strain is also engineered to be resistant to the smallpox vaccine. Vaccine resistance is assumed to be driven by the introduction of the Interleukin-4 gene, as demonstrated in previous mousepox studies.[12] We assume a case fatality rate of approximately 10 percent, which is consistent with previously described monkeypox outbreaks.[13]

Modeling State Descriptions

The following bullet points summarize the states of the SEIR model and how individual model agents progress through them. (Additional details on each parameter are provided in Tables B-1 and B-2 on pages 30 and 31.)

- **Susceptible.** Initial state for all individuals in a fully predictive run. In cases where the model run is initiated based on prior cases, the susceptible group includes the proportion of individuals not previously exposed.
- **Exposed.** Individuals move from Susceptible to Exposed when they come into contact with infectious individuals at a rate that is determined by the number of contacts individuals have with one another. All exposed individuals transition to mild cases (Infected1) after eight days.

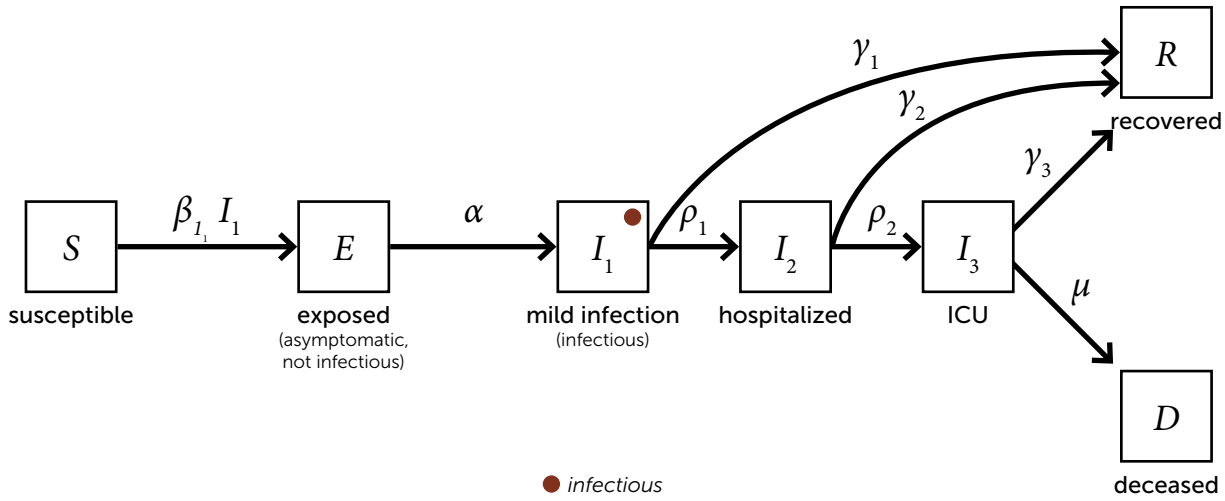
[11] Rebecca Grant, Liem-Binh Luong Nguyen, & Romulus Breban, "Modelling Human-to-Human Transmission of Monkeypox," *Bulletin of the World Health Organization* 98, no. 9 (September 1 2020): 638–640, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7463189/.

[12] R.J. Jackson, A.J. Ramsay, C.D. Christensen, S. Beaton, D.F. Hall, & I.A. Ramshaw, "Expression of Mouse Interleukin-4 by a Recombinant Ectromelia Virus Suppresses Cytolytic Lymphocyte Responses and Overcomes Genetic Resistance to Mousepox," *J Virol* 75, no. 3 (February 2001):1205–10. doi: 10.1128/JVI.75.3.1205-1210.2001. PMID: 11152493; PMCID: PMC114026.

[13] WHO, "Monkeypox–Democratic Republic of the Congo," *Disease Outbreak News* (October 1, 2020), https://www.who.int/emergencies/disease-outbreak-news/item/monkeypox-democratic-republic-of-the-congo.

- **Infected1.** These are mild cases. After approximately one week, 50 percent of these cases worsen, and require hospitalization (the Infected2 state) whereas the remaining 50 percent progress to the Recovered state.
- **Infected2.** These are severe, hospitalized cases, requiring non-ICU treatment. After approximately one week, 40 percent of these cases worsen, thus requiring ICU (Infected3), whereas the remaining 60 percent progress to the Recovered state.
- **Infected3.** These are critical cases requiring ICU treatment. This model assumes all deaths must first pass through this category. After approximately one week, 50 percent of these cases lead to death, whereas the remaining 50 percent progress to Recovered.
- **Recovered.** This compartment includes all individuals who have already had the disease (excluding those who died). For the purposes of the model, recovered individuals are considered to be immune from future infection.
- **Deceased.** Individuals who have died as a result of the disease. All deaths result from ICU (Infected3) cases and make up approximately 10 percent of all cases.

Figure B-1. SEIR Compartmental Model Structure



Associated parameters for each are described in Table B-1, below.

Table B-1. Key Parameters

Parameter	Symbol	Value	Source
Transmission rate	Beta (β)	0.175	scenario assumption
Pre-symptomatic period	–	8 days	[14]
Mild infection duration	–	14 days	[15]
Hospital stay (recovery/death)	–	18 days	ibid.
Asymptomatic cases	–	0%	[16]
Hospitalization rate	Rho1 (ρ_1)	50%	[17] and scenario assumption
ICU need for hospitalized	Rho2 (ρ_2)	40%	ibid.
Death for ICU cases	Mu (μ)	50%	ibid.
Total Case Fatality Rate (CFR)	–	10%	[18]

The release in Brinia results in 150 initial infections on May 15, 2022, and 10 inadvertently infected Arnicans. By June 1, travel from Brinia has seeded infections in the rest of the world. Elements of national-level response were also included in the model using a basic framework of adjusting the contact rate, Beta (which impacts R), to represent the effects of social distancing on transmission (including lockdowns and stay-at-home orders). The global population, excluding those living in Arnica and Brinia, were divided into three categories, reflecting the quality of public health response at the national level—designated as "Effective," "Modest," or "Poor." The population of countries with "Poor" responses represent 4.4 billion people, whereas those with "Modest" and "Effective" responses represent 1.5 billion people each. Brinia's response is defined as "Poor"; and Arnica's response is defined as "Moderate." Additionally, the fictional countries of Cardus and the Republic of Dranma have "Poor" and "Effective" responses respectively, and each have populations of 60 million and 10 initial cases. The specific dates and impacts on transmission of each response are listed in Table B-2 page 31.

All countries react to the emerging outbreak in Brinia after Move 1 on June 5, 2022. These actions impact the transmission rate but do not bring the total effective reproductive number of the virus below 1. All countries act again in early 2023. For the countries with a "Poor" response, this action is still too small

[14] Ellen M. Beer & V. Bhargavi Rao, "A Systematic Review of the Epidemiology of Human Monkeypox Outbreaks and Implications for Outbreak Strategy," *PLOS Neglected Tropical Diseases* (October 16, 2019), https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0007791.

[15] Andrea M. McCollum & Inger K. Damon, "Human Monkeypox," *Clinical Infections* Diseases 58, no. 2 (January 2014): 260–7, https://academic.oup.com/cid/article/58/2/260/335791.

[16] Daniel B. Di Giulio & Paul B. Eckburg, "Human Monkeypox: An Emerging Zoonosis," *Lancet Infect Dis* 4, no. 1 (January 2004):15–25, https://pubmed.ncbi.nlm.nih.gov/14720564/.

[17] Estimated from moderate/hospitalized and severe cases to achieve case fatality rate. Inger K. Damon, "Status of Human Monkeypox: Clinical Disease, Epidemiology and Research," *Vaccine* 29 (2011): D54-D59, https://www.sciencedirect.com/science/article/pii/S0264410X1100524X.

[18] WHO, "Monkeypox," 2019, https://www.who.int/news-room/fact-sheets/detail/monkeypox.

and leaves the R well above 1. The "Moderate" response countries open up in January, increasing R to approximately 2.2, before locking down in the summer of 2023 when the outbreak is undeniable. Finally, the "Effective" response countries lock down aggressively in February 2023 and keep R below 1 throughout the remainder of the exercise.

The combined global pandemic leads to more than three billion cumulative cases and more than 270 million deaths by the end of December 2023. At the peak of the pandemic, nearly 500 million individuals are infected at the same time, and there are 161 million people simultaneously in need of hospitalization.

The model was written in Python, with configuration and visualization through Jupyter notebooks.

Table B-2. Non-Pharmaceutical Intervention Dates and Impacts

Effective National Response		
Date	Beta	R
6/6/22	0.09	1.89
2/7/23	0.01	0.77
Modest National Response		
Date	Beta	R
6/6/22	0.08	1.75
1/11/23	0.11	2.17
3/11/23	0.08	1.75
7/15/23	0.007	0.728
Poor National Response		
Date	Beta	R
6/6/22	0.15	2.73
1/15/23	0.085	1.82

About the Authors

Jaime M. Yassif, Ph.D.
Senior Fellow, Global Biological Policy and Programs, NTI
Dr. Jaime M. Yassif is Senior Fellow for Global Biological Policy and Programs at NTI, where she is leading several major biosecurity projects focused on strengthening governance of dual-use bioscience and reducing global catastrophic biological risks. Yassif previously served as a Program Officer at Open Philanthropy, where she led the Biosecurity and Pandemic Preparedness initiative. In this role, she recommended and managed approximately $40 million in biosecurity grants, which rebuilt the field and supported work in several key areas, including developing new biosecurity programming at several leading think tanks, establishing the Global Health Security Index, initiating new biosecurity work in China and India, and framing a new public discourse about global catastrophic biological risks. Prior to this, Yassif served as a Science and Technology Policy Advisor at the U.S. Department of Defense and worked on the Global Health Security Agenda at the U.S. Department of Health and Human Services.

Kevin P. O'Prey, Ph.D.
Managing Partner, The Palisades Group, LLC
Dr. Kevin P. O'Prey has served as the facilitator for the annual Nuclear Threat Initiative's Biosecurity tabletop exercises at the Munich Security Conference. As Managing Partner at the Palisades Group, O'Prey oversees analytical and facilitation projects for the U.S. Federal Government, private sector, and international organizations. Previously, he was co-founder and president of Obsidian Analysis, Inc. and president of DFI Government Services. He earned his Ph.D. in political science at MIT's Security Studies Program.

Christopher R. Isaac, M.Sc.
Program Assistant, Global Biological Policy and Programs, NTI
Mr. Christopher R. Isaac is a Program Assistant for Global Biological Policy and Programs at NTI. Isaac has been involved with synthetic biology through the Internationally Genetically Engineered Machines (iGEM) Competition since the start of his scientific career and brings with him a mixture of skills in policy, biochemistry, and programming. Isaac holds a B.Sc. in Biological Sciences with a minor in Philosophy and a M.Sc. in Biochemistry (Bioinformatics) from the University of Lethbridge. He is an alumnus of the Emerging Leaders in Biosecurity Fellowship at the Johns Hopkins Center for Health Security and is a member of the iGEM Safety and Security Committee.

About the Nuclear Threat Initiative

NTI is a nonprofit global security organization focused on reducing nuclear and biological threats imperiling humanity. www.nti.org

More from NTI | bio

June 2019

A Spreading Plague: Lessons and Recommendations for Responding to a Deliberate Biological Event

Beth Cameron, Ph.D., Rebecca Katz, Ph.D., M.P.H., Jeremy Konyndyk, M.S.F.S., and Michelle Nalabandian, M.F.S.

September 2020

Preventing Global Catastrophic Biological Risks: Lessons and Recommendations from a Tabletop Exercise Held at the 2020 Munich Security Conference

Beth Cameron, Ph.D, Jaime Yassif, Ph.D., Jacob Jordan, Ph.D., and Jacob Eckles, M.P.H.

For more information visit www.nti.org/bio.

20 YEARS OF NTI
BUILDING A SAFER WORLD

1776 Eye Street, NW | Suite 600 | Washington, DC 20006 | **@NTI_WMD** | **www.nti.org**