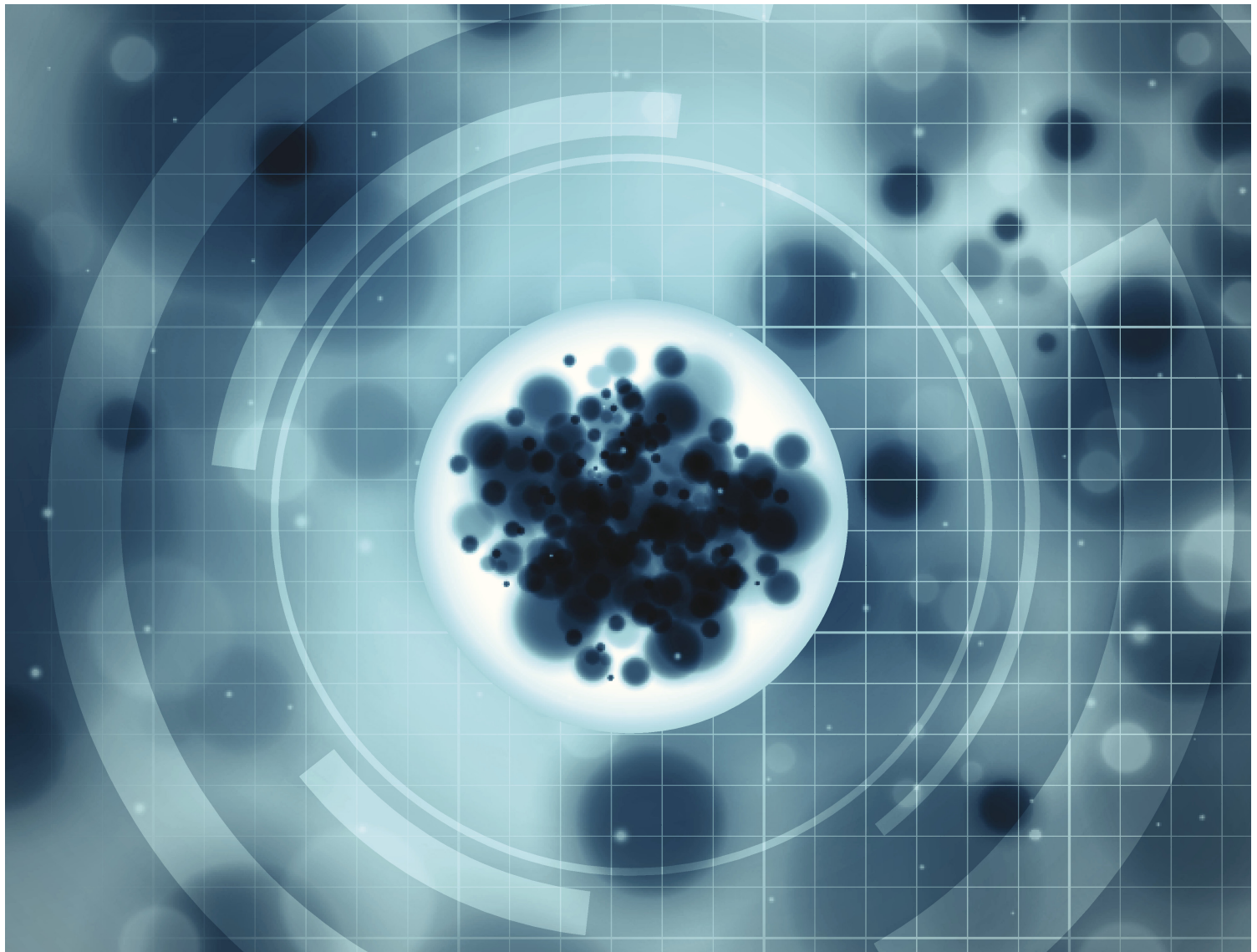




COMBATING TERRORISM CENTER AT WEST POINT

# CTCSENTINEL

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**SPECIAL ISSUE: THE BIOLOGICAL THREAT - PART ONE**

FEATURE ARTICLE

## A New Age of Bioterror

Anticipating exploitation of tunable viral agents

STEPHEN HUMMEL AND F. JOHN BURPO WITH JEREMY  
HERSHFIELD, ANDREW KICK, KEVIN O'DONOVAN, AND  
JASON BARNHILL

A VIEW FROM THE CT FOXHOLE

## Lawrence Kerr

FORMER DIRECTOR, OFFICE OF  
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OFFICE OF GLOBAL AFFAIRS, U.S.  
DEPARTMENT OF HEALTH AND  
HUMAN SERVICES

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### FROM THE EDITOR

The COVID-19 pandemic has claimed nearly one million American lives. It has upended many more and produced disastrous consequences around the world. But it could have been even more catastrophic had Western nations and companies not developed highly effective vaccines. As the world hopefully begins to emerge from the pandemic, it is important to reassess the global biological threat landscape, including the possibility that bioterrorists or other bad actors might seek to exploit advances in biotechnology to engineer a future pandemic.

In a joint effort, the Combating Terrorism Center and the Department of Chemistry and Life Science at West Point have assembled some of the best and brightest thinkers in the counterterrorism, policy, and scientific communities around the world for their perspectives and analysis on the evolution of the biological threat picture. The result is a two-volume set of special issues, with the second volume being published next month.

The feature article of this volume anticipates how bioterrorists may exploit tunable viral agents in a new age of bioterrorism. The article is authored by Major Stephen Hummel and Colonel F. John Burpo with Lieutenant Colonel Jeremy Hershfield, Lieutenant Colonel Andrew Kick, Kevin O'Donovan, and Colonel Jason Barnhill. They write: "Components of a disease such as transmissibility, lethality, and the infectious window can potentially be modified for desired tactical, operational, or strategic effects. While this capability is currently beyond the skills and knowledge of the biology enthusiast, a trained individual would possess such skills and knowledge, though they may lack the necessary material and infrastructure support. Hence, it is necessary to develop and maintain capabilities that can respond to a variety of pathogens and possible effects."

This issue features an interview with Lawrence Kerr, who until his retirement from government service earlier this year was the Director of the Office of Pandemics and Emerging Threats in the Office of Global Affairs at the U.S. Department of Health and Human Services. We also interview Brad Ringeisen, the Executive Director of the Innovative Genomics Institute. Before his retirement from government service in July 2020, Dr. Ringeisen served as the Director of the Biological Technologies Office at the Defense Advanced Research Projects Agency (DARPA).

Filippa Lentzos, Gregory Koblentz, and Joseph Rodgers argue "the biological risk landscape is rapidly evolving and presents significant new challenges to preventing the accidental, reckless, or malicious misuse of biology. At the same time, oversight systems to ensure that life sciences research is conducted safely, securely, and responsibly are falling behind. An urgent overhaul to realign biorisk management with contemporary risks is needed."

Paul Cruickshank, *Editor in Chief*

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*This issue is a joint effort of the Combating Terrorism Center and the Department of Chemistry and Life Science at West Point. The CTC is grateful to CLS Department Head Colonel F. John Burpo and his team for their insights and expertise in the production of this volume.*

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*Cover: Abstract background of a virus - stock illustration (traffic\_analyzer via Getty Images)*

# A New Age of Bioterror: Anticipating Exploitation of Tunable Viral Agents

By Stephen Hummel and F. John Burpo with Jeremy Hershfield, Andrew Kick, Kevin J. O'Donovan, and Jason Barnhill

Advances in technology, particularly biotechnology, over the past decade have dramatically changed the world. Scientists are employing gene editing tools to cure genetic diseases, reduce the effects of climate change, and generate sustainable food sources. These same tools, however, can be used to modify pathogens to develop and deploy novel biological weapons. The nature of these tools and our understanding of specific viral genomes makes this process tunable. Components of a disease such as transmissibility, lethality, and the infectious window can potentially be modified for desired tactical, operational, or strategic effects. While this capability is currently beyond the skills and knowledge of the biology enthusiast, a trained individual would possess such skills and knowledge, though they may lack the necessary material and infrastructure support. Hence, it is necessary to develop and maintain capabilities that can respond to a variety of pathogens and possible effects.

The emergence of the SARS-CoV-2 virus in Wuhan, China, in November 2019 and its subsequent worldwide spread has had tremendously destabilizing effects, which are still being felt more than two years later. Lessons from COVID variants include immediate impacts at the local level (initial variant), global pandemic effects from the Delta variant to include significant and protracted economic impact, and the more sub-lethal, sustained economic, political, and healthcare impacts of the Omicron strain. The global SARS-CoV-2 pandemic has also highlighted the ongoing biological revolution that has resulted in the rapid development and employment of new diagnostic tests, vaccines, and other targeted treatments including monoclonal antibodies and antiviral drugs. Over the past decade, the intersection of technology (e.g., computer science, automation, DNA sequencing) and biology has expanded exponentially, becoming embedded in economies and society. This intersection, along with the demonstrated impacts of SARS-CoV-2, is fraught with opportunities and risks. The tools for curing genetic diseases, reducing the effects of climate change, and generating sustainable food sources are now being developed and tested. Yet, these same gene editing tools could be employed to generate and modify biological weapons, making it important for both the counterterrorism community and scientific community to

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*The views expressed in this article are those of the authors and do not necessarily reflect those of the United States Military Academy, U.S. Army, Department of Defense, or U.S. Government.*

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anticipate how the scientific advances may change the bioterrorism threat landscape.<sup>1</sup>

In this article, the authors consider the theoretical potential for bioterrorists to select a viral platform and genetically modify viral transmissibility, incubation and infectious time windows, and lethality along with the manner of death, creating what are in essence tunable bioweapons. Such bioweapons could achieve targeted effects tailored to timescale, physical and psychological effect, with intended tactical, operational, and strategic levels of impact, with the most impactful viral agents producing all three effects.

To anticipate the potential future threat posed by tunable viral agents, the article first examines the advancing biotechnological toolkit that bad actors may be able to exploit. It then delves into the singular threat posed by viral agents compared to other potential forms of weaponized pathogens such as bacteria, with the COVID-19 pandemic underscoring the threat posed by highly transmissible viruses. The next section describes how biotechnology tools allow for the bioterrorist to select a viral “chassis” and then prospectively genetically tune the respective system variables of lethality, transmissibility, and infectious window for tactical, operational, or strategic effects, or, to maximize impact, combinations thereof. The piece then discusses the duality of emerging biotechnology tools for developing and deploying potential bioweapons as well as their countermeasures. The article closes with some concluding observations.

### The Advancing Biotechnology Toolkit

While there is a variety of biological gene editing tools, perhaps the most notable is the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) Cas9 system.<sup>2</sup> This system comes from the adaptive immune response of bacteria to prevent viral infection. During the process of viral invasion, the virus hijacks the host cell to replicate its genetic material to make multiple copies of itself to infect other cells. Bacteria utilize the CRISPR system to identify the invading viral genome and to subsequently cut the viral genetic material using the associated Cas9 protein. The critical capability of the bacterial CRISPR-Cas9 system is the recognition of the pathogen genome using a target sequence that is complementary to a portion of the target viral genome. The CRISPR can then quickly identify a known invader’s genetic code and rapidly digest and incapacitate it upon recognition.

The great technological leap of CRISPR is its application to edit plant and animal genomes. With several advancements in biotechnology, including rapid and affordable whole genome sequencing and nucleic acid (DNA and RNA) synthesis, both scientific investigators and prospective bioterrorists with the requisite scientific knowledge and equipment can now with relative ease design and manipulate specific target sequences to modify, insert, or delete portions of the genetic material. The ease of ‘copy/cut/paste’ modifications of specific genetic sequences has the potential to cause either a loss or gain of biological function. While the potential impact on human diseases can be tremendous, as evidenced by recent news of a patient being possibly cured of HIV infection,<sup>3</sup> so too can the negative consequences. In 2018, Dr. He Jiankui, a Chinese biophysicist, employed CRISPR to delete a portion of the CCR5 gene in embryos with at least one HIV-positive parent. The CCR5 gene “encodes a protein that allows HIV to enter immune cells,” and a small deletion (CCR5-delta32) therein had

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been previously shown to protect cells from HIV infection.<sup>4</sup> This use of CRISPR not only shocked the world but was also undertaken without the consent of the Chinese government. Jiankui was subsequently found guilty of “illegal medical practice” and sentenced to three years in prison, while several of his colleagues received shorter sentences.<sup>5</sup> Even though Jiankui was an established scientist, his employment of CRISPR to edit human embryos less than six years after the 2012 *Science* article by Jennifer Doudna and Emmanuelle Charpentier first reported the programmable nature of CRISPR illustrates its relative ease of use.<sup>6</sup>

The combined lessons of the COVID pandemic, along with an increasing effective biotechnology toolkit, add to a possible playbook for bioterrorists who seek to use viral platforms to achieve effects along a continuum of targeted, local endemic effects all the way through to inducing a global pandemic. This playbook might also be leveraged by state actors or state actors through proxies.

### The Singular Threat of Viral Agents

The suite of viral outbreaks in the 21st century, including COVID-19, Ebola, Zika, SARS, MERS, swine flu, and avian flu, readily highlights the dangers of these highly transmissible agents. When factoring in their respective varying lethality, routes of infection, and overall infectivity, viral agents clearly pose a considerable security threat. However, the most well-developed biological warfare agents have historically been bacterial. *Bacillus anthracis*, the etiological agent of anthrax, has been studied extensively and developed both at home and abroad as a potential offensive bioweapon, largely due to the microorganism’s ability to exist almost indefinitely as inert spores. There have been multiple instances of the intentional release of anthrax spores and millions of research dollars spent on developing antibiotics to potentially treat inhalational anthrax.<sup>7</sup> Similarly, *Francisella tularensis*, the causative agent of tularemia, sometimes known as “rabbit fever,” has been similarly studied extensively for both offensive and defensive purposes.<sup>8</sup>

But bacteria and viruses are completely different. First and

foremost, bacteria are a domain of life. Bacteria are microscopic living organisms, normally existing as single cells that contain the essential biomolecules—sugars, proteins, lipids, and nucleic acids—and are fully capable of reproducing according to their respective genetic codes. Viruses, on the other hand, are not living organisms. Rather, they are variably comprised of a nucleic acid, DNA or RNA, that encodes for a small number of capsid coat proteins and virus-specific enzymes. They are obligate intracellular parasites that are only capable of replicating within other organisms. Viruses are known to infect all types of living organisms, from bacteria through plants to animals, hijacking the machinery of life to read their genetic code and produce proteins that aid in their propagation within an organism and inevitably to the next organism, via infection by many different mechanisms.

Therefore, it is imperative to remember that bacterial threats are not viral threats. They are completely different. Bacteria are several orders of magnitude larger than viruses, incredibly more complex, diverse, and must be provided nutrients to stay alive. Viruses, on the other hand, along with their appropriate host cell must be maintained to survive and propagate. Bacteria that produce spores as evolutionary adaptations to survive in nutrient-poor conditions lend themselves to large-scale production and an ability to infect on a relatively large scale. Otherwise, in a laboratory setting, bacteria are typically stored either in solid or liquid media, wherein they pose little to no harm. Viruses, due to their extraordinarily small size and lack of complexity, are much easier to spread via surface contact or in the air, either intentionally or unintentionally, and depending on the diseases they cause may be appropriately categorized as much more dangerous than bacteria. Common and uncommon bacterial infections are nowhere near as transmissible as most viruses due to their larger size and relative inability to be effectively aerosolized and passed from organism to organism via coughs and sneezes. This is illustrated by the etiology of pneumonia infections where one study showed 46.4 percent were viral, 14.4 percent were bacterial, and 25.4 percent were co-infections of both virus and bacteria.<sup>9</sup> By most measures, bacterial infections are localized and commonly transmitted via direct contact, water, insect vectors, or small animals. Viruses, on the other hand, know little of such boundaries.

Finally, drugs developed to treat bacterial infections are known as antibiotics and either stop bacteria from reproducing or outright kill them. Drugs developed to treat viral infections are known as antivirals and typically either disrupt host cell mechanisms or target the hallmark nucleic acids and proteins of the disease-causing viruses. There is also a variety of broad-spectrum antibiotics that can kill a wide range of bacteria, while antivirals typically are targeted to a small number of viral species, at most. Both due to their completely different targets, as well as the fundamental difference that bacteria are living organisms and viruses are non-living replicative units, antibiotics and antivirals are fundamentally not interchangeable. The differences in infectivity and treatment make viruses a logical choice as a starting “chassis” to design a bioterror weapon.

### **Tailoring the Attributes of Viral Agents for Intended Effects**

The process for biological design is simple and relies on the genetic sequence of the target pathogen. Within the genetic code of viruses and eukaryotic cells are two distinct regions known as exons and introns. During the transcription process, where the genetic

**“The relationship between viral genome and desired system variables to achieve bioterror effects may not be clearly understood today, but the rapid development of biotechnology tools and scientific understanding portends the elucidation of these structure-function relationships in an ever-expanding toolkit that could just as easily serve the common good as it could serve purposely nefarious intentions.”**

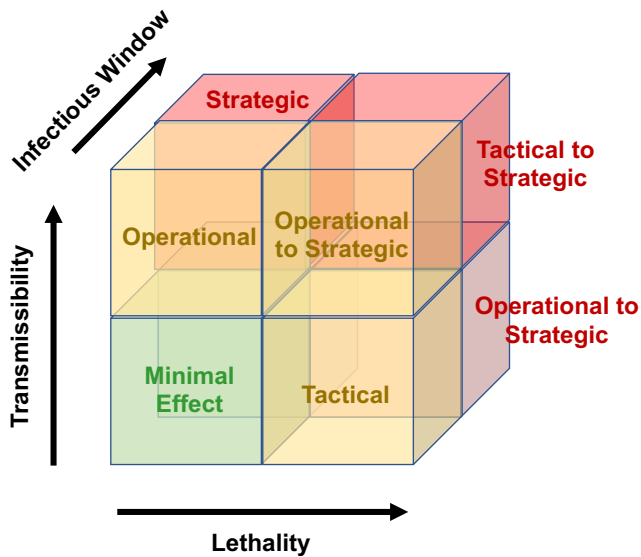
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material (DNA or RNA) is converted to messenger RNA, the introns are spliced out and the exons encode for specific proteins. To edit the genetic code, it is critical to understand these regions since editing a non-coding region will have little to no effect on the function of the process. Depending on the pathogen, information about exons and introns may not be known or at the level of detail required. Editing the genetic code also requires understanding the desired effects of the manipulation in terms of gain or loss of function. These desired effects may require the simple deletion of a portion of the genetic code or the slightly more complicated insertion of a genetic sequence. The CRISPR-Cas9 system enables both options and requires the correct configuration guide RNA prior to the actual development of the pathogen.

Biotechnology tools allow for the bioterrorist to select a viral “chassis” and then prospectively genetically tune the respective system variables of lethality, transmissibility, and infectious window (see Figure 1).<sup>10</sup> The availability of these tools reduces many technical hurdles. However, the development of a biological weapon through substantive modification of any sort of virus requires the bioterrorist to have considerable knowledge and awareness about both the virus and the desired outcomes. The relationship between viral genome and desired system variables to achieve bioterror effects may not be clearly understood today, but the rapid development of biotechnology tools and scientific understanding portends the elucidation of these structure-function relationships in an ever-expanding toolkit that could just as easily serve the common good as it could serve purposely nefarious intentions.

### **Tactical to Strategic Bio-Pathogens**

U.S. military operations are a *continuum* of three categories: tactical, operational, and strategic.<sup>11</sup> The tactical level of war can be viewed as battles and engagements at the unit or task organization level such as division or corps.<sup>12</sup> The operational level builds upon the tactical level and is the level of war where campaigns and major operations are planned to achieve strategic objectives, generally occurring at the corps to field army level.<sup>13</sup> These campaigns and operations are generally conducted at the theater level. The strategic level is greater and occurs when a nation employs its national resources to achieve the nation’s security objectives. From



**Figure 1:** The 3D plot illustrates relationship between desired effects (tactical, operational, and strategic) and tunable factors (X-axis: lethality/death rate, Y-axis: transmissibility, and Z-axis: infectious window). Lethality is the ratio of deaths among infected individuals. Transmissibility is the infectivity of the pathogen or how easy it spreads. The infectious window is the period of time between the point of infection and when the pathogen is reliably detectable, with a short window (a low Z-axis value) meaning fast detection and a long window (a high Z-axis value) entailing slow detection and more severe public health impacts. As previously mentioned, operations are a continuum of three categories: tactical, operational, and strategic. A tactical to strategic effect (right, upper, back box) means a viral agent can be expected to produce an effect end point that is tactical, operational, or strategic with lower-tier outcomes inclusive. By examining the relationship and interconnectivity of the tunable factors, it is possible to determine the desired effects. Conversely, it is possible to identify the levels of the tunable factors to achieve the desired effect level.

a military perspective, this can entail a corps to joint force land component commander.<sup>14</sup> At the strategic level, a nation can be part of a multinational coalition.<sup>15</sup>

These definitions of military operations can also be used to describe and understand the effects of a bioterrorist threat. A biological weapon that only produces tactical effects would be one limited to a local or confined area. For example, in 1984, the Rajneeshee cult “contaminated salad bars at 10 restaurants” with Salmonella to sicken the local population of The Dalles, Oregon, in order to influence the county elections. This relatively simple attack led to 751 reported cases of Salmonella poisoning in a county where there are typically fewer than five per year.<sup>16</sup> The 2001 Amerithrax attack could be considered a biological attack with primarily operational and strategic effects. The fact that multiple letters were sent to political leaders and journalists in multiple states created operational effects. Letters sent over a two-month period achieved strategic effects by disrupting the federal government as it endeavored to recover from the September 11th attacks and amid emerging operations in Afghanistan. While it could be argued that the letters did generate tactical outcomes, in terms of isolating buildings and personnel, the detection of Anthrax immediately elevated the issue beyond local control to the state and federal

governments.

Along these same lines, the SARS-CoV-2 pandemic is a biological pathogen incident that has been full spectrum, from tactical to strategic effects, with the disruption of whole economies and concomitant political and social unrest (e.g., mask mandates and lockdowns). Specifically, it was reported in July 2021 that the U.S. economy had contracted by nearly 20 percent from the fourth quarter of 2019 to the second quarter of 2020.<sup>17</sup> At a tactical and operational level, the healthcare system was overwhelmed in many areas, forcing assets to be shifted between states and requiring the support of FEMA and the National Guard to set-up field hospitals.

Depending on the objective a bioterrorist may have, a virus can be modified to achieve tactical, operational, and strategic end states or combinations thereof. Selecting a virus is perhaps the first critical step. Merely selecting a virus is an academic process and does not mean that the bad actor has access to or the ability to acquire purified quantities of the virus to be modified. Some of the elements to be considered are inherent transmissibility, infectious window, and lethality. The infectious window is the period of time between the point of infection and reliable detection of the pathogen and is often confused with the incubation period, which is the time elapsed between infection and the onset of symptoms.<sup>18</sup> These components may be directly tied to the overall desired tactical, operational, or strategic effects, and selecting one that most closely aligns with the overall objective reduces the amount of modification required. For example, modifying a seasonal influenza virus to achieve the same hemorrhagic fever hallmarks of an Ebola virus would require significant modification to the viral genome that may not produce a viable virus.

After a virus is selected, it would be necessary for the bioterrorist to modify the genome to achieve the desired effects. This design process is not easy and requires an in-depth knowledge of the viral genome and which sequences encode specific proteins. The biochemical process of inserting a gene is easy, but designing the sequence, knowing where to insert the sequence, and ensuring that the sequence does not affect other parts of the genome that encode for proteins is critical.

To imagine this selection and design process, the cube in Figure 1 highlights the relationship between the attributes of the modified pathogens (inherent transmissibility, infectious window, and lethality) and tactical, operational, and strategic effects or, for the most impactful viral agents, a combination of those effects. For example, a virus with low transmissibility, short window before detection, and high lethality rate might be employed as a tactical weapon, and shifting the factors of transmissibility and infectious window would shift a tactical pathogen to a weapon that produces operational or strategic effects or both. Manner of death would also amplify psychological effects, potentially elevating what would otherwise have been merely tactical outcomes to also include operational or even strategic effects, allowing for broader and longer-lasting effects from local execution of bioterrorist acts. For instance, a dramatic, gruesome public manner of death involving significant blood profusion from bodily orifices would heighten the perception of a threat, compared to victims quietly expiring from low blood oxygenation out of sight in a medical facility.

As previously mentioned, development and implementation of modified pathogen requires sophisticated knowledge and capabilities. An April 2019 *CTC Sentinel* article highlights the relative difficulty for a non-state actor to develop a modified



pathogen bioweapon, as illustrated in Figure 2.<sup>19</sup> While a nuclear weapon is the most complex and difficult weapon of mass destruction to develop due to the constraints of acquiring fissile material, biological weapons do not have similar acquisition limitations. Quite literally, bacteria and viruses are everywhere. Transforming relatively benign bacteria and viruses in significant quantities is difficult, as it requires infrastructure, knowledge, and technical skill.<sup>20</sup> Infrastructure relates to controlling the environment for optimal growth and modification. This also includes personal protective equipment, such as gloves, masks, and suits, along with supplied air and hoods as necessary.

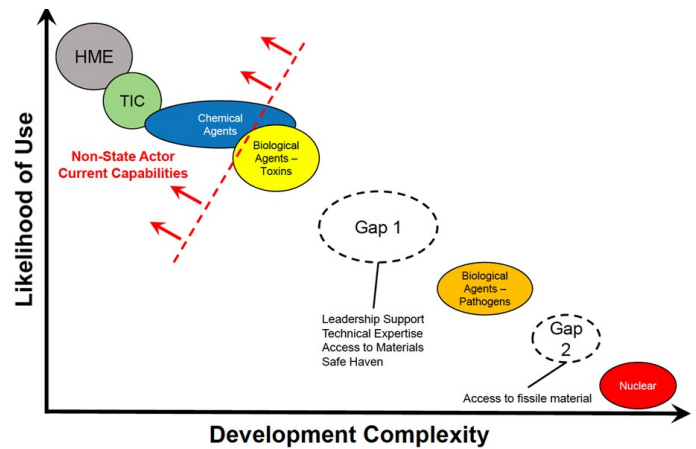
While the necessary infrastructure and equipment can be acquired through legitimate and non-legitimate channels, knowledge and technical skill are more difficult. Reading journal articles can provide information about a virus or a method, but it is not the same as knowledge or technical skills that are only achieved through laboratory experience. It is the gap in knowledge and technical skill that drastically increase the complexity of viral and bacterial biological agents (e.g., Smallpox and anthrax, respectively) compared to biological toxins (e.g., ricin),<sup>a</sup> as shown in Figure 2. Compared to the general population, those individuals with said skills and knowledge are relatively few. However, advances in biotechnology, coupled with the democratization of gene editing tools, are slowly but steadily diminishing this barrier.

### Medical Countermeasures

Just as the bioterrorist's ability to potentially tune and tailor viral agents for enhanced lethality and other means of disrupting society continues to increase, so too does the ability to rapidly develop and utilize a scalable defense. Medical countermeasures broadly include three lines of defense: detection via diagnostics, treatment via therapeutics, and prevention through vaccines. More specifically, they are categorized as "medicines and medical supplies that can be used to diagnose, prevent, or treat diseases related to chemical, biological, radiological, or nuclear (CBRN) threats."<sup>21</sup>

The ongoing COVID-19 response has highlighted the U.S. government's capabilities for responding to a novel viral agent. Precision, accuracy, and availability of detection kits continues to be a critical frontline method for identifying infected individuals. Classical medicine itself provides a standard middle barrier. Then, experimental therapeutics, such as convalescent plasma, antibody cocktail treatments, and more traditional small molecule antiviral drugs, have all made their way into popular conversations as a final line of defense against advanced disease progression. But ultimately, the greatest defense against a novel viral agent continues to be vaccination, and the COVID-19 response has showcased extraordinarily successful private-public partnerships that have yielded multiple FDA-approved vaccines, which have been made widely available to nearly the entire U.S. population in a matter of months.

One can then reasonably conclude that subsequent viral events, possibly of a bioterror nature, will demand an even faster and



**Figure 2:** The relative complexity for weaponization and likelihood of use for nuclear, biological, and chemical weapons. The red dotted line and red arrows highlight that space in which non-state actors currently operate. HME refers to homemade explosives and TIC refers to toxic industrial chemicals, such as chlorine.<sup>22</sup> As previously highlighted, biological toxins are chemicals/compounds that are extracted from biological organisms such as ricin and botulinum. The pathogen biological agents are bacterial and viral requiring greater knowledge, infrastructure, and other materials to develop and deploy. The gaps should be visualized as a continuum. For example, non-state actors have to overcome the elements of gap 1 as well as gap 2 in order to be able to use a nuclear weapon.

more impressive response from the whole of U.S. government in terms of diagnostic testing, therapies, and care modalities. This precedent to rapidly develop therapies perhaps began during the response to the Ebola outbreak in 2014-2016<sup>23</sup> and has continued more recently as drugs to treat Ebola have obtained both normal and special FDA approvals through military partnerships.<sup>24</sup> The development of medical countermeasures that are tailored to treat novel viral bioagents, however, will inevitably lag behind the initial deployment of such novel agents. Sustained anticipatory development of broadly applicable countermeasures, especially at the strategic level, is required to react to novel agents.

### Conclusions

The sophisticated bioterrorist, using common biotechnology tools, may be able to tune transmissibility, infectious window, and lethality rates to achieve tailorable effects at the tactical through global strategic level. However, such individuals and organizations are currently rare and, based on their scarcity, can be targeted through their support networks, which provide material, information, and infrastructure.<sup>25</sup>

Anticipating threats and the methods used to develop such threats continue to place a premium on the importance of comprehensive and rapid detection and mitigation strategies. Such detection strategies might include massively networked wearable biometric sensors embedded in smart watches and sensor devices such as those under development with the Defense Threat Reduction Agency (DTRA) and Defense Advanced Research Projects Agency (DARPA).<sup>26</sup> Rapidly developable mRNA vaccines and monoclonal antibody therapies offer a starting point for relatively rapid mitigation, but are currently still far too slow to prevent a bioterrorist's desired effects.

a A biological toxin is defined as a chemical produced by metabolism in an organism, whereas a biological agent is a viral or bacterial pathogen and causes varying levels of health impacts based on lethality, transmissibility, and panic/social disruption. "Case Definitions for Chemical Poisoning," Morbidity and Mortality Weekly Report, Centers for Disease Control and Prevention, January 14, 2005; "Bioterrorism Agents/Diseases," Emergency Preparedness and Response, Centers for Disease Control and Prevention.

The SARS-CoV-2 pandemic has highlighted the global impact of one viral pathogen, but the tools to modify and tailor countless other viruses for a specific target and effect currently exist. Efforts must be undertaken to stay ahead of how these threats are applied. This includes using the same technology and knowledge to design rapid medical countermeasures and detection equipment. This effort begins with a comprehensive strategy for not only the U.S.

government and the Department of Defense, but also allies of the United States as viruses do not recognize international borders. As preventing the development of biological weapons by non-state actors is increasingly difficult, domestic and international policies, funding, and organizational resourcing must coalesce to match the speed of science. **CTC**

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# A View from the CT Foxhole: Lawrence Kerr, Former Director, Office of Pandemics and Emerging Threats, Office of Global Affairs, U.S. Department of Health and Human Services

By Paul Cruickshank, Don Ressler, and Kristina Hummel

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*Editor's Note: This interview was recorded in February 2022 before Dr. Kerr's retirement from government service.*

**CTC: For the last six years, you served as Director of the Office of Pandemics and Emerging Threats at the Office of Global Affairs in the Department of Health and Human Services, having held a variety of positions related to public health policy and preparedness over the last 20 years in the executive branch and the intelligence community. But firstly, you are a scientist. You began your career leading a research lab at Vanderbilt University. What drew you to public service?**

**Kerr:** I originally thought that I was going to go the traditional medical school faculty route while at Vanderbilt. I really enjoyed research science, teaching, and working in an academic health center. I was very fortunate that I was given the chance to do a Robert Wood Johnson Health Science Policy Fellowship, which brought me to Washington, D.C., and I have to admit, I caught the policy bug or “Potomac fever,” and found that when you had someone who had a science and medical background that was advising on making good policy, it was a critical skill set. After working on Capitol Hill, the opportunity to join the federal government arose, and by chance, I was working for Dr. Anthony Fauci at the NIH/NIAID when then President Clinton called to ask if he had anybody who had done policy work. I was sent to the Office of Science and Technology Policy, and that's where I kind of cut my teeth, if you will, on policy development and what launched my career. It was that sense of contributing one's scientific and medical skill sets to greater policy good for the public.

**CTC: Could you explain the role that your office plays and its key focus areas?**

**Kerr:** We are the one policy office within the Immediate Office of the Secretary of HHS that is focused completely internationally. Most people think of HHS and its domestic mission, or that the vast majority of HHS' budget is Medicare and Medicaid, but we are the office that focuses on international policy. So everything internationally focused that the Secretary does—whether engaging the World Health Organization (WHO) or ministers of health around the world or the United Nations—our office works on that. My team is the one that deal specifically with the global health security agenda, working with the International Health Regulations at the WHO; preparing for pandemic influenza, which is how the office actually got its initial funding start; antimicrobial resistance, looking at future threats; and then a team that's focused on emerging infectious diseases, which today means the COVID-19 response.

**CTC: Looking back on your career in government, what aspect of your work are you most proud of?**

**Kerr:** In the policy world, you're often thinking in three, five, sometimes 10 years out. And I've been fortunate, being in the government 23 years, to actually see the outcome and impact of some early policy work. When I was in the National Security Council (NSC) in 2005 and wrote the National Strategy for Avian and Pandemic Influenza and worked with OMB [Office of Management and Budget] and Congress, we got \$6.9 billion devoted to implement that Strategy. At the time, we were worried about H5N1 influenza being the next pandemic, but low and behold, in 2009 the H1N1 influenza pandemic strain became *the* pandemic. And while moderate in disease severity at the time, we had already started to see some of the benefits of implementing that 2005 Strategy domestically and globally. But even then, in the 2014-2016 Ebola outbreak in West Africa and particularly then in the COVID-19 outbreak, we saw all of the programs that we had put in place across the public health systems—the detection systems across our public health laboratories that had been built from those initial investments starting back in 2006—actually come to fruition. It's been a very, very interesting look-back to see where those dollars are, the impact that they had, and then how they've impacted this pandemic.

**CTC: Two years after the outbreak of the COVID-19 pandemic that has killed nearly a million Americans and a year after the rollout of the highly effective vaccines against it, what are the**

### key lessons that you've learned or that you think we should be learning in preparing for the next pandemic?

**Kerr:** Whenever we go through tabletop exercises on pandemic preparedness, almost every single after-action review highlights communication and risk communication as top priorities to address during a pandemic. I would say, unfortunately, in this pandemic we saw a very deleterious politicization of the COVID-19 response arise early and continue in a way such that messaging around public health guidance, medical guidance, and simple personal measures to protect individuals, communities, states, and local governments just go down a route that I don't think we ever, ever envisioned in pandemic preparedness. It truly eats at the soul of a public health person when you know that we have what are some of the most safe and effective vaccines that we have against any pathogen, that we have therapeutics that save lives, and there are still individuals and groups who, for reasons that are not aligned along public health and medical guidance, just oppose their use. We know we can save more lives, and it's horrible not to be able to see that acceptance. I think it will be studied for decades, how the messaging and the communication went awry.

One aspect that really accelerated the development of those safe and effective vaccines/therapeutics was having the available resources to tap very quickly and to be able to really gather the breadth that the United States has in terms of basic science and innovation and to harness that to be able to get these countermeasures into people quickly. That availability of those resources, through Operation Warp Speed that then became the CAG<sup>a</sup> that is now H-CORE [HHS Coordination Operations and Response Element], really provided for groundbreaking vaccines in a time period that we've never seen before, and one we hope we'd be able to marshal once again if another pathogen comes to bear of epidemic or pandemic potential.

**CTC: The COVID-19 pandemic caused unprecedented strain and stress on all healthcare systems. Certainly, we saw that here in the United States, but from your vantage point, looking across the globe, could you speak to the ways that public health systems can be improved ahead of a future pandemic?**

**Kerr:** Unfortunately, in non-pandemic times, we often forget that the basis of our health systems lies in root public health disciplines and practices. And when you talk about the resources, the infrastructure, you mean the people, the money, the basic programs. They're not sexy. For example, most people don't think about getting children measles vaccinations and other childhood vaccines; it's something that people take for granted, and there are diseases that we often don't even talk about unless there's an outbreak. But those trained public health professionals, with clinics and laboratories, whose data and results are networked to state and federal health officials are the systems that are in place to protect our people day-in and day-out so that it is rare that we experience those outbreaks. From 2005 to the present, we lost over 50,000 public health professionals across the United States, and that slow decline over the years is what has left us vulnerable and



*Lawrence Kerr*

it's in systems where you can't just pay people and surge to regain it. That expertise is something that you need years of continued investment, mentorship, the availability of resources to provide for those when they are needed, not only day-to-day but in the surge during an epidemic or an outbreak condition.

You also have to make sure that your surveillance systems are finely tuned, that they are constantly operating. And in the United States, that is a challenge. We're seeing now the debate play out between how the federal government operates versus how we work with basically 57 independent states and territories. It's similar to the way we work with other countries, where the governors' rights versus those of the federal government and the information exchange between the federal and state governments challenge a robust national pandemic response. Those systems and how that information is used to help and provide the best available guidance really is something that during non-pandemic periods we could definitely improve. And finally, continued investment in basic and applied research is what will get us the jump ahead for whatever that next pathogen of pandemic potential may be when it comes.

**CTC: Operation Warp Speed, which you just referenced, saw the employment of vaccine development technology at an unprecedented pace and scale. How has Operation Warp Speed changed the way we will develop vaccines moving forward?**

**Kerr:** Operation Warp Speed was something of a gamble. It was the brainchild of people who envisioned that the U.S. government could advance the development of vaccines with the vaccine manufacturers, at risk. Let's say that there were six to eight vaccine candidates out there in the hopes, at the time, that even one would prove to be safe and effective. Remember, when this pandemic started, no one had ever developed a vaccine against a coronavirus. In fact, clinical trials of vaccines against known coronaviruses,

<sup>a</sup> Editor's Note: CAG is an acronym for the HHS-DOD COVID-19 Countermeasures Acceleration Group.

such as SARS or MERS, had failed, so there was a gamble. The \$10 billion investment in the initial six Operation Warp Speed candidates, fortunately for all of us and the entire globe, paid off. And the question is, should another pathogen—a non-influenza, a non-coronavirus—arise, would we be able to marshal the resources and the expertise to be able to do something similar in order to get countermeasures quickly into people?

**CTC:** In late 2021, as you're aware, U.S. Army researchers announced that "preclinical study results show that the Spike Ferritin Nanoparticle (SpFN) COVID-19 vaccine developed by researchers at the Walter Reed Army Institute of Research ... not only elicits a potent immune response but may also provide broad protection against SARS-CoV-2 variants of concern, as well as other coronaviruses."<sup>21</sup> How hopeful are you that the Walter Reed effort will succeed? Could a universal coronavirus vaccine be a gamechanger in reducing the severity and impact of future pandemics?

**Kerr:** Am I hopeful? Oh yes. It would be phenomenal. We are all hopeful. Pardon me if I'm a little bit war-torn, from my influenza days, however, because we've been looking for a pan-influenza or universal influenza vaccine for many, many years. And so, while I'm hopeful on one arm, on the other arm I'm saying, "OK, we need to be careful of Mother Nature and of hubris." Mother Nature can create billions of variants, and humans can in no way match that. 'Universal' is also a concept that in lay terminology has an attractiveness. But does it truly mean across all sub-species and all sub-lineages? Or are we looking at, for example, taking SARS-CoV-2 off the table or an effective vaccine against one of its lineages? So, am I hopeful? Absolutely. We will just have to see how it actually does once these vaccine candidates make it into human clinical trials. Because the other thing is that Mother Nature has the ability to generate vaccine-resistant strains. And viruses do what viruses do best, which is mutate. So I'm hopeful, but we'll see.

**CTC:** To pivot to synthetic biology, the 2018 National Strategy for Countering WMD Terrorism<sup>2</sup> noted that "in contrast to chemical, radiological, and nuclear weapons, some biological agents are contagious and may thus spread in an uncontrolled manner. Furthermore, such agents are the only other class of WMD that has the potential to match nuclear weapons in the scale of casualties they produce." However, retired Lieutenant General Michael Nagata stated in 2020 in our publication that "during my time as a CT [counterterrorism] operational practitioner, all the way through my final years as the senior CT strategist at NCTC [National Counterterrorism Center], the amount of energy, focus, and resourcing devoted to bioterrorism is a small fraction of what is still given today to more conventional threats."<sup>23</sup> For more than two decades, you have played a key leadership role in U.S. biosecurity efforts. How would you characterize the evolution of the United States' approach to bio threats across the arc of your career? Are there assumptions that you've seen that have changed as a result of the COVID-19 pandemic?

**Kerr:** It's a great observation. And as I think about it, I have to describe it in terms of a series of fits and starts, attention and then neglect. The anthrax attacks of 2001 initiated a profound

surge and interest in resources, both financial and personnel, devoted to countering biological threats and biodefense efforts. In 2005, there were the counter-BW [biological warfare] efforts because of perceived intelligence threats overseas, and then with the 2009 pandemic, there was the change from counter-BT [bioterrorism] or BW to counter-bio threats. So, we saw an evolution in language from bio threats of natural, accidental, and man-made origin to encompassing *all* of them. In the 2017 National Defense Authorization Act, the mandate to create the National Biodefense Strategy was really the first time that we collectively as a government came together and looked holistically at these threats, whether man-made, natural, or accidental. And yet, the Strategy was completed, the implementation plan was created, the new American Pandemic Preparedness plan has been released, and the Global Health Security Strategy created, but none of these have been funded. And so, the problem goes back to, we have strategies, but strategies are pieces of paper that sit on bookshelves until they are actually funded and turned into programs that can operationalize these implementation plans. My concern is that we slide back into a period of neglect where these critical elements that Mother Nature is warning us about, and that intelligence is warning about, will not be addressed.

The second part of your question, my community, the flu community, for two decades has been saying the same thing: We predict the most likely pathogen to cause the next pandemic is influenza. Even to this day, there are at least 10 strains around the world circulating between predominantly chickens and humans that have already acquired pandemic potential, and we're just waiting to see when Mother Nature will flip that next mutation that will allow human-to-human transmission. There are definitely guardians who are watching for this at all times, and many of us look back and said, "Wow, if this had been a flu pandemic, how very differently and more rapidly we would have been able to take care of it." But that also puts us on guard: "OK, we've had a coronavirus. We know that flu is out there. What is the next one that we aren't necessarily watching for right now?"

**CTC:** In August 2020, West Point scientists assessed that advances in synthetic biology and widening access to the technologies involved "is leading to a revolution in science affecting the threat landscape that can be rivaled only by the development of the atomic bomb."<sup>24</sup> Synthetic biology is an enormous force for good, but as the 2018 U.S. Strategy for Countering WMD Terrorism noted, "advances in biotechnology could theoretically allow even a single individual working in a laboratory to engineer pathogens that could have catastrophic effects."<sup>25</sup> What is your view of the transformative potential of threats from this sphere, and what can be done to prevent a bad actor from engineering a pathogen more virulent and even more transmissible than the virus that causes COVID-19?

**Kerr:** It's a very salient question, and I agree with the assessment. A single bad, high-end molecular biologist that wishes to create a pathogen can do so. I gave a presentation to a PACOM [United States Indo-Pacific Command] commander years ago where I said entirely hypothetically, "If you give me the exact requirements for what you want to do to someone or a group—do you want to incapacitate? Do you want to kill? How many? For how long?—we can design you that pathogen. That is the power of biology." And



just thank God we have not seen anyone—single actor or state—use that power yet. But that is one of my fears, that should we see that day when actually it's easier to make a biological weapon than it is to get a gun, what will happen? Because our defenses will not be ready for that when it arises. If you look at some of just the existing pathogens, the ones that we've worried about for many decades such as smallpox, we now have highly effective vaccines against them. We have highly effective therapeutics. But just a single-point mutation can change that, and it is possible that our therapeutics would be useless against that resistant strain.

Synthetic biology is a powerful tool that is being used for beneficent research that is allowing us to have the types of innovations that we have today. The ability to take, for example, the mRNA vaccines and evolve them to a new sub-strain—Omicron or Delta lineage—is being promoted by these advances in biotechnology. But those advances in biotechnology can be used for harm, and finding ways to deter that use is what the entire efforts around biosecurity and biosafety are all about.

**CTC: Given your medical research background and your background on the security side, can you discuss other pathogens of concern when it comes to bad actors, such as antibiotic-resistant bacteria?<sup>6</sup>**

**Kerr:** There are reasons that certain pathogens have repeatedly over many decades been looked at by non-state actors as well as state actors for their properties to do harm. When you look at pathogens such as anthrax, cholera, tularemia, Brucellosis, and plague, the list goes on and on, there are reasons that those have been selected by both former and current biological weapons programs, and the ability to then modify them to make them antibiotic-resistant certainly throws up challenges to detection and treatment. The time in which it would take us during a response to figure out that an antibiotic-resistant pathogen has been used and then what we have in our arsenal in order to be able to treat it, all of that would profoundly complicate a response, and so that absolutely remains a concern and one on which, during our biodefense efforts, we think about from both a detection, a medical response, and then in microbial forensics and attribution disciplines.

**CTC: In January 2021, David Lasseter, then Deputy Assistant Secretary of Defense for Countering WMD, said, “What most concerns me are lethal, man-made, or genetically altered agents whose source is difficult to attribute.”<sup>7</sup> How do you view the challenge of attribution? Do you share that concern, specifically when it comes to genetically engineered pathogens?**

**Kerr:** I absolutely share that concern. If you look at the current situation, we do not know the origins of SARS-CoV-2 even two years later. We certainly have advanced our forensic capabilities, but you can see that they remain limited. And not only as it pertains to the origins of the actual virus, but what allowed this particular virus to proliferate and become epidemic within Wuhan that allowed the further spread then to become a pandemic? In 2009, we drafted a National Research and Development Strategy for Microbial Forensics—this was a combination of efforts of multiple intelligence agencies, the FBI, DHS, and several others—and funding went into that effort and there were significant efforts made and progress being made that would have certainly elevated our capabilities.

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Unfortunately, it's an example where that program was defunded in 2013, and so again, it goes back to fits and starts. You need sustained investment because those are disciplines and professionals that need to culture those long-term strategies in order to get us possibly ahead of where an actor may be and advance forensic capabilities. It is certainly a discipline that I think needs attention and more resources.

**CTC: How, if at all, has the pandemic changed your view of the security measures currently in place at laboratories and facilities handling dangerous pathogens?**

**Kerr:** Again, we don't understand where this virus came from. Certainly, questions have been raised as to whether or not it arose in a laboratory, whether it could have been a potential result from a laboratory accident, or neglect within a laboratory, but it simply reminds us that in all instances, the conduct of safe and secure laboratory practices must be maintained. Vigilance must be maintained around the globe. Biosafety is one aspect, and certainly understanding that when we talk about evolution in microbial sciences and the ability to manipulate organisms, we are dealing in areas that require higher and higher levels of safety and security. We're seeing the proliferation of more BSL-3 and BSL-4 labs worldwide, and with that needs to come the expertise to be able to work in those facilities and the resources to be able to maintain what are very, very expensive labs to operate at that appropriate biosecurity level. So, I think there is appropriate concern that the globe needs to think about standards, and we don't actually have any entity that now is responsible for those types of norms globally. Who would that be? Does it reside at the United Nations? Is it something that's within the remit of the World Health Organization? I think this is an appropriate time for the world to think about what has happened in this pandemic, and what could happen with the state of our research environment, and try to improve our overall understanding and practice of good norms for biosecurity and biosafety.

**CTC: How do you view the do-it-yourself bio community that has emerged in recent years and the potential for a deliberate or accidental threat emerging from these communities?<sup>8</sup> As you just noted, there are still improvement areas and challenges when we talk about BSL-3 and 4 labs globally, given their**

proliferation.

**Kerr:** I've had the real honor and privilege of working with the iGEM<sup>b</sup> community for exposing young scientists to synthetic biology for over a decade now, and seeing high school and college students take on projects who have never dealt with biology before. They bring in different disciplines and they work on these projects and they're doing what I would consider to be very high-end and progressive and innovative work; that is a community that has also really taken on the true elements of biosafety. From the very onset, when the students design something, there is an element of oversight where they are taught, is this responsible use at the level at which you will be working? Are the individuals trained in a proper way? And so, where there are systems in place around the DIY community, I think one sees very, very responsible conduct by the community for being not in an academic setting, or away from private sector or government oversight.

Do I fear that there could be that one bad actor out there that would be able to do something? Of course I do. It is balanced by the fact that there's a lot of equipment and resources that are needed to really do ultra-high-end molecular biology, but those are also now bought often in kits that are available to anyone who can purchase them. Getting the actual pathogen is a different story. There are three overlapping elements that are needed to create a bioweapon: (1) the intent, motivation, and access to resources to develop such a weapon; (2) access to the desired pathogen; and (3) the scientific and technical skills to grow, manipulate, and disseminate that weapon. When these three circles overlap—having the intent to actually do harm combined with the skill set to manipulate a particular pathogen—you always worry about that. But my highest concern is that intersection of those three circles where that bad actor who has access to a particular pathogen attempts to create something that could potentially be used as a weapon. We have seen very good engagement between the domestic and international DIY amateur biologists with institutionalized and government bodies to seek guidance and advice in biosafety and biosecurity. These engagements are critical to promote safe and secure laboratory practices and to protect both the DIY biologists and the community in which they live. It's progressing very well.

**CTC:** No terrorist group has come close to carrying out a highly lethal biological attack, and even the well-resourced Aum Shinrikyo cult in Japan in the 1990s fell well short.<sup>9</sup> However, the landscape appears to be shifting in relation to this area, as in 2018, German police thwarted an alleged plot in Cologne in which a jihadi terrorist in the West for the first time successfully produced the toxic biological agent ricin.<sup>10</sup> In your assessment, how has the bio terror threat landscape changed, specifically as it pertains to terrorist use, and what types of terrorist threat actors or groups are the most cause for concern from your vantage point?

**Kerr:** My time in the intelligence community really heightened my

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concern around the class of terrorists that really don't care about blowback effects. That is often the group that we describe as 'the apocalyptic actor.' At one point in time, there were 3,000 named apocalyptic groups around the world— for example, environmental terrorists who believe that humans are basically a contaminant to the Earth and therefore really don't care about synthesizing an antidote to themselves or to protect followers, but are solely interested in annihilation of humans. Fortunately, we have not seen any of those gain capabilities yet, but clearly with a philosophy or an intent like that, that certainly raises a high level of concern around, if they were to acquire a pathogen and the skill set to use it, what could potentially be done.

With regard to potential threats posed by an individual bad actor, a group—whether it be militant or philosophical, all the way through to state actors—I think there's high concern in each one of those areas, but there are significant challenges, too, to finding one bad actor or understanding the true capabilities of an organized group. And then there are really profound difficult targeting and collection challenges associated with nation-states. So, there's no easy answer to these threats. Long-term, time-on-target analysis and collection needs to be done in order to really understand them better.

**CTC:** You make such an important point about the blowback question, and a key obstacle for the most sophisticated of actors, state actors, for deploying pathogens as biological weapons, is concern their own population or others they don't wish to target could also become infected. But one analyst has noted, “the merger of the biological data revolution with computing power,” especially machine and deep learning, has opened up the possibility of “ultra-targeted biological warfare” whereby “malicious actors could deploy a biological weapon over a broad geographic area but only affect targeted groups of people, or even individuals.”<sup>11</sup> And in 2020, the U.N. Institute for Disarmament Research warned that “access to millions of human genomes—often with directly associated clinical data—means that bioinformaticists can begin to map infection susceptibilities in specific populations. This kind of information could also be used to develop ethnically targeted weapons.”<sup>12</sup> How concerned are you about the potential future

<sup>b</sup> Editor's Note: “The iGEM Foundation is an independent, non-profit organization dedicated to the advancement of synthetic biology, education and competition, and the development of an open community and collaboration. This is done by fostering an open, cooperative community and friendly competition.” For more, see the iGEM website at [igem.org](http://igem.org)

## threat of ultra-targeted biological warfare?

**Kerr:** It is a concern, and clearly, the more that we in legitimate, beneficent science understand host-pathogen interaction, the way in which our immune systems as humans respond to pathogens, and the way that we can manipulate the immune system in order to respond gives us greater insights into how one could philosophically, theoretically operationalize in a laboratory the concept of genetic-based targeting. It is a concern. I think we are still a distance away, and hopefully, ethics and norms that demonize even going down such routes will preclude the development of such weapons. But we have seen, for example, in the case of the reports from China of gene-edited babies,<sup>13</sup> there may be societies that do not follow the same ethical standards and norms that we do. And so, it is a concern that as biology progresses and the ability to manipulate both pathogens as well as our own human immune systems increases, that such threats, which are still in the realm of science fiction today, could actually become reality. I think it is something where we need to have people attuned to these concerns and then have a community that is aware of and constantly following its progress so as to assess whether or not there are adversaries seeking such capabilities.

**CTC:** You mentioned that strategies are pieces of paper unless they're resourced and supported, so to pick up on that thread, a report published in the U.K. in February 2022 called for the Biological Weapons Convention (BWC) to be revamped as it is currently "not fit for purpose" because it is "poorly funded and supported at the UN and has no organisation to regulate and police it." The report contrasted the Biological Weapons Convention with "the Chemical Weapons Convention (CWC) policed by the Organisation for the Prohibition of Chemical Weapons (OPCW) [which] has removed most proscribed chemical weapons from the globe and is well-funded and well-supported by most members of the UN."<sup>14</sup> This November, governmental delegates are due to gather in Geneva for the Biological Weapons Convention Ninth Review Conference.<sup>15</sup> Ahead of the conference, the U.S. government has stated, "the status quo is neither acceptable nor up to the task" and that it is necessary to "examine possible measure to strengthen implementation of the Convention, increase transparency, and enhance assurance of compliance" in order to address "not only the latest challenge [of the COVID-19 pandemic], but those that may lie ahead whether natural, accidental or deliberate

## in origin."<sup>16</sup> How can the Biological Weapons Convention be strengthened, and how hopeful are you that this can be achieved?

**Kerr:** I am hopeful that it can be achieved. The BWC is the one overriding norm that we can point to, to say, "As a biologist, as a life science person, as any discipline associated with the life sciences, the philosophy is 'do no harm.'" The BWC is the set of principles by which individuals and nations follow that guidance and through which nations can report their progress towards achieving transparency in their work with pathogens—solely for defensive purpose. So, can the BWC be strengthened? Absolutely. Those are matters of intense policy debate right now to try and figure out what does that actually mean, while also allowing the advances and beneficial science to be achieved and not do anything that would harm *that* progress but putting up any barriers to the nefarious or bad use of the life sciences. What exactly those measures should be, I don't have an answer for you today. They're a matter of ongoing debate, and this is something where there are literally weekly interagency meetings with the NSC to try to define what those could be.

There are ways of trying to promote greater transparency, but doing so in a responsible manner such that, for example, we aren't revealing intellectual property and trade secrets that we need to protect both within a government, within academia, and within the private sector. So, it's this delicate balance that we walk, and trying to find those you know exact steps to strengthening the BWC is something that is being worked on as we speak.

## CTC: Is there anything else you'd like to add?

**Kerr:** The counter BW world is small compared to the nuclear world. Of 'NBC' [nuclear, biological, chemical], the 'B' is always the smallest portfolio of the three files, and it always has the smallest community and the smallest amount of resources to address the threat. I wonder whether the pandemic may change that a little bit to create a more robust community and hopefully get the resources that are needed—and not just from a pandemic threat potential, but also the recognition that biology has the ability to topple governments and to create instability in entire global systems. While we've seen what Mother Nature can do, we certainly need to do everything we can to make sure that a man-made pandemic is prevented to the maximum extent possible. **CTC**

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# A View from the CT Foxhole: Brad Ringeisen, Executive Director, Innovative Genomics Institute

By Paul Cruickshank and Don Rassler

*Brad Ringeisen, Ph.D., is Executive Director of the Innovative Genomics Institute (IGI). Before his retirement from government service in July 2020, Dr. Ringeisen spent four years at the Defense Advanced Research Projects Agency (DARPA), most recently in the role of Director of the Biological Technologies Office where he managed a division working at the cutting edges of biology, physical sciences, and engineering. Dr. Ringeisen's office overlapped with IGI on several occasions, on the Safe Genes program, which works to develop safe and more precise genome editing tools while preventing misuse of the technology, as well as IGI's research into innovative solutions to mitigate acute radiation sickness.*

*Prior to his role at DARPA, Dr. Ringeisen served between 2002 and 2016 as the head of the Bioenergy and Biofabrication Section at the U.S. Naval Research Laboratory and spent two years developing point-of-care diagnostics for the Defense Threat Reduction Agency in the early 2010s.*

*In addition to his deep leadership experience, Dr. Ringeisen is a physical chemist with a Ph.D. from the University of Wisconsin-Madison and a pioneer in the field of live cell printing.*

**CTC: Over the course of your career, you've dedicated many years to the application of science to protect and advantage the U.S. warfighter, as well as serve the general public at the U.S. Naval Research Laboratory, at the Defense Threat Reduction Agency (DTRA), and at the Defense Advanced Research Projects Agency (DARPA) as well. What drew you to public service?**

**Ringeisen:** I grew up in a university town; I grew up in Clemson, South Carolina. My father worked for a public school as the chair of the math department at Clemson University. I considered him a public servant as an employee of the state of South Carolina. And so, when I was finishing graduate school, I looked at non-traditional postdocs outside of the academic world. But I'll be honest, I had just had my first child with my wife, and I needed a job. I needed a paycheck. So, it started as a job, and the DoD postdocs paid really well. It also gave me an opportunity to start my career on a strong footing. And it was exciting. I joined a lab that was putting pretty much every piece of biology in front of a laser. Who wouldn't want to do that? It was a great opportunity to explore how to make thin films of biological materials and biosensors, and then we ultimately got into tissue engineering and bio printing. So, it was a really exciting opportunity.

From a broader perspective, the U.S. Naval Research Lab did great science, there's great people there, it had a great mission, and you could basically wake up every day and ask yourself, "What can I do today for the military?" It gave you a mission every single

day—help the warfighter, help the soldier—and I really enjoyed that mission. I did it for 15 years of my life, and I wouldn't trade it for anything. Protecting against chemical/biological threats, helping understand traumatic brain injuries, helping soldiers heal better, creating clean energy options for the Navy—these are things that I did on a day-to-day basis. For me, biology and biotechnology for the Department of Defense, it was about helping people. It was about trying to help the environment. That's what we did. And so, I could have done that in an academic lab, but for me, the Department of Defense gave me that umbrella to be able to help guide pursuits. You always had that mission that you were looking for.

**CTC: You started at the U.S. Naval Research Lab just prior to 9/11. What impact did those attacks have on your view of the role of science in national security?**

**Ringeisen:** Everything changed. The Naval Research Lab was founded as the first national lab. It was a fundamental, basic science laboratory. There's a bust of Thomas Edison as you drive into the lab. And what he said was, 'We need a lab for the Department of Defense and a national lab that gives you that level of expertise so you can avoid strategic surprise.' Then 9/11 hits. I remember sitting in traffic for six hours trying to get home that day. I remember picking my kids up and driving my wife to West Virginia because the fighter jets were scrambled and flying around D.C. We were all scared. It was an impactful event for all of us.

And then the science changed. It became less about the fundamental basic science, and it became about what can you do right now in Iraq for chemical and biological threats, for Afghanistan for improvised explosive devices and all the brain and the spinal cord injuries. So, we started doing bio-printing for spinal cord repair. We started looking at blood-brain barriers to look at traumatic brain injury. The shift was pretty monumental. It's one of those events, much like COVID-19, where it just changes the trajectory of science. And I don't think the Naval Research Lab has ever really been the same since because people are constantly focusing on this very application-driven research now.

**CTC: Can you talk specifically about the Biological Technologies Office (BTO) at DARPA, what it does, and how it developed during your time there?**

**Ringeisen:** I'm really proud of what I did at the Biological Technologies Office. This was an office that was started in 2014. Prior to that, biology at DARPA was kind of hit-or-miss. It was supported by some office directors. It was supported by some program managers. There wasn't a cohesive office to explore what biotechnology could do. [DARPA Director] Arati Prabhakar in 2014 founded the BTO, which I think was a phenomenal idea. The first director [of the BTO] was Dr. Geoff Ling. I still consider

Geoff one of my mentors. He's an amazing individual. He served as a military doctor in the Middle East. He has saved lives. Geoff is an amazing person. But when I joined the office in 2016, two years after, they had a scattering of new programs that they had started. It was kind of fits and starts. The number of program managers in the office was dwindling. So, when I came in, it was clear that we had to spend the money, create innovative new programs, and just hire. We needed to hire program managers. I was lucky enough to have a strong network of colleagues that I was able to reach out to and interview and tap to build up the portfolio of program managers that we had in that office. And boy, did they deliver. I am thankful to this day for a group of program managers that I hired. We went from maybe four or five program managers up to, by the time I left, 13 or 14 program managers—allowing us, in my opinion, to pretty much produce as much good science and as many new programs as any office in the agency. And we were one of the smallest budgets in the agency. I think during my tenure there, we pushed out 25 or 26 new programs totaling well over a billion dollars of research dollars. This was really innovative work.

We had four major program areas. We did pandemic prevention, we did warfighter health, we did warfighter performance, and we did something that we called operational biotechnology, which was basically the ability to use synthetic biology or the natural world to protect warfighters, to protect infrastructure, to do bio manufacturing for supply chain stability, and then, what could biology do to potentially provide for soldiers in field-forward situations.

Let me give you a couple flavors of things that we did. We looked at new ways of detecting and diagnosing disease. We invested in DNA and mRNA vaccines. We developed new CRISPR tools. We made foundational investments in things called engineering living materials. I just saw that Biomason went to Series C funding at \$65 million;<sup>1</sup> we were some of the initial investors in that company. We discovered rapid ways to find antibodies to protect and treat warfighters exposed to emergent disease. And we did some pretty cool brain machine interfacing; robotic arms with tremendous degrees of freedom, being able to control those prosthetics with just your brain and thoughts alone; some pretty cool stuff. It was a playground of science. It was a sandbox of science across pretty much every possible area of biotechnology, and I found myself lucky to be able to lead it.

**CTC:** You're currently the executive director of the Innovative Genomics Institute, founded by Nobel Laureate Jennifer Doudna to drive forward scientific research, advance public understanding of genome engineering, and guide the ethical use of these technologies.<sup>2</sup> Could you describe some of the cutting-edge research being done there and the broader work you do?

**Ringeisen:** Thank you for mentioning the ethical aspect of this work as well, because Jennifer Doudna, who is the founder of this organization, is I think the most inspirational and best scientist in the world. Jennifer founded this institute in part to not just innovate and push the science, but also to push it in an ethical way, an accessible way. We want to lower healthcare costs. We want to expand the accessibility of these technologies to farmers in the world that need them, to populations in the world that need them. It's not just for those that can afford them. That's at the core of what

Jennifer and I want to do at the Innovative Genomics Institute.

Now, it's a pretty amazing place as well. I know I just talked about DARPA, but one of the reasons I was attracted to the IGI is we don't just work in human health. Yes, we do tremendous work in human health: We're developing cures for sickle cell disease, for rare genetic diseases; we're looking at ways to affect more complex and common diseases like cancer and neurodegenerative disease. But we're also looking at feeding the world and creating food security and also trying to mitigate climate change and make agriculture more resilient to climate change. And so those are the areas that I'm tremendously excited about, tremendously passionate about, and when I interviewed for this job, Jennifer agreed that these were areas we also wanted to address. What other institute in the world uses a powerful tool like CRISPR and genome editing and looks at not just health, but also at feeding people, providing the nutrition that they need and doing it in a sustainable way. And that's the IGI.

I count myself really lucky for being able to work with Jennifer and all the amazing professors and scientists that are there. We have people that are working on photosynthesis and trying to improve crop yields and carbon capture through photosynthesis. We're currently performing the most extensive study of the rice microbiome, looking at carbon flow in that system, looking at methane and nitrous oxide emissions; we're going to find some secrets and hopefully unlock approaches to reduce emissions from rice patties around the world.

And then we're creating new editors and new ways to do editing, like epigenetic editing, ways that you don't have to do double-strand breaks for editing. And we have a tremendous number of people that are innovating in ways to deliver editors to different cells, like plants and mammalian cells, as well as new ways to edit in general. There was a recent publication by Jill Banfield and Jennifer Doudna that showed they could edit communities of microorganisms.<sup>3</sup> What are communities of microorganisms? That's essentially the microbiome. How amazing would it be if you could unlock the potential of CRISPR to tune and tweak and manipulate the metabolism that's going on in these complex environments, whether that's a gut of a cow or the GI tract of a human or maybe on the skin or in soil? The potential there is pretty amazing. That's the kind of innovation that the IGI works on.

**CTC:** As mentioned, you worked at DTRA, the U.S. Naval Research Laboratory, and the BTO at DARPA. Can you describe how the threat landscape has evolved over the last 10, even 20 years, particularly with respect to bioterrorism?

**Ringeisen:** Let's start with the anthrax attacks in Washington, D.C. I moved to Washington, D.C., in 2000, 9/11 hits, and then shortly thereafter the anthrax attacks occurred. So that shaped and dramatically influenced the CBRN—chem, bio, rad, nuke—defense program in the United States within the Department of Defense. There was a shift to state-sponsored, big, impactful military-scale attacks involving things like aerosolized anthrax, just as an example. Could you weaponize smallpox? These scenarios were the focus from 2001 all the way through 2015. Most of the work and people were sort of tunnel-visioned on these very, what I would call, 'traditional' bio threats.

When I joined DTRA in 2012, there was a small group of people that were influenced by DARPA pretty significantly that came to DTRA and said, "Those are big threats and we have to think



about those, but we really need to think about emergent disease, too. There are diseases emerging from animals that, with climate change, are going to just extend and happen more frequently. You've got populations colliding with these animal populations." These were the things we were saying back in 2012, and we started to try to develop platforms—diagnostics platforms, bio surveillance platforms—to try to understand and better characterize emergent disease. It was not fully accepted by the CBRN community. If we flash forward another two years, you've got Ebola;<sup>a</sup> people are starting to see this zoonotic transfer of disease. And all of a sudden, the Department of Defense is starting to pivot, and they're starting to realize that emergent disease threats and spreading zoonotic disease may actually be a bigger threat than that more state-sponsored, big, militaristic kind of action. I'm pretty proud of the fact that in 2012, we were starting to think in that kind of way.

And then when I got to DARPA, we really started to push platforms that could rapidly respond to emergent disease. Because you don't really ever know: Is it going to be Ebola? Is it going to be hantavirus? Is it going to be Lassa fever? Is it going to be coronavirus? Well, it turned out to be coronavirus, but you need rapid platforms to be able to pivot, and I think the Department of Defense started to do this. DARPA started to do this. And I credit the Department of Defense for seeding some of the technologies that were able to be put into play very, very quickly when COVID-19 hit. So, I'm actually pretty proud that they did pivot back in that 2016 to 2018 range, probably most likely because the 2014 Ebola outbreak, which started this attitude shift to help 'stock the cupboards' a little bit with some emerging technologies that helped us respond more rapidly when COVID-19 hit.

**CTC: We're two years into the global pandemic today and a year after the rollout of some highly effective vaccines for COVID-19. DARPA was an early buyer on mRNA vaccines, with a \$25 million investment in Moderna in 2013.<sup>4</sup> How consequential was that early investment to the development of the COVID-19 vaccines less than a decade later?**

**Ringeisen:** Very consequential. I will mention Dan Wattendorf, a colonel in the Air Force who retired and became a program manager at DARPA. Dan had the foresight to invest in Moderna when not very many people were investing in this type of technology. There's no money in infectious disease. The big biopharmaceutical companies were sitting on the sidelines for the most part; they were outsourcing vaccine production and vaccine manufacturing. And here you have Dan Wattendorf finding this tiny little company and saying, "I believe in your technology." But I will also say that it's not like Dan was clairvoyant and just pushed all of his money onto Moderna. That's what DARPA does. They invest in portfolios of technology. Dan was looking at antibodies; he was looking at ways to filter viruses out of blood. He was looking at gene-encoded antibodies. He was looking at DNA vaccines. He had an entire



*Brad Ringeisen*

portfolio of technologies for pandemic preparedness, and a few of them ended up panning out and playing a big role. And the two biggest ones were Moderna, which BTO funded to develop an mRNA vaccine for chikungunya.<sup>5</sup> We saw safety data early on, so when COVID hit, we all thought, "Well, Moderna is going to be on this." Because we had seen the phase one clinical trial data. So those investments were tremendously consequential.

The second company backed by DARPA that turned out to be important was this company called AbCellera.<sup>6</sup> AbCellera was a company that had high throughput ways to screen B cells for antibody production, and you could basically have one cell per microwell and hundreds to thousands of wells per plate and then you could screen thousands and thousands of cells and antibodies to be able to pick out the most neutralizing antibody against SARS-CoV-2. Guess what? Eli Lilly picked up the best neutralizing antibody that AbCellera found, and it was manufactured under a label by Eli Lilly.<sup>b</sup> So you never know when something is going to pay

a Editor's Note: According to the World Health Organization (WHO), "the 2014–2016 outbreak in West Africa was the largest Ebola outbreak since the virus was first discovered in 1976." According to the Centers for Disease Control and Prevention (CDC), "overall, eleven people were treated for Ebola in the United States during the 2014-2016 epidemic." "Ebola virus disease," WHO website; "2014-2016 Ebola Outbreak in West Africa," CDC website.

b Editor's Note: According to a company press release, "AbCellera initially mobilized its pandemic response platform against COVID-19 in March of 2020, resulting in the discovery of bamlanivimab, the first monoclonal antibody therapy for COVID-19 to reach human testing and to be authorized for emergency use by the U.S. Food and Drug Administration (FDA). Bamlanivimab alone and together with other antibodies has treated hundreds of thousands of patients, preventing COVID-19-related hospitalizations and death." The press release also noted that "AbCellera's pandemic response capabilities were developed over the past three years as part of the Defense Advanced Research Projects Agency (DARPA) Pandemic Prevention Platform (P3) program. The goal of the P3 program is to establish a robust technology platform for pandemic response capable of developing field-ready medical countermeasures within 60 days of isolation of an unknown viral pathogen." "Lilly to Supply 614,000 Additional Doses of AbCellera-Discovered Bamlanivimab Together with Etesevimab to the U.S. Government for the Treatment or Post-Exposure Prevention of COVID-19," AbCellera via Business Wire, November 2, 2021.

off, but that's why DARPA is special: You can seed, and you're given the freedom to make investments. And it's not done in a vacuum. It's not just Dan making those decisions. It's Dan with his team of contract-support Ph.Ds. It's the deputy director and the office director, and it's the deputy of the agency and the director of the agency. And I can tell you from past experience that those decisions for the pandemic preparedness portfolio were made all the way at the level of the director of the agency. Arati [Prabhakar] was very active in the programs that Dan selected. Talk about a sandbox. The sandbox of DARPA enabled those investments to be had. So it's a very special place, and you've got to preserve and protect it.

**CTC: Do you think the pandemic has changed the government's prioritization of science research and funding from perhaps a more 'fits and starts' approach before to a recognition today that a more sustained investment model is required?**

**Ringeisen:** I'll go back to the early days of DARPA; we were investing in rapid response platforms and bio surveillance. We wanted to try to predict and know what was going to be next, or rapid response platforms that could, if something did emerge, see if you could rapidly try and respond to it. That was a unique perspective. I think now you're hearing people like Anthony Fauci and others echo some of those sentiments. We're talking much more about pan-viral approaches, things that could be resilient against mutation. These are good ideas. If you could do pan-viral approaches and rapid response platforms, then you won't be caught as unprepared as we were back in 2019 and 2020. So, I do think there's been a shift, and I think it's been a shift to the benefit. People realize now that you can make money in combating infectious disease, and that helps because that gets some of the private capital and equity off the bench as well. But I think the government realizes you need an entire pipeline. You've got to have the basic discovery work in a place like NIAID [National Institute of Allergy and Infectious Diseases], but you also need translational and innovative work at a place like DARPA. And then you also need to connect that to a place like BARDA [Biomedical Advanced Research and Development Authority] or JPEO-CBRND [Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense] to be able to hand off those technologies. So, my job at DARPA was that hand-off. The program managers would develop, but then I would communicate with JPEO. I would communicate with Jason Roos at the time, who was the deputy at the JPEO, to be able to find a landing spot, to be able to help fertilize that ground so that when something matured, there would be a home for it to be able to take off. So, it's getting all the way from basic research to that translational work. And I think DARPA did a really great job of accomplishing that.

**CTC: As you think about the past two years, what are the key lessons that you think should be learned from the pandemic in protecting the United States from biological threats moving forward?**

**Ringeisen:** It's those rapid response platforms. It's a tragedy that we have not funded pan-viral approaches more than what we have. When I gathered our sort of 'war room' team very early—probably January, February of 2020. It was a solemn time, but I also told my program managers that this was a singular moment, a

defining moment for DARPA BTO. We sat down for the entire day, and we white-boarded what the country really needed. We asked ourselves what we could do in the near-term (those were things like the antibody discovery platforms and the mRNA vaccines and the gene-encoded antibodies that we were developing), but then we also had half the white board on 'if we just could dream the dream and we had a billion dollars, what would be the target?' And that side of the white board was dominated by mutation-resilient technologies, pan-viral approaches for detection and treatment or prevention of disease. We didn't get the billion dollars. So we did most of the work on the left side of the white board, which was the more near-term projects, with the Pentagon plus-up funding we did receive, and I never got the bigger payday to be able to pursue some of that longer-horizon work. Let's hope that the people that are still in the government now are able to do that. But I think that really is where you need to go.

The last piece of that is bio surveillance. We need to be doing more testing. We need to be focused more on zoonotic disease, but you have to do it in a safe and responsible way. Dual-use research of concern is real, and you need boards of people to look at and vet this research before and after funding.

**CTC: As somebody who was in an early 'war room' before the pandemic really took off, as somebody who had been tracking and thinking about biological threats, investing in mitigation measures and detection, are there aspects of where we are now two years later that are surprising to you, or are you not surprised by where we are now?**

**Ringeisen:** That's a hard question. If you look back on it, you can say, 'We could have done a lot better in diagnostics. If we had identified early outbreaks and isolated earlier, we probably could have prevented a lot of deaths and a lot of early spread of the disease. If we'd had better distributed diagnostics like I was thinking about back in 2012 and 2013, perhaps that may have been managed better, but that didn't happen.' But when you look back on it honestly, with the spread that was going to go on in the world, we weren't going to be able to become fully isolated. This was going to be something that was going to affect the entire world. The entire world was not prepared.

So, you can throw stones on the early days of what happened, about how we could have handled it better, and you absolutely probably could have prevented many deaths. If you could have pushed the timeline another three or six months, we would have been more prepared. Those antibody treatments, the vaccines, they would have been closer to being ready. And so, it was a tragedy. It was. But when you look at it from the perspective of now two years later, the disease was going to spread across the world regardless. This is going to become endemic. The best we can do is to try to mitigate and try to lessen the impact on the populations that are most dramatically affected. I think the mRNA vaccines are doing that. You're seeing now testing becoming less of an issue as it becomes endemic. How often do we test for influenza? 10-20,000 people in United States die of influenza every year. Is COVID going to become like that? I think that's the goal; as sad as it sounds, that's the goal. We want it to become something like influenza, where you get a shot, you get a vaccine, it helps mitigate. The risk then is lessened as much as it can be for those that are most at risk. For me, it's 'how can we do better next time?' Is it going to be COVID-25?

Is it going to be Lassa fever? Is it going to be hantavirus? How can we do better for the next one?

**CTC:** Synthetic biology has increasingly come to the fore in national security conversations. For our readers, can you briefly describe what synthetic biology is and outline the benefits and risks associated with its use?

**Ringeisen:** Synthetic biology is basically a very natural step in a long history of understanding how we use and benefit from genetic information. It really started with the Human Genome Project; that was focused on sequencing and bringing down the cost of sequencing, sort of bringing sequencing to the masses. You have to be able to ‘read’ the genome before you can do anything like synthetic biology, which is more *writing* the genome. So, it started back 20-25 years ago with the genome sequencing revolution.

The next step from there was something called systems biology, where you wanted to try to more thoroughly understand the complexities that is life: the complexities that occur inside of cells, inside of plant cells, inside mammalian cells, how they fit and form tissues. That is a tremendously complex problem, and there was a field that emerged together with genome sequencing that was systems biology that used computational approaches to try to untangle essentially the mechanisms of life. And then systems biology slowly just merged and became synthetic biology when gene editing tools like zinc fingers and TALENs [transcription activator-like effector nucleases], and then ultimately CRISPR came on board. Now, all of a sudden, you can read, you can start to understand, and you can actually start to manipulate and modify the genome. Synthetic biology is essentially a catch-all term now that refers to being able to *create* with biology—almost like an engineering tool kit for biologists. An electrical engineer has their breadboard and they’re controlling it and use it as a testbed; biologists now have that same kit. Between the use of computers and the use of molecular tools and sequencing, you essentially have that tool kit.

There was a program at DARPA that we called Living Foundries<sup>7</sup> that was basically one of the early starters of synthetic biology, and the core of that program was a design-build-test-learn cycle. That’s what it was: Let’s make biology like engineering, where we can do a design, build, test, and learn. That’s essentially synthetic biology.

**CTC:** And what are your views on the benefits and risks associated with the use of synthetic biology?

**Ringeisen:** First of all, there’s enormous benefit. We are talking about food security. We are talking about climate. We were talking about green manufacturing. We are talking about revolutionizing the way health care is performed. Just look at T-cell and CAR T<sup>c</sup> therapies and now CRISPR-based approaches, like being able to cure sickle cell disease in small populations of people right now. So, the potential is enormous. One of my friends and colleagues, Fyodor Urnov, was just quoted in an article about whether CRISPR is actually going to ‘live up to’ the expectations.<sup>8</sup> Like ‘maybe this is actually going to happen. Maybe it’s actually going to live up to

**“Synthetic biology is essentially a catch-all term now that refers to being able to *create* with biology—almost like an engineering tool kit for biologists. An electrical engineer has their breadboard and they’re controlling it and use it as a testbed; biologists now have that same kit. Between the use of computers and the use of molecular tools and sequencing, you essentially have that tool kit.”**

its expectations.’ And I think people are starting to realize that this might actually live up to its expectations and that there’s an enormous amount of potential. So, the list goes on and on in terms of the upside.

But we want to do this in an ethical way, in a way that is safe, that is in concert with regulators. *That* is the key. You need to bring in the FDA [U.S. Food and Drug Administration]. You need to bring in the USDA [U.S. Department of Agriculture]. You need to bring in the EPA [U.S. Environmental Protection Agency]. You would need to have focus groups for the populations of people that are going to be affected by the food that you make or the treatments that you innovate. This has to be done from the start, and that’s what the IGI does. The IGI has a public impact team led by Melinda Kliegman. She thinks about the ethical questions. She thinks about the regulatory pathways at the beginning. We have her embedded in the teams of scientists. I just met with her for 30 minutes before talking with you all to try to understand how we can do better at getting her speaking more frequently with IGI scientists so that when we make programmatic decisions about what scientific projects we’re going to do, that they are in line with the ethical and regulatory pathways that she sees as being viable. So, to me, there are risks. There will always be risks with new technology. There will be risks with the molecular tools that provide the ability to edit the genome. But if you do it openly, if you publish it openly, if you work with regulatory bodies, then the risk can be mitigated and minimized.

**CTC:** Your close colleague Jennifer Doudna’s groundbreaking development of the CRISPR-Cas9 system for genome engineering technology saw her and Emmanuelle Charpentier awarded the 2020 Nobel Prize in Chemistry and “forever changed the course of human and agricultural genomics research.”<sup>9</sup> CRISPR-Cas9 gene-editing technology holds massive promise in transforming human health and curing diseases, yet huge scientific advances also generate unpredictable and unforeseen risks. In a June 2020 *CTC Sentinel* roundtable, Audrey Kurth Cronin noted that “with the ability to alter DNA through easily accessible tools like CRISPR/Cas9, individuals can change known bacterial or viral pathogens to make them more dangerous. Far more people have access to the means to do this, much more rapidly than

c Editor’s Note: “CAR T cell therapy is a type of immunotherapy used to fight cancer with altered immune cells. These specially altered white blood cells, called T cells, are modified to find and attack cancer cells in the body.” “CAR T Cell Therapy: Using Immune Cells to Fight Cancer,” Abramson Cancer Center, Penn Medicine.



ever before.”<sup>10</sup> In your view, what is the benefit/risk matrix of CRISPR-Cas9 technology?

**Ringeisen:** That’s a great question. I’ll start again just by reiterating the potential. We cannot *not* use this technology to help society. We have to use this technology to help society. The benefits are just too many: We could save lives; we could mitigate or potentially reverse climate change. We *have* to use it. So, the question then is, how do we use it safely? How do we try to set up the guardrails to be able to use it safely? And again, I’ll go back to DARPA and Safe Genes.<sup>d</sup> Helping put up some of those safety bumpers—some of those guardrails, the regulatory agencies, the BWC dual-use research of concern there—we have the guidelines to be able to help do this. You can go to those resources and say, ‘Is what I’m doing a dual-use research concern? Is what I’m doing going to produce ethical quagmires?’ We need to make sure that scientists are asking those questions. We need to make sure that the do-it-yourself scientist that might be in the garage is asking those questions. But the resources exist to do that. The regulatory agencies exist to be able to do that. The peer review process to publish manuscripts is there to be able to help buffer this as well. Program management offices in the government are there to help vet and think about these things.

So, I guess what I’m trying to say is having spent many, many years funding government research, the tools are there, the management structures are there, the review process is there in the funded research work. But it’s the unfunded, do-it-yourself-er—a grad student experimenting on the side, which all good grad students do—that we also need to think about. We need to help promote conversations and discussions that bring to light potential ethical, potential dual-use research of concern. These are conversations that have to be had. We have to have open forums to discuss these things. And as long as you’re going to have internal review boards to vet your science, to be able to get regulatory approval, to be able to do animal studies before you do human studies, to ensure safety, to have the characterization experiments in place to be able to ensure safety and minimize off-target effects, I think the tool kits are there to be able to do things safely. So yes, there are risks, but hopefully, those risks can be minimized by doing open science, by publishing, by holding these open forums to be able to discuss all of these issues.

**CTC:** You just stressed how important it is for do-it-yourself scientists to be asking the right questions about the safety of their research. In recent years, there has been tremendous growth in the DIY bio-community and biohackers. Do you see these communities as advantageous to pushing scientific boundaries (e.g., “Hewlett Packard Garage – Birthplace of Silicon Valley,”) or as a risk for unintentional development of biological pathogens? Or both?

**Ringeisen:** DIY is a good thing. There could be advances that stem from it. Crowd-sourcing is real. I’m a physical chemist. I’m a trained

**“We cannot *not* use this technology to help society. We have to use this technology to help society. The benefits are just too many: We could save lives; we could mitigate or potentially reverse climate change. We *have* to use it. So, the question then is, how do we use it safely? How do we try to set up the guardrails to be able to use it safely?”**

physical chemist. The experiments that I did in graduate school looked at surface dynamics, gas-liquid interfaces, and essentially, interfacial chemistry. I now lead a genomics institute at the cutting edge of genome engineering and CRISPR-Cas. So outside perspectives and looking at problems from different perspectives adds value to science. So, the last thing I want to do is to squash DIY scientists or people from asking questions that are not necessarily trained to be asking those questions. I think there’s true value in doing that. It’s just that they also need to be in the fold. They need to be in the mix of the conversation so that they understand the potential risks of something that they may be doing. And I think that’s a role of a place like IGI. I think it can help do that. We can have open forums, we can convene people from that community so that they can mix and interact with the Ph.D. scientists and the regulators, so that they can speak a little bit more knowledgeably about what some of those risks might be.

**CTC:** In *CTC Sentinel*, we examine the threat of terrorism across a range of different manifestations, including the misuse of technologies by nefarious groups or actors. How would you describe the risk of a non-state actor using synthetic biology and other advanced tools for malintent? How likely or unlikely is such a scenario?

**Ringeisen:** It’s a great question, and it’s probably the most frequently asked question that I received while I was at DARPA. Biology is complicated. Remember I was talking about systems biology? You look at a mechanistic map of what a living cell does on a day-to-day basis; it’s tremendously complex. When you then scale that to an entire organism or an entire population of organisms, it exponentially becomes more and more complex. So let me just emphasize that biology is complex.

Trying to determine genotype to phenotype is complicated. So, from A’s, G’s, C’s, and T’s<sup>e</sup> to actual production of proteins and to actual realization of what life does, trying to make those connections is very, very difficult. Just going in and making one change in the genome, it’s very difficult to understand often what the phenotypic outcome of making that change is going to be. So,

<sup>d</sup> Editor’s Note: “DARPA launched the Safe Genes program in 2017 to establish a ‘safety by design’ strategy for guiding the development of an array of powerful, emergent genome editing technologies ... to mitigate the risks and security concerns related to the accidental or intentional misuse of such technologies and, at the same time, enable the pursuit of novel genetic solutions that support public health and military force protection and readiness.” “Safe Genes Tool Kit Takes Shape,” Defense Advanced Research Projects Agency, October 15, 2019.

<sup>e</sup> Editor’s Note: There are “four types of bases found in a DNA molecule: adenine (A), cytosine (C), guanine (G), and thymine (T).” NIH website.

genotype to phenotype is difficult.<sup>11</sup> Delivery of these reagents to the specific cell or to the specific organism that you're looking at is tremendously difficult. The IGI has entire teams looking at three or four different, very complex chemistries to try to get these reagents into the very specific cell types that you want to get them into. So, delivery is a tremendously, tremendously big challenge.

The efficiency of editing is tremendously difficult—again, entire teams of people looking at trying to go from one or two percent efficiency to five or 10 percent efficiency up to maybe 50 or 70 percent efficiency. So the picture I'm trying to paint here is that the biology is complicated, but then you also have delivery. You also have the efficiency of editing. You have the genotype to phenotype challenge to try to understand what you would even try to target. Consider the scenario where there is one individual with malintent—I think it's just impractical to think that person is going to be able to make enormous strides in trying to do something very nefarious and very bad. That does not mean we can discount that threat, but we need to think about the threat and how to mitigate it and how to publicly start these conversations so that when a well-intending person in their garage starts doing things, they're thinking about some of the risks associated with it—whether it's a risk to themselves or a risk to their neighbors or a risk to others. So that's the answer that I give. I still believe in that answer. Now that I'm at the IGI, I see the talent that it takes to be able to make significant inroads on these technologies and the use of these technologies, so I'm even more convinced that it is a challenge for a non-state actor to be able to try to make real inroads and do something nefarious.

**CTC: One analyst has noted that “the merger of the biological data revolution with computing power,” especially machine and deep learning, has opened up the possibility of “ultra-targeted biological warfare” whereby “malicious actors could deploy a biological weapon over a broad geographic area but only affect targeted groups of people, or even individuals.”<sup>12</sup> In 2020, the United Nations Institute for Disarmament Research warned that “access to millions of human genomes—often with directly associated clinical data—means that bioinformaticists can begin to map infection susceptibilities in specific populations. This kind of information could also be used to develop ethnically targeted weapons.”<sup>13</sup> A concern is that ultra-targeted biological weapons may be more palatable to rogue states and other actors because of the lower risk of ‘blowback.’ What thinking needs to be done about this future potential threat?**

**Ringeisen:** Another great question, and it's a question that's circulated inside the Beltway quite frequently. Verbatim to what I just said, copy and paste here. So that's said and done: All of those challenges would be equally as challenging for this scenario as well, number 1. Number 2, yes, computational advances, algorithmic advances, artificial intelligence, machine learning and ways to scan data in very rapid, very meaningful ways, of course that's going to make it easier to identify *potential* similarities in somewhat more homogeneous populations. But I want to also emphasize that small variations in genomic information can lead to very significant differences in, again, expression of traits in populations. Even in a somewhat homogeneous population—maybe an ethnic population—there are still going to be genetic variations. And even if those genetic variations are small, it could affect the susceptibility of any of these types of approaches. So not only do you have all of the challenges that I just talked about, but you now also have

to accept the challenges of biology and biology's way of evolving and diversifying. Even in very similar populations—maybe they look similar from an outward perspective—but their genomic information still has significant variations, and so those that are similar, those components of the genome that might be ‘conserved,’ those might not be the targets that would allow you to do something nasty and nefarious.

The toolkits of AI and machine learning can provide an amazing aspect to be able to narrow in on targets for diseases and for ways to be able to help climate resilience of crops; that's what those tools can be used for. And yes, they potentially could help aid in this type of nefarious work that you're talking about. But I still think there are enormous challenge to really try to enact that.

**CTC: You mentioned the Safe Genes program earlier. DARPA funded and instituted the Safe Genes Initiative during your time there, and its mission includes “protect[ing] warfighters and the homeland against intentional or accidental misuse of genome editing technologies.”<sup>14</sup> What was that effort? Why was it important, and what other guardrail measures, that you can talk about, are in place?**

**Ringeisen:** Absolutely. Again, I'll have to give credit to Renee Wegrzyn, who was one of my colleagues at DARPA the whole time I was there. She left a few weeks after I left; she's now at Ginkgo Bioworks. But Renee had the foresight. It was a great DARPA program. This was back in probably 2015, 2016 when she was starting to ideate this program. Again, that's like three or four years after the discovery of CRISPR-Cas9. So, Wegrzyn realized that there was a gap in the development of safety measures for this technology, and perhaps we needed to do something to put up some guardrails. And there were three areas that Safe Genes was going to invest in. It was to try to make the technology safer. It was to try to create the capacity to block and stop and control gene-editing, and then potentially to even remediate or reverse it. Flash forward five-plus years later, what you see now is a diversification in technologies of gene editing. It's not just CRISPR-Cas9. You've got base editing, you've got prime editing, you've got epigenetic editing.<sup>15</sup> The propensity for off-target effects has gotten better so that you're more precise and more accurate in your edits that you make. I credit Safe Genes for starting to think about those types of issues at a very, very early date. The forethought and vision of Renee was really exciting.

The other great part about Safe Genes was its transparency. We were the Department of Defense. And having that giant D in front of your name, as at DARPA, put a big target on our backs. So for Renee, to her credit, from the very beginning, transparency of this work was of the utmost importance. She went to the regulatory bodies, she held open forums, she gave interviews. She insisted that everybody publish their work in open and peer-reviewed journals. She worked with the EPA, USDA, and the FDA, and all of that was done in concert. And so, Renee set the mark. She said, ‘If you're going to do work in this area, you should still be able to do this work for the Department of Defense, but you need to do it in an open and very transparent way.’

**CTC: The Biological Weapons Convention entered into force in 1975, well before advances in biotechnology enabled rapid nucleotide synthesis, gene editing, genome sequencing, and so forth. From your perspective as a scientist and someone with**

**extensive government experience, how could or should the BWC be updated to mitigate the risk associated with non-state actors and state actors developing or employing a biological weapon agent?**

**Ringeisen:** It's a great question. And honestly, the devil is going to be in the details here and in the interpretation of what's going on. My personal opinion—this is just me speaking; I'm not a government employee anymore—I think that you want broad definitions and broad interpretations of things that are stated in the BWC. It should be a living, breathing, flexible document. There shouldn't be a rigidity that says, 'You can only consider these 10 biothreat organisms.'

All the things we talked about earlier in this interview—where we were talking about zoonotic disease, emergent disease, potentially nefarious actors doing things that they shouldn't be doing with dual-use research of concern—I personally believe that BWC already covers all of those things, that if you take a broad interpretation, it's basically there. So, for me, I think the framework is there and then it also has to be done in concert with regulatory agencies and boards for dual-use research of concern. We have these things set up. NIH has these things set up; the Department of Defense has these things set up. When I was at DARPA, we would go down to the Pentagon and talk with the lawyers about interpretations of the BWC prior to launching any program that might be crossing blurred lines there. And so, to me, all of those mechanisms, all those frameworks are already set up; it's just a matter of 'the devil in the details' and referencing the right documents and having conversations about the interpretations. Now, if the regulatory bodies say, 'Look, something's emerged, some new technology has emerged that doesn't quite fit into these' or 'We need to be more explicit to make sure that state actors and countries abide by these rules,' then yes, that's their job, and they need to do that. But for me, in my day-to-day jobs in the government, I felt the toolkit and the framework were there and the resources were there for me to be able to make the necessary decisions.

**CTC: Given your background as a scientist and your lengthy government service, what do you think the next big threat is when it comes to the misuse of science? What keeps you up at night?**

**Ringeisen:** I'm going to pivot on this question. I left DARPA in part because of climate change. I worked for the Department of Defense for 18 and a half years, 20 and a half years if you count the postdoc that I worked on at the Naval Research Lab as well. I thought about bio threats. I thought about chemical weapons. I thought about the effects of radiological weapons and radiological exposures. I thought about traumatic brain injury. I thought about blood coagulants and trying to stop hemorrhagic bleeding. I thought about these things and was passionate about them for 20 years. So, I could talk about the next bio threat, but I'd probably be wrong. One thing I know I'm *not* going to be wrong about is climate change, and I will insist to my grave that climate security is national security, that water security is national security, and that food security is national security. So, to me, the big elephant in the room that we all need to address to help stabilize the world is climate security, food security, and water security.

And to me, CRISPR and genome engineering and the ability to be able to modify plants, modify microbes, and modify human cells has the potential to dramatically affect these areas. And so, to me, there's just so much that can be done. We are moving towards a carbon economy. Maybe it's 20 years from now, maybe it's 50 years from now, but if I was advising the president or if I was advising the Secretary of Defense, I would say the superpower of the future is going to be the superpower that can control carbon, that can use carbon, that can use greenhouse gases to provide what their country needs so that they're not reliant on other countries. That, to me, is the best way to provide long-term security for our country. So, I'm trying to work to make crops resilient to climate, to absorb more carbon, to pump more carbon underground in root systems and soil carbon; I'm trying to work to have crops use less water so that we can use fresh water to drink and to minimize irrigation. I don't want to go to war over water. I'm living out in Berkeley, California, now; we're under threat of forest fire all the time. What can we do to try to help mitigate forest fires, to have forests store more carbon so that we can help neutralize the effects of climate change?

One of the reasons I left DARPA is because of the opportunity I now have to partner up with places like California-Berkeley, the University of California-Davis who we work closely with, the DOE [Department of Energy] laboratories like Lawrence Livermore and Lawrence Berkeley. The IGI is partnering with a tremendous number of smart scientists to try to create innovative biotechnology-drive solutions in these areas. **CTC**

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# The Urgent Need for an Overhaul of Global Biorisk Management

By Filippa Lentzos, Gregory D. Koblentz, and Joseph Rodgers

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**The biological risk landscape is rapidly evolving and presents significant new challenges to preventing the accidental, reckless, or malicious misuse of biology. At the same time, oversight systems to ensure that life sciences research is conducted safely, securely, and responsibly are falling behind. An urgent overhaul to realign biorisk management with contemporary risks is needed. This must include not only an international framework to establish values and principles for biorisk management and guidelines to develop and implement governance tools and mechanisms, but also an authoritative international institution with a mandate to systematically register and track maximum containment facilities and to oversee extremely high-risk research.**

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**T**he origin of COVID-19 is hotly debated and heavily politicized. It is possible that the virus naturally spilled over from animals to humans. Another theory is that the virus escaped from a lab, most likely the Wuhan Institute of Virology, or that scientists were infected when doing fieldwork with bats. There may never be a credible international investigation into the origins of COVID-19.

Yet, regardless of what sparked the pandemic, what is known

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is that accidents happen and that dangerous viruses can escape from labs around the world. And the risks of this happening are increasing. Ironically, greater efforts to prevent future pandemics and to strengthen biopreparedness—by prospecting for dangerous viruses in animals or engineering viruses in the lab to anticipate and better understand dangerous viruses that could emerge from nature—could actually lead to increased risks of accidental or deliberate pandemics. The answer is simple. The international community needs to strengthen local and global biorisk management. The hard part is making this happen in practice.

This article first examines the evolving biorisk landscape, before evaluating the woefully insufficient international and national efforts at biorisk management. The final section provides recommendations for strengthening global biorisk governance.

## Increasing Biological Risks

Globally, there are now around 60 maximum containment laboratories, commonly referred to as biosafety level 4 (BSL-4) labs, that are designed to work safely and securely with pathogens that cause life-threatening diseases and for which there are limited or no vaccines or treatments.<sup>a</sup> BSL-4 labs work with the most dangerous pathogens such as smallpox, Ebola, Marburg, and Lassa fever. Half of the labs for which dates of establishment are available began operating in the last 10 years.<sup>1</sup> They are spread over 23 countries. About half of them are in Europe. Most of them are in big cities. Before the pandemic, China completed two BSL-4 labs, and it has signaled that it intends to follow through with plans to build up to five more.<sup>2</sup> Since the beginning of the pandemic, five countries have announced plans to build 19 new BSL-4 labs, including 15 labs in Russia,<sup>3</sup> one in the Philippines,<sup>4</sup> one in Taiwan,<sup>5</sup> one in India,<sup>6</sup> and one in the United States.<sup>7</sup> While BSL-4 labs take several years to design, build, and commission, one can expect that as these new labs come online, the risk of accidents will increase.

But it is not simply more labs that increase biosafety risks. There is also an upward trend in high-risk research. Creating dangerous viruses has regularly occurred in labs. In 2005, for example, scientists recreated the 1918 influenza virus that had led to the deadliest pandemic of the 20th century.<sup>8</sup> In 2011, scientists manipulated the bird flu virus to enable it to transmit between

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a Laboratories that work with infectious agents and toxins are categorized by their level of necessary safety measures with BSL-1 being the lowest and BSL-4 being the highest. BSL-4 labs are equipped with positive pressure suits or biosafety cabinets to prevent the infection of researchers as well as HEPA filters and effluent treatment systems to prevent the escape of a pathogen from the lab. In addition, these engineering controls are supplemented by policies and procedures to reduce the chance of an accidental infection or environmental release. World Health Organization, *Laboratory Biosafety Manual, Fourth Edition* (Geneva: World Health Organization, 2020), pp. 59-64.



*Special airlock doors are seen in front of a security level 3 laboratory in a building of the Friedrich-Loeffler-Institut on the island of Riems, Germany, on July 2, 2020. (Jens Büttner/picture alliance via Getty Images)*

mammals, including humans.<sup>9</sup> Before then, the virus had only been transmitted from birds to humans, with a fatality rate of 30-60 percent.<sup>10</sup> In comparison, COVID-19 has a fatality rate of approximately two to three percent.<sup>11</sup> In 2018, scientists announced they had created horsepox, a close cousin of smallpox, from chemically synthesized DNA fragments.<sup>12</sup> This research highlighted some of the dangers of synthetic biology. David Evans, who led the synthetic horsepox project, stated, “Have I increased that risk? I don’t know. Maybe yes, but in reality, that risk has always been there.”<sup>13</sup>

The COVID-19 pandemic will likely increase the number of laboratories and scientists creating novel, ‘chimeric’ viruses that combine the genes of two or more strains. The colloquial term used to describe the creation of these engineered viruses is ‘gain-of-function’ research since the resulting, lab-made strain of the virus may have enhanced virulence or transmissibility compared to the naturally occurring version. This research is used to characterize the potential for newly discovered viruses to cause pandemics by providing a better understanding of how easily these viruses can infect human cells, which is indicative of the potential for the virus to jump from animals to humans and to spread human-to-human.<sup>14</sup> There was a significant increase in this type of research by influenza virologists following the 2005 H5N1 and 2009 H1N1 outbreaks.<sup>15</sup> There has been a dramatic surge in scientific publications about SARS-CoV-2, the virus that causes COVID-19, and related coronaviruses over the last two years.<sup>16</sup> It also appears that a lab in the United States has been interested in adding genetic material from the original SARS virus, which first emerged in 2003, to the COVID-19 strain to create an aggressive chimeric virus of the two

strains.<sup>17</sup>

Research activities outside of labs are also increasing biosafety risks. The current pandemic will likely increase large-scale viral prospecting, which involves collecting biomedical samples from wild animals to identify potential pandemic pathogens.<sup>18</sup> For example, in 2021, USAID announced a five-year, \$125 million viral characterization program called Discovery & Exploration of Emerging Pathogens - Viral Zoonoses (DEEP VZN), which is expected to identify 8,000-12,000 new viruses and characterize the risk they pose of causing a pandemic.<sup>19</sup> Chinese researchers have also called for more field research to improve their ability to predict the risk of zoonotic spillover events.<sup>20</sup> The emergence of SARS, MERS, and SARS-CoV-2 has already demonstrated that such viruses are currently circulating in animals and can jump to humans and spread internationally under the right conditions. Actively searching for these viruses will increase the risk of infection in the field by a novel and potentially pandemic-capable virus. Yet, standards for field biosafety are much less developed than for laboratory biosafety. Neither the United States nor China, for example, have national field biosafety standards, and there is no international guidance available on this subject. Similarly, the increasing use of mobile laboratories, while very helpful in containing outbreaks, may also increase the risk of accidental or deliberate contamination. Many of these labs were constructed and deployed by the international community to respond to the 2014-2016 Ebola epidemics in Africa.<sup>21</sup> While these labs are largely for diagnostic purposes, projects such as the European Mobile Laboratory Project work with risk group 4 pathogens in mobile lab conditions.<sup>22</sup> This diagnostic capability is important when responding to emerging biological threats, but the



trade-off between safety and mobility also introduces new areas of risk that need to be examined in greater detail.

### ***Increasing Concerns over Security and Dual-Use***

The increase in laboratories and scientists working on dangerous pathogens has created more opportunities for these agents to be stolen, particularly by insiders. Historically, laboratories and culture collections have been the preferred source of pathogens for terrorists and criminals. There is no evidence that any terrorist or criminal group has successfully acquired a pathogenic microorganism from nature.<sup>b</sup> Aum Shinrikyo, for example, was only able to acquire a harmless vaccine strain of anthrax.<sup>23</sup> The increased number of individuals with expertise in and access to dangerous pathogens also poses increased security risks. According to the Federal Bureau of Investigation, Bruce Ivins, a scientist at the U.S. Army Military Research Institute of Infectious Diseases (USAMRIID), the U.S. military's premier biodefense facility, was the sole perpetrator of the 2001 anthrax letter attacks in the United States that sickened 17 and killed five.<sup>24</sup>

A different type of security risk is that the knowledge and methods used to understand and manipulate the biological and epidemiological properties of pathogens for public health purposes is repurposed to cause harm. Advances in science have the potential to provide new knowledge and tools to national militaries, international terrorist networks, criminal groups, religious extremists, disgruntled or mentally ill scientists, or even ill-intentioned 'biohackers'—do-it-yourself biologists who are not necessarily motivated by politics or religion, but possibly by curiosity, revenge, greed, or boredom. Biodefense research on dangerous pathogens is especially susceptible to this 'dual-use dilemma' since it is frequently focused on studying characteristics such as infectivity (ability of a microorganism to infect a host), pathogenicity (ability of a microorganism to cause disease), virulence (severity of the disease caused by the organism), and transmissibility (ability of the pathogen to spread from person to person).

The biosecurity landscape has also been altered by changes in how scientific research is disseminated. The emergence of pre-print servers, where scientists can post their findings before going through the peer review process, has removed one of the layers of review that could be used to check for dual-use research of concern before the dissemination of the research. The urgency of responding to the pandemic led to a dramatic rise in the use of pre-print servers. During the first nine months of the pandemic, half of all scientific publications on SARS-CoV-2 were posted to pre-print servers.<sup>25</sup> In contrast, during previous outbreaks, only five percent of scientific research was disseminated this way.<sup>26</sup> In addition, the rise of the open science movement, which seeks to make protocols,

**“Approaching the domains of biosafety, biosecurity, and oversight of dual-use research collectively under the rubric of biorisk management has the advantage of recognizing and capitalizing on how they are interconnected without sacrificing the specific demands, challenges, and risks that each presents. Yet biorisk management has significant gaps and weaknesses globally.”**

datasets, and computational tools as widely available as possible, has introduced new potential risks of misuse.<sup>27</sup> For example, the publication of a detailed protocol for how to synthesize SARS-CoV-2, the virus responsible for COVID-19, has raised concerns that such protocols have lowered the barrier to creating engineered versions of the virus.<sup>28</sup>

Important developments taking place in fields of the life sciences other than microbiology and molecular biology, such as immunology, population genomics, gene therapy, viral vectors, genome editing, gene drives, synthetic biology, and neuroscience, are not covered by existing biosecurity and dual-use research policies.<sup>29</sup> These policies also do not sufficiently take into account how security and dual-use risks can be generated by the convergence of multiple disciplines within the life sciences or by the application of emerging technologies, such as machine learning, artificial intelligence, data analytics, and nanotechnology, to the life sciences.<sup>30</sup> Overall, these scientific and technical advances have created new potential attack vectors and the means for rapidly identifying novel ones. Many of these new attack vectors do not involve actual pathogens, but instead relate to genetic constructs and associated means of delivery such as viral vectors and lipid nanoparticles.<sup>31</sup> For example, the National Academies of Science has identified dual-use risks posed by the manipulation of the human immune system and microbiome, which can be accomplished with CRISPR genome editors delivered by viral vectors.<sup>32</sup>

High-risk pathogen research congruently poses challenges to peace and international security. While biodefense activities such as the development of protective gear, medical countermeasures, and detection and diagnostic systems are justifiable, the proliferation of laboratories and research institutions handling dangerous pathogens may instill a fear of the weaponization of biology among the public or policymakers. In turn, this heightened perception that biological weapons are an increasing threat may provide the justification for a country to initiate or expand an offensive biological warfare program.<sup>33</sup> One particularly sensitive research area is related to threat assessment, which involves research on pathogens to characterize their potential utility as biological weapons. While such research can be used to inform the development of medical countermeasures and other biodefenses, it can also generate knowledge potentially useful for offensive biological weapons

b W. Seth Carus, *Bioterrorism and Biocrimes: The Illicit Use of Biological Agents since 1900* (Washington, D.C.: National Defense University, 2001), p. 8. While this source is dated, this finding is supported by more recent research. According to Markus Binder, architect of the National Consortium for the Study of Terrorism and Response to Terrorism's POICN database, which is comprised of 517 CBRN-related incidents between 1990 and 2016, "There don't appear to have been any efforts, at least not publicly revealed, to obtain bio-agents from nature and then use the isolated agent to produce a significant quantity of agent for use in an attack." Author (Koblentz) email communication, Markus Binder, April 2022.

applications.<sup>34</sup>

### Insufficient Biorisk Management

Traditionally, biosafety, which is designed to prevent the accidental release of a pathogen from a lab, has gained more attention than biosecurity, which is designed to prevent the malicious misuse of pathogens and biotechnology, and dual-use research, but all must be better governed. The umbrella term ‘biorisk management’ is an overarching framework to discuss the full spectrum of risks associated with the life sciences enterprise. A biorisk is a risk that a biological event—such as a naturally occurring disease, an accidental infection, an unexpected discovery, an unauthorized access, loss, theft, misuse, diversion, or intentional release of a biological agent or biological material—adversely affects the health of humans, non-human animals, or the environment. Approaching the domains of biosafety, biosecurity, and oversight of dual-use research collectively under the rubric of biorisk management has the advantage of recognizing and capitalizing on how they are interconnected without sacrificing the specific demands, challenges, and risks that each presents. Yet biorisk management has significant gaps and weaknesses globally.<sup>35</sup>

A 2021 survey of biorisk management policies around the world found that most countries do not have comprehensive, or ‘whole-of-government,’ systems for biosafety and biosecurity, and that virtually none have national policies regulating dual-use life science research.<sup>36</sup> Only six countries, or one-quarter of the 23 countries with maximum containment laboratories, were scored as having high levels of biosafety and biosecurity. Only five of these 23 countries had policies on dual-use research. This means that a large majority of countries with BSL-4 labs do not have specific oversight of ‘gain-of-function’ research on potential pandemic pathogens that has been a central feature in the debate on COVID-19’s origin.<sup>37</sup>

Even countries such as the United States that scored high on biosecurity and biosafety have demonstrated less than stellar implementation of those policies in practice, as exemplified by questionable oversight of ‘gain-of-function’ research funded by the National Institutes of Health (NIH).<sup>38</sup> As revealed by documents obtained through FOIA requests, NIH did not submit proposed research that could be reasonably anticipated to enhance the virulence or transmissibility of a potential pandemic pathogen for review by the Department of Health and Human Services (HHS) as required under HHS’ 2017 Potential Pandemic Pathogen Care and Oversight (P3CO) policy.<sup>39</sup> NIH reportedly funded at least eight projects since 2017 that appear to have involved ‘gain of function’ research, but only forwarded three of these projects to HHS for review under the P3CO policy.<sup>40</sup>

Among the few countries that do have biosecurity and dual-use oversight policies, they are usually focused on the potential misuse of a short list of specific pathogens such as those that cause anthrax, plague, Ebola, and smallpox. Aside from the microbiology and molecular biology communities that work with these listed pathogens, called ‘select agents’ in the United States, awareness of biorisk management principles and practices in the wider scientific community is limited.<sup>41</sup> And, each of these areas—biosafety, biosecurity, and dual-use research—is typically stove-piped within multiple government agencies, which results in fragmented oversight. In some countries, such as the United States, oversight of dual-use research is almost entirely limited to institutions and individuals in receipt of government funds and

**“In some countries, such as the United States, oversight of dual-use research is almost entirely limited to institutions and individuals in receipt of government funds and conducting experiments on select agents. A private company that does not receive federal funding for life sciences research can modify a select agent (with a few minor exceptions), or other pathogens not included in that list, with no obligation to review the research for potential dual-use implications or seek approval from a government agency before conducting the research.”**

conducting experiments on select agents. A private company that does not receive federal funding for life sciences research can modify a select agent (with a few minor exceptions), or other pathogens not included in that list, with no obligation to review the research for potential dual-use implications or seek approval from a government agency before conducting the research. This means that almost all dual-use research based on non-government sources of funding—such as from corporations, foundations, wealthy individuals, and crowdfunding sites, which is increasingly driving the innovation process in the life sciences—is not covered. For the first time, federal funding in the United States accounted for less than 50 percent of national spending on scientific research in 2013.<sup>42</sup> In 2015, more Ph.D. researchers in the United States were employed in the private sector than in academia, including 40 percent of those in the life sciences.<sup>43</sup> The risks posed by privately funded research is illustrated by the aforementioned synthesis of the horsepox virus, which was financed by an American biotech company for only \$100,000.<sup>44</sup> In 2021, synthetic biology companies raised nearly \$18 billion, almost as much as the total investment that the industry had received since 2009.<sup>45</sup> Given the increasing size of the global bioeconomy and the growing commercialization of products generated with synthetic biology and genome editing tools, the exclusion of almost all of the work of the private sector from dual-use research oversight is an increasingly large loophole.

At the international level, there is no body that standardizes principles for biosafety, biosecurity, and dual-use research oversight and monitors compliance with these standards. As the spread of the original SARS-CoV-2 virus and its subsequent variants has demonstrated, global health is only as strong as its weakest link. A failure in biosafety or biosecurity anywhere in the world could have repercussions around the globe.

### Recommendations for Strengthening Global Biorisk Governance

Given the increasing number of countries developing dual-use

biotechnologies and conducting risky research with pathogens, the transnational nature of modern life sciences research, and the potential global impact of an accidental or deliberate release of a pandemic-capable pathogen, international mechanisms for ensuring that this research is being conducted safely, securely, and responsibly are crucial.

At the lab-level, institutions must work to cultivate a culture of biosafety, biosecurity, and responsible research with high-risk pathogens. This does not just apply to BSL-4 labs; lower-containment level labs should also be nurturing a culture of safe, secure, and responsible working practices. This should encompass all levels, from students and technicians to principal investigators to laboratory directors. It is also important to stress that developing a culture of safe, secure, and responsible working practices is not a one-off event, but a continual effort.<sup>46</sup>

At the national level, all countries, but particularly countries where high-risk pathogen work is conducted, should have laws and regulations in place that maintain oversight of BSL-4 labs, and that require comprehensive risk assessments of proposed research for safety, security, and dual-use activities with significant potential to be repurposed to cause harm. In addition to laws and regulations, countries and the BSL-4 labs within them should also implement and share best practices, and participate in peer reviews of practices in other BSL-4 labs. Countries with experience in designing and operating high-containment laboratories should share their expertise in building risk-based laboratory infrastructure that is fit for purpose, is safe and secure, and can be maintained over the long-term. Countries with BSL-4 facilities must also provide complete, regular, and transparent reporting under the annual confidence-building measures of the Biological Weapons Convention and under U.N. Security Council Resolution 1540. While most countries with BSL-4 facilities generally submit these documents, there is no international requirement mandating this information. The information should also be made publicly available by all countries. So far, for example, only nine of the 22 countries that report their BSL-4 labs under the confidence-building measures of the BWC make these reports public. Only 55 percent of the BSL-4 labs in operation provide links to their publications on their institutional websites.<sup>47</sup> Making BWC and 1540 reporting publicly available should not be a difficult task since the existence of these facilities is not secret and nearly every BSL-4 laboratory has a website. This measure would strengthen international transparency and confidence, and would assist in further research to strengthen global biological lab governance.

At the international level, frameworks establishing values and principles for biorisk management and guidelines for developing and implementing governance tools and mechanisms should be developed. In addition, an authoritative international institution with a mandate to systematically register and track maximum

containment facilities and to oversee extremely high-risk research should be put in place to ensure all such research is being conducted safely, securely, and responsibly. One relatively easy way to do this would be for all BSL-4 labs and those engaged in gain-of-function research with potentially pandemic pathogens to adopt the ISO 35001 standard on “biorisk management for laboratories and other related organisations.” Created by the International Organization for Standardization (ISO) in 2019, ISO 35001 is an international standard for a biorisk management system. The system is ready for use by laboratories and provides recommendations for laboratory leadership, planning, support, operation, performance evaluation, and how to implement improvement in an iterative manner.<sup>48</sup> The system could also be used by lower-containment level labs to strengthen their culture of biosafety and security. The standard uses third-party validation, and to maximize the potential of ISO 35001, there needs to be an international structure to ensure compliance. While national regulators could act as the third-party, this would have limited credibility internationally, especially for jurisdictions without proven track records for transparency and accountability. One alternative would be to build out the current International Experts Group of Biosafety and Biosecurity Regulators to take on the role.<sup>49</sup> Another would be to mandate the World Health Organization to make it directly responsible, in much the same way that it conducts biennial biosafety and biosecurity inspections of the variola virus depositories in the United States and Russia.<sup>50</sup>

Lastly, while these structural and policy steps should be taken to reduce biological risks, it is crucial that the life sciences continue to develop and maintain a culture of biosafety, biosecurity, and responsible conduct. To support this process, the World Health Organization should establish regional collaborating centers on biorisk management to conduct education and training, provide forums for exchanging best practices, and support organizations and activities that foster cultures of safety, security, and responsibility within the life sciences.

The development of medical countermeasures in record time to prevent and treat COVID-19, which built on decades of studying coronaviruses and developing advanced biotechnologies, demonstrated the importance of a robust biomedical research enterprise for pandemic response. While the benefits of such research are undeniable, it is also clear that this research poses safety, security, and dual-use risks. In a worst-case scenario, research intended to prevent the next pandemic could cause one by accident or through reckless or malicious misuse of biotechnology. Unfortunately, the current national and international systems to ensure that life sciences research is conducted safely, securely, and responsibly is already inadequate. A major overhaul of global biorisk management is needed to ensure that humanity’s efforts to limit the scourge of infectious disease do not inadvertently make the problem worse. **CTC**

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