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BIOSECURITY REALLY

A Strategy for Victory

By Drew Endy, Sarah Moront, Vassilis Andrea Alexopoulos, Raj Patel, Rhea Jain, and Britney Bennett

BIO-STRATEGIES AND LEADERSHIP

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Drew Endy
Sarah Moront
Vassilis Andrea Alexopoulos
Raj Patel
Rhea Jain
Britney Bennett

Hoover Institution | Stanford University

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Preface

A family gathers for their Sunday meal. Dad is a middle school teacher. Mom is a part-time dental hygienist. Their daughter is visiting. She works as a courtroom illustrator. Their son is still in high school. He has a runny nose and has been sneezing. Mom is worried she might get sick and won't be able to see patients next week. Dad jokes that he has been sick three times already this school year. He has no idea what caused his colds. Their conversation is cautious. The daughter leaves early without hugs goodbye. Dad skims the news. There is a story about Russia's reputed biowarfare program. He doesn't know what to think. Mom calls in sick on Tuesday. She is running a fever.

Let's talk about a different dinner.

The son knows his sniffles are caused by one of many viruses contributing to the "common cold"—HRV-B14 specifically, a relatively mild human rhinovirus strain. Given her work, Mom elected to take a multivalent common cold vaccine earlier in the year and is well protected. Dad's school is warned in advance when different viruses are circulating. Modern air-treatment systems prevent viruses from spreading within the classrooms. Dad hasn't gotten sick all year. "Smart" facial tissues give the family confidence that their son is no longer infectious. They enjoy a warm meal and rich conversation.

Which dinner happens will depend on what we make real over the next three, five, and fifteen years. The stakes are not simply whether we continue to suffer with the common cold. Existing and emerging technologies are increasing the risk of more-serious biological accidents and purposeful misuse. Do we continue to wait for biology to happen to us, passively awaiting the next pandemic, lab accident, or biological attack?

I led this report to help spark a different conversation. In serving on the United States' National Science Advisory Board for Biosecurity, I experienced firsthand how well-intentioned policies regarding gain-of-function research failed to adapt to changes in technology and created ambiguity regarding pandemic origins. In serving on the World Health Organization's (WHO) Advisory Committee on Variola Virus Research, I have learned how a public vaccination campaign eradicated the scourge of smallpox and how research with dangerous pathogens might be well governed. In chairing the United States' Defense Advanced Research Projects Agency's (DARPA) synthetic biology study, I saw how perceived risks of emerging biotechnologies can lead to decisions that cut off flourishing futures while making us all less secure.

We can choose to act strategically to secure biology—to build a world in which infectious

diseases become obsolete from a public health and biodefense perspective. Doing so requires navigating three challenges. First, we must understand how risks in biology are changing without becoming consumed by unfounded hypotheticals (i.e., too many "mights" or "coulds"). Second, we should explore how biology itself can be leveraged to secure biology, similar to how software is required to secure software. Third, we need to consider and be open to changing how we govern work with biology, not just in governance of scientists but also in how diverse publics engage with biology and how fierce competitors or bitter adversaries navigate toward shared goals. As our colleagues at the Tony Blair Institute for Global Change recently noted, international cooperation on biosecurity is essential.[1]

Now is the critical period to secure biology, before and as biology becomes a general-purpose technology. If we do not make significant progress within the next thousand days and continue thereafter, we should expect that biosecurity risks will increase significantly. In developing a strategy for biosecurity victory, we have drawn on decades of experience advancing biotechnology and advising on biosecurity policy; engaged with dozens of subject matter experts; considered how challenging biosecurity may become; and examined whether and how biology itself can offer critical solutions. The opinions, examples, conclusions, and policy recommendations offered here, along with any errors or misjudgments, are our own.

At the start of the project I was unsure whether realizing a calm and stable "biosecurity victory" might be possible. Today, I am optimistic that we can succeed in securing biology. Careful consideration of which steps are taken and in what order is key. Sustained support for strategic actions is essential. Finding shared interest, creating trust, and coordinating among competing or adversarial parties is crucial. By taking action, biosecurity victory becomes feasible.

This report is not just for experts in biotechnology and biosecurity. Those not yet thinking about or involved with biosecurity will be among the report's most important readers. Anyone with a basic education should be able to make sense of the report's examples, explanations, and conclusions. Let's go!

Drew Endy

Stanford, California

August 2025

1. Worst-Case Scenarios

INTRODUCTION

In the fourteenth century, a bacterial "Black Death" killed 150 million people, roughly half the population of Europe.[2] The influenza that began in 1918 killed roughly seventy-five million people, more than twice the number killed in World War I.[3] From 1870 to 1970, the scourge of smallpox killed an estimated four hundred million people before a vaccination campaign eradicated the virus (figure 1).[4] Since 2019, SARS-CoV-2 has killed more than seven million people, nearly one of every one thousand friends, family members, and strangers.[5] While biology is life's wellspring, we have come to accept and expect that biology hurts, biology kills.

The dangers lurking within the possibilities of biology are worse than those in nature. A highly lethal and contagious pathogen—which might be selected against in nature—is straightforward to imagine and attempt.[6] From terrorists to nations, people have used biology for harm. The 2001 anthrax attacks in the United States caused dozens of casualties while striking fear across America.[7] The 1984 poisoning of salad bars in Oregon with salmonella sickened over 750.[8] The 1950 classified mock bioattack on San Francisco—"Operation Sea Spray"—proved that an entire city could be infected by bacteria released from one ship in the fog (figure 2).[9] The Japanese used plague against the Chinese in World War II.[10] As scientists and engineers advance biology as a general-purpose technology, the risks associated with the purposeful misuse of biology must be well minded by all.[11]

Securing biology presents daunting challenges. A toxin or pathogen that took years to create and deploy must be detected and countered immediately. Any part of the living world we depend upon could be targeted—not just people, but also plants or animals. Our infrastructure, from travel and trade to food production and distribution, offers

DEFINITION

General-purpose technology is a technology that has the potential to affect the entire economic system. Historical examples include the steam engine, railroads, electricity, the automobile, the computer, the internet, and money.

Elhanan Helpman, ed., *General Purpose Technologies and Economic Growth* (MIT Press, 1998); and Joe McKendrick, "Why GPT Should Stand for 'General Purpose Technology' for All," *Forbes*, August 8, 2023, https://www.forbes.com/sites/joemckendrick/2023/08/08/why-gpt-should-stand-for-general-purpose-technology-for-all/.

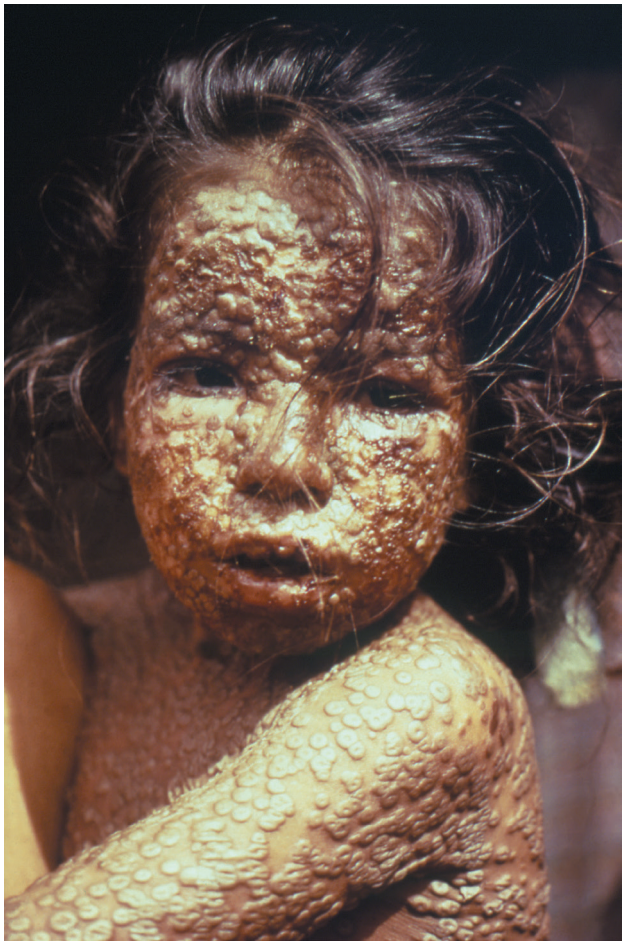


FIGURE 1 A young girl infected with smallpox in Bangladesh in 1973
Source: Centers for Disease Control and Prevention, girl with smallpox rash being held by her father (photo by James Hicks, Bangladesh, 1973), Public Health Image Library (PHIL) ID 3265, accessed August 12, 2025, https://phil.cdc.gov/Details.aspx?pid=3265.

many targets. Must all living creatures and infrastructure be "locked down" to secure biology?

Another challenge is an underlying mismatch between reality and expectations. The natural living world embodies Darwinian competition and survival of the fittest. Democracies defend individual rights against oppression. A virus that kills 90 percent of its hosts might be no big deal to Darwin; the host species survives. In a democratic society, small numbers of casualties create terror and significant numbers create stories. For example, most reading this sentence have heard of an ancient Black Death but have never been infected with bubonic plague or known anyone who has. Yet, from an evolutionary perspective, humanity is doing great; Europe today is fifteen times more populous compared to 1375. Reconciling political expectations focused on individual freedom with a physical system—the living world—that has evolved to tolerate great loss adds another challenge to the puzzle of securing biology.

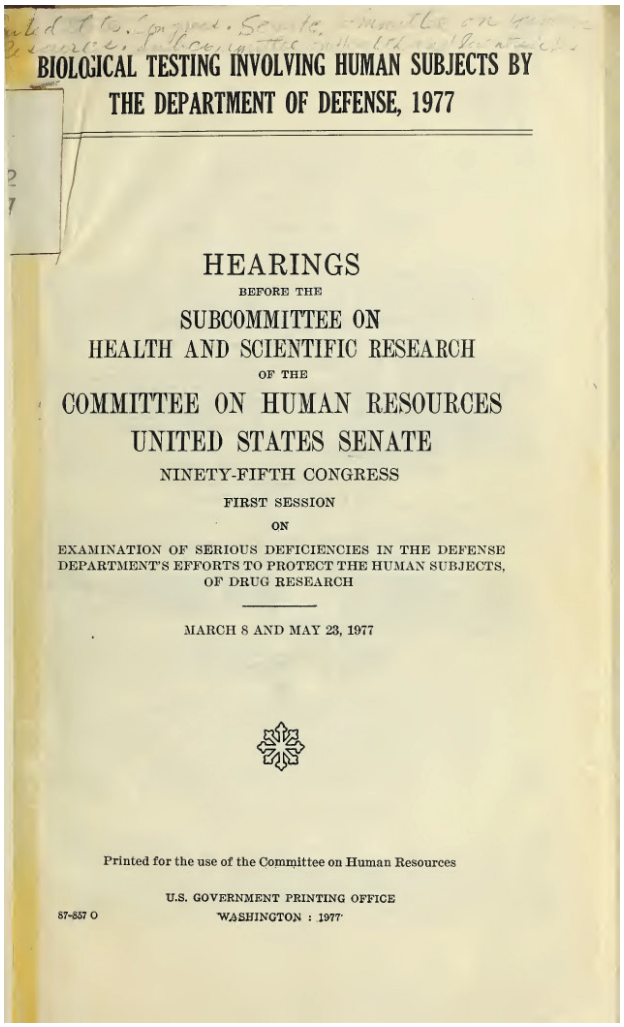
Right now we are on a dangerous path. Imagine one version of the year 2050. Technological advances offer most the option of accessing or making nearly any toxin or pathogen. Artificial intelligence (AI) can suggest novel toxins and pathogens. Conflict and suspicion incentivize nations to remilitarize biology with the tools and

DEFINITIONS

Toxins are "poisonous substances produced within living cells or organisms. Toxins can be small molecules, peptides, or proteins."

Pathogens "are organisms that can cause disease. The different types of pathogens and the severity of the diseases that they cause are very diverse."

"Toxin," ScienceDirect Topics, accessed May 11, 2025, https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/toxin; and "Pathogens: Definition, Types, Diseases, Prevention, and More," Medical News Today, accessed May 11, 2025, https://www.medicalnewstoday.com/articles/pathogens-definition.



BIOLOGICAL TESTING INVOLVING HUMAN SUBJECTS BY THE DEPARTMENT OF DEFENSE, 1977

HEARINGS

BEFORE THE

SUBCOMMITTEE ON
HEALTH AND SCIENTIFIC RESEARCH

OF THE

COMMITTEE ON HUMAN RESOURCES
UNITED STATES SENATE

NINETY-FIFTH CONGRESS

FIRST SESSION

ON

EXAMINATION OF SERIOUS DEFICIENCIES IN THE DEFENSE DEPARTMENT'S EFFORTS TO PROTECT THE HUMAN SUBJECTS, OF DRUG RESEARCH

MARCH 8 AND MAY 23, 1977

Printed for the use of the Committee on Human Resources

U.S. GOVERNMENT PRINTING OFFICE
87-857 O WASHINGTON : 1977

FIGURE 2 Congressional hearings on "Biological Testing Involving Human Subjects by the Department of Defense" revealed earlier large-scale bioexposure tests demonstrating how entire civilian populations could be effectively targeted via simple mock bioattacks

Source: US Senate, Ninety-Fifth Congress, First Session, March 8 and May 23 (US Govt. Print. Off., 1977), http://archive.org/details/biologicaltestin00unit.

knowledge of the twenty-first century. Individuals and amorphous groups grasp the asymmetric leverage and power advantages of bioterrorism. Cultural and political norms forestalling the use of biology to cause harm have fallen. Threats emerge faster than countermeasures can be made real. The United States is no longer the world leader in biotechnology. How bad could the challenge of biosecurity get?

TRENDS MAKING BIOSECURITY WORSE

Scientists and policymakers have long labored to prevent or limit access to dangerous organisms and powerful biotechnology tools. "Limit-access" strategies work until they don't.[12] Biology is naturally everywhere. New tools make working with biology ever more commonplace. Positive uses of biotechnology—food security, biodiversity conservation, and essential medicines manufacturing—are no longer optional. While it can be smart to buy time by working to restrict access or slow proliferation, we must also acknowledge what is ultimately arriving so that we can start now to secure the future.

Consider the ability to build DNA from scratch. Anyone with an internet connection can access DNA sequence information encoding potentially dangerous biology, from the smallpox virus to snail toxins. When such sequence information is sent to a DNA printer, actual DNA molecules encoding poxviruses or toxins are made.

Today most DNA printers are run by companies whose business is to build DNA for customers seeking to do good. To manage real and perceived risks, many, but not all, DNA-synthesis companies coordinate and implement best practices for checking who their customers are and what sequences are being requested.[13] Companies do not wish to unknowingly build the DNA encoding Ebola and ship it to a disgruntled teenager in Montana. But screening customers and sequences takes time and money. What about a competing company that cuts corners? What if customer privacy concerns incentivize gray or black markets for DNA synthesis? What about when personal DNA printers make a comeback?

We need to take care that the relatively easy-to-approach aspects of biosecurity do not consume

all or even most of our attention. We also need to be clear-eyed and honest about the longer-term trends. Imagine airport security if passengers could simply elect to skip the screening line. Imagine airports without any fences around the runways.

History is littered with lessons of fighting the last war. France placed its trust in concrete by building the Maginot Line following the trenches of World War I, leading to 1940's "Strange Defeat."[14] The United States confronted guerrilla warfare in Vietnam with policies from World War II.[15] Today, the United States builds aircraft carriers even as satellites and drones become more pervasive and powerful.[16] Failing to anticipate and act in the face of quantitative and qualitative change risks false comfort and security collapse.

PROLIFERATION OF CAPACITIES THAT MAKE CREATING OR DEPLOYING BIOLOGICAL THREATS EASIER

Biology is naturally distributed. Consider trees. Leaves await no factory, task force, commission, or military order to begin growing. Instead, leaves—self-assembling "solar panels" that recycle themselves—grow from locally available energy and materials. By mid-century, we expect that biology as a technology will connect with biology as it exists, leading to new forms of biotechnology that are as pervasive and distributed as personal computers and smartphones. Ongoing advances will also make biotechnology increasingly accessible to the general public.[17] Biosecurity presents different challenges compared to security domains that rely on limited physical access, such as nuclear weapons. Yet much of the thinking underlying our legacy biosafety and biosecurity practices (e.g., containment) arose from strategies for managing nuclear weapons.

People everywhere are increasingly taking advantage of biology's accessibility and promise.

DEFINITIONS

Biosafety involves preparing for expected uncertainties involving living systems (e.g., preventing or responding to laboratory accidents).

Biosecurity includes preparing for the natural emergence (i.e., public health) or purposeful release (i.e., biodefense) of biological agents that cause harm. Our definition is inclusive of both pandemic preparedness and biodefense.

Biosecurity becomes impossible without **biosafety**.

"Biosafety," Administration for Strategic Preparedness and Response, accessed February 24, 2025, https://aspr.hhs.gov/S3/Pages/Biosafety.aspx; and "Biosecurity," Administration for Strategic Preparedness and Response, accessed February 26, 2025, https://aspr.hhs.gov/S3/Pages/Biosecurity.aspx.

More than 430 teams are competing in the 2025 genetic engineering "olympics," up from five in 2004 (figure 3).[18] The newest engineering departments at Stanford University and the Massachusetts Institute of Technology (MIT) are focused on bioengineering. "Do-it-yourself" biology movements have taken root and already engage thousands via events, community spaces, and groups.[19] Increasing interest in biology and biotechnology is being pulled forward by economic opportunity. The US National Academies of Sciences, Engineering, and Medicine (NASEM) estimated that the economic contribution of biotechnology to the United States was approximately $960 billion in 2016.[20] The World Bioeconomy Forum estimated that the global bioeconomy will grow to $30 trillion by 2050.[21] A next generation is waking up to biotechnology's personal, professional, and economic potential.

FIGURE 3 Participants at the International Genetically Engineered Machine Grand Jamboree taken in October 2024 in Paris, France

Source: "iGEM from Above," November 4, 2024; photo courtesy of the iGEM Foundation, https://www.flickr.com/photos/igemhq/54115986017/.

In 2016, three researchers in Alberta, Canada, unilaterally built horsepox virus from scratch for roughly $100,000. Horsepox is closely related to human smallpox. Although well intended, the work was controversial.[22] The eventual 2018 scientific paper describing the work was itself critiqued, with one Stanford University professor declaring, "This paper should not have been published."[23] While it had been possible to build poxviruses for two decades prior, all who were then capable of doing so chose not to. But as tools become more powerful and available, more people can act. Eventually someone will act. This sort of risk can be summarized as the "unilateralist's curse."[24] Inevitably, someone well intended will do something dangerous, stupid, or both.

Access to biotechnology tools is also increasing. Gene-editing kits, open-source DNA parts libraries, and consumer bioengineered organisms are already available.[25] One expert predicted that within the next several years "tens of thousands of skilled individuals will be able to access the information required for them to single-handedly cause new pandemics."[26] The good news, for now at least, is that most if not all of these "skilled individuals" have no interest in causing pandemics. But recall that the first computer virus released outside of a research lab was created by a high school student in 1982.[27] Imagine returning to 1975 with full knowledge of the computer and networking security challenges of 2025. Would we have done anything different to make computer security easier or more effective today?

DEFINITIONS

DNA sequencing is the process of **reading** all the nucleotides or bases (A, T, C, G) present in a DNA molecule. Reading the order of DNA bases provides foundational information about what traits an organism may have.

DNA synthesis involves constructing DNA from scratch starting from nucleotides. The process is akin to **writing** using an alphabet of four letters (A, T, C, G) to build a desired genetic molecule.

"DNA Sequencing," Talking Glossary of Genomic and Genetic Terms, National Human Genome Research Institute, May 7, 2025, https://www.genome.gov/genetics-glossary/DNA-Sequencing; and "DNA Synthesis: The Basics," Lab Life, Integrated DNA Technologies, April 29, 2024, https://www.idtdna.com/pages/community/blog/post/dna-synthesis-the-basics.

Many argue that the artisanal nature of biology research and apprentice-like approach to biotechnology training secures biology.[28] Some things can only be learned in a lab. Maybe. What happens as large language models (LLMs) are trained on a century of research literature, including encyclopedias of research recipes and experimental protocols?[29]

Specialized versions of ChatGPT already provide unfettered access to everything from legal advice to pool repair.[30] A 2023 study reported that chatbots had "suggested four potential pandemic pathogens, explained how they can be generated from synthetic DNA using reverse genetics, supplied the names of DNA synthesis companies unlikely to screen orders, [and] identified detailed protocols and how to troubleshoot them" in less than an hour.[31] A 2025 study found that some LLMs outperformed "PhD-level virologists in problem-solving in wet labs."[32]

In 2009, when a gifted electronics hacker theorized ways to make influenza more deadly, most biosecurity experts did not worry that someone naive would actually make the virus real and risk a potential pandemic.[33] Today, as experts debate and disagree on the likelihood of who can do what with biology and by when, the trend should be obvious. A conservative strategy would presume that by or before 2040 anyone sufficiently motivated to build viruses will have access to the knowledge and tools required.

In 2002, the FBI responded to over 2,500 reports of the use or threatened use of anthrax or similar biological materials.[34] The 2001 anthrax attacks had taught many that biology could be leveraged for nefarious purposes. If the cultural, practical, and operational barriers to misuse of biology are sufficiently eroded, we should expect significant increases in the number of false and real threats. Bioterrorism is not only a potential domain of action for groups with apocalyptic ideologies.[35] Relatively simple acts could add up and overwhelm systems of deterrence, investigation, and public health. Biological "denial of service" attacks that flood supply chains or treatment

DEFINITIONS

CRISPR (clustered regularly interspaced short palindromic repeats) is a fourth-generation gene-editing technology that enables specific, targeted changes to existing DNA molecules.

Synthetic biology (SB) makes building with biology easier by advancing the science and engineering of composing living systems including from scratch (e.g., DNA synthesis).

Artificial intelligence (AI) involves "machine-based system(s) that can, for a given set of human-defined objectives, make predictions, recommendations, or decisions influencing real or virtual environments."

Generative biology combines AI models trained on natural DNA sequences with SB to create and test functions encoded within novel DNA sequences.

"Science & Tech Spotlight: CRISPR Gene Editing," US Government Accountability Office, April 7, 2020, https://www.gao.gov/products/gao-20-478sp; "Science & Tech Spotlight: Synthetic Biology," US Government Accountability Office, April 17, 2023, https://www.gao.gov/products/gao-23-106648; and "Artificial Intelligence (AI)," US Department of State, accessed July 3, 2025, https://2021-2025.state.gov/artificial-intelligence/.

facilities with overwhelming demand are not hard to imagine.[36]

We have long secured biology by limiting access to harmful biological agents. Screening DNA for potentially harmful DNA sequences and limiting advice from LLMs continues this practice, seeking to hold the line. We do not wish to erode or undermine such efforts. "The Hole in the Dike" (1975) and "The Little Hero of Holland" (1910) share the story of a boy who saves his village by plugging a leak in a dike with his finger.[37] The strategy works only if the rains stop, tides recede, and sea levels lower. Metaphorically speaking, none of these trends are true for biology. Protecting, repairing, and strengthening the existing barriers of biosecurity make sense, but not as our only long-term strategy.

ROUTINIZED CREATION OF NOVEL TOXINS OR PATHOGENS

Novel toxins and pathogens have historically emerged only from nature. A new influenza arrives each year thanks to evolution. Yet our public health and biosecurity systems struggle to keep pace. Seasonal influenza vaccines are typically 50 percent effective in preventing illness. Between 30,000 (US) and 450,000 (global) die of flu annually.[38] Most of us act as though this is how things must always be.

Building viruses from scratch became nothing special earlier in this century. Such advances helped create ambiguity and debate regarding the origins of SARS-CoV-2.[39] Regardless of how the COVID-19 pandemic started, ongoing improvements in biotechnology tools suggest that novel toxins and pathogens will arise via human activity faster than we are accustomed to. The tools do not cause harm in themselves and will largely be used for good.[40] But if used to purposefully cause harm, such tools, sharpened for beneficial purposes, will cut differently.

Proteins are biomolecules that carry out diverse functions. The shape of a protein helps determine its function. Tools such as AlphaFold—an AI tool for predicting protein structure—can compute the expected shape of a protein from its primary amino acid sequence.[41] Protein structure simulation tools pose limited direct biosecurity risks. The shape of the protein, while informative, does not absolutely determine what the protein does (i.e., the protein's function).[42]

Protein design tools "can predict the sequence of proteins with specified structural or functional properties."[43] Thus, protein design tools are slightly more risky in that they could be used to change a viral protein so that an existing vaccine might no longer work.[44] Advancements in computational tools are expected to allow the creation of "proteins, enzymes, and potentially even whole organisms optimized across different functions."[45]

What happens next when generative artificial intelligence and synthetic biology combine? "Generative biology" results. For example, Evo and ESM3 are biological foundation models. Evo is an LLM trained on natural DNA sequences.[46] Evo generates novel DNA sequences in response to user-generated prompts, akin to how ChatGPT generates human-readable text. Evo can already generate novel sequences for individual genes that, when synthesized, encode functional biomolecular components (e.g., DNA editors).[47]

Another foundation model, ConoDL, was developed for marine snail toxins, among the most deadly poisons known.[48] The Select Agents and Toxins List—a list maintained by the US government of biological agents and toxins that have the potential to seriously threaten human, animal, or plant health—already seeks to prohibit snail toxin availability.[49] Could anyone use models like ConoDL to make novel toxins? In 2022, Collaborations Pharmaceuticals, a company using AI for drug design, repurposed their publicly

trained toxicity-prediction model to quickly design forty thousand potentially toxic chemicals, rediscovering the nerve agent VX.[50] While foundation models for biomolecules will be developed and almost exclusively used for good, it is increasingly straightforward to imagine that such models could be used to make novel biological toxins.

In 2025 the US National Academies of Sciences, Engineering, and Medicine (NASEM) noted that AI models are becoming capable of suggesting modest changes to existing pathogens that could enhance lethality, help evade detection or diagnostics, or confer drug resistance.[51] Should we expect more? Could an LLM ever be used to generate an entirely novel pathogen from scratch? Not yet. But researchers are pushing the frontiers of LLMs to generate genomes encoding bacterial viruses. These initial attempts are motivated by benevolent reasons. An antibiotic-resistant infection might need to be treated with an AI-designed bacterial virus specifically optimized to clear the infection.

"Directed evolution" allows researchers to create new biological functions without needing to perfectly understand how the biology works. Instead, by carefully sculpting selection pressures in a laboratory environment, researchers can influence how molecules and organisms evolve. Such tools have been used to create cancer-fighting viruses and bacterial viruses that can clear infections resistant to all known antibiotics, and even to predict and avoid the development of antibiotic resistance.[52] Directed evolution can also be used to create new enzymes, allowing for new chemical-synthesis techniques.[53] While not a direct threat, directed evolution could be used alone or with other methods to select for mutant virus proteins that are, for example, less likely to be recognized by existing antibodies.[54]

AI, directed evolution, and related tools make the creation of novel toxins and pathogens easier. Already, such tools are powerful enough to make biosecurity more challenging. The issue is not only the novelty of potential toxins or pathogens that could be produced, but also the potential for widespread proliferation of such explorations. The future promises a world in which new biological threats arise more quickly than we are accustomed to, and not only from nature.

NATION-STATES REEMBRACE BIOLOGICAL WEAPONS PROGRAMS

A world in which nations acknowledge and use biological weapons is hard to fathom. Yet some declare such futures inevitable.[55] The United States stopped its offensive bioweapons program in 1969. What came before and why did we stop?

In 1915, the German military sought to infect Allied horses with anthrax and glanders.[56] In response, the Geneva Protocol banned the use of chemical and bacteriological warfare. The protocol was ratified before World War II by all great powers except for the United States and Japan.[57] Unfortunately, the Geneva Protocol was toothless, lacking sufficient enforcement mechanisms and excluding key biothreat agents.[58] Before and during World War II, at least six countries began or deployed biowarfare programs.[59] After the war, at least fifteen nations operated bioweapons programs.[60]

Concern over offensive biological weapons programs eventually prompted a concerted effort to "lower the temperature" and strengthen the Geneva Protocol.[61] Several nations ended their biological weapons programs, including the United Kingdom (1956) and the United States (1969).[62] The UK then led a push for stronger international consensus against the use of biological weapons, culminating in the Biological Weapons Convention (BWC).[63] Unlike the Geneva Protocol, the BWC banned development and testing of bioweapons, not just their use. One

hundred eighty-nine state-parties and four other signatories have ratified the BWC since it came into force in March 1975.[64] Four nations have neither signed nor ratified the BWC: Chad, Djibouti, Eritrea, and Israel.

Why did most countries stand down their offensive biological weapons programs? While reasons vary, the United States offers an important example. President Richard Nixon leveraged a three-pronged argument for abandoning biological weapons work. First, the United States already had weapons sufficient for strategic deterrence (e.g., nuclear). Biological weapons—as a distinct category—were not needed to secure America. Second, as the world's largest economy, the United States holds a relative security advantage if weapons remain expensive; biological weapons, once developed, are relatively cheap. Third, President Nixon recognized that bioweapons have limited tactical utility on the battlefield, meaning that once released, bioweapons are indiscriminate and could harm one's own troops or population. Taken together, these reasons offered a compelling and logical case for standing down offensive bioweapons programs.[65]

Not every nation was so persuaded. As of April 2025, an unclassified US Department of State (DOS) report noted that North Korea and Russia have, to this day, failed to shut down their offensive bioweapons programs.[66] The DOS elaborated that North Korea "continued its program despite having become a State Party to the BWC in 1987" and maintains a "dedicated, national-level offensive BW program." Russia has "absorbed, not dismantled" the Soviet-era program and is "extensively modernizing Soviet-era biological warfare infrastructure that could support its present-day offensive program." In October 2024, the *Washington Post* reported that Russia may be expanding its covert bioweapons program, rebuilding much of a Soviet-era bioweapons compound.[67]

China and Iran may also be in noncompliance with the BWC despite being party to it. According to the DOS, the United States "does not have sufficient information to determine whether China has fulfilled its BWC obligation to eliminate its assessed historical biological warfare program" but does assess that in 2024 "Chinese military medical institutions conducted toxin and biotechnology research and development with potential BW applications." The DOS also notes that Iran has not "abandoned its intention to conduct research and development of biological agents and toxins for offensive purposes."[68]

Despite the US government's findings, no nation brags openly about having an offensive biological weapons program. However, nations increasingly accuse one another of having such programs. The escalating pace and explicit rhetoric is potentially dangerous in and of itself. In May 2023, China accused the United States of making race-specific bioweapons to target opponents, a claim the Pentagon strongly denied.[69] In March 2022, Russia and China both accused the United States of funding biological weapons labs in Ukraine for use against Russian soldiers.[70] In October 2022, Russia specifically charged the United States and Ukraine with being in noncompliance with the BWC before the United Nations Security Council, invoking Article VI of the BWC for the first time, prompting strong US denials.[71] The current situation creates a climate in which the behaviors of the 1920s and 1930s could repeat, leading to the remilitarization of biology among nations with the tools of the twenty-first century. Some security experts argue that these types of accusations are intended to sow confusion and distort perceptions over offensive bioweapons programs.

Public perception that the United States and other nations have continued their offensive bioweapons programs undermines diplomatic efforts to de-escalate globally. In 2022, 47 percent of Americans believed or were unsure about whether

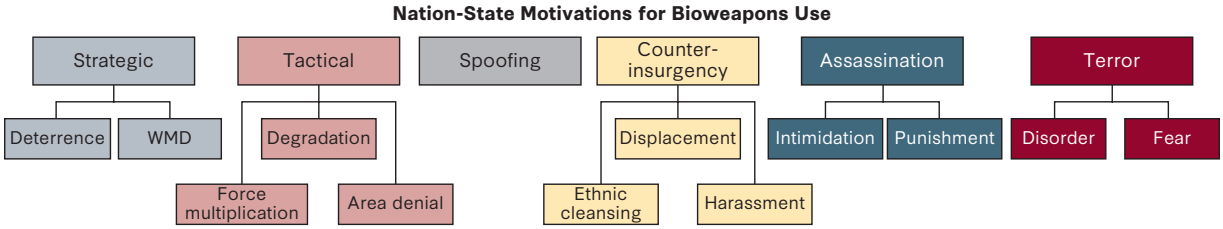


FIGURE 4 Categories of nation-state motivations for developing and using biological weapons
Source: Adapted from a chart by Brett Edwards. Image by Sarah Moront and Raj Patel.

the United States was assisting Ukraine in developing chemical or biological weapons.[72] Public funding for beneficial emerging biotechnologies routing through the US Department of Defense (DOD) risks reinforcing the perception that biotechnology research is closely aligned with military needs and goals.[73] Even seemingly innocuous projects, such as the US Defense Advanced Research Projects Agency's (DARPA) Insect Allies program, which aimed to alter insects to protect the US food supply from pathogens, drought, and flooding, sparked bioweapons concerns.[74]

With reference to the nuclear-security doctrine of deterrence known as M.A.D. (Mutual Assured Destruction), we imagine and refer to the possibility that nations revitalize bioweapons programs via doctrine driven by ignorance and mutual insecurity as S.A.D. (Stupidly Assured Destruction). While M.A.D. was a well-developed strategy that contributed to geopolitical stability, S.A.D. would represent a complete failure of strategy and absence of leadership, contributing to significant public health, biosecurity, and geopolitical risks.

Rational reasoning could also result in the remilitarization of biology (figure 4). In a world that has failed to eliminate nuclear weapons, bioweapons can serve as strategic deterrents.[75] Bioweapons as "the poor man's atomic bomb" would likely cost an order of magnitude less to build than nuclear weapons.[76] If nuclear weapons were ever used, bioweapons could offer a strategic response, harming or eliminating a large adversarial population.[77] Imagine an Operation Sea Spray–like scenario involving multi-drug-resistant, pathogenic microbes.

Nations might also use bioweapons to maximize their warfighting capabilities. Tactical use of a biological weapon could be useful in a limited-campaign area like Taiwan. In one 2024 planning scenario, a coronavirus variant yet again impacts the readiness of the US Navy while simultaneously creating a public health emergency among Taiwanese civilians; China capitalizes on this vulnerable moment by "rescuing" Taiwan.[78] In the hypothetical scenario, invading Chinese troops and essential workers are protected against the new variant via a surreptitious vaccine rolled out under the guise of a standard SARS-CoV-2 booster campaign.

Even the threat of a biological weapon could be useful—spoof or not (figure 5). Consider if Russia announced a new SARS-CoV-2 variant circulating in and around Moscow. Researchers reportedly sequence the genome, finding that thirteen silent mutations result in the following changes—agc ctg gcg gtg gcg gtg aaa cgc gcg att aac att taa—which, when translated to single-letter amino acid abbreviations, spell SLAVA VKRAINI ("Glory to Ukraine!"). Russia declares it is under biological attack and falsely represents that they have traced the source of the variant back to a company in the United States that sent synthetic SARS-CoV-2 genome fragments to a Lithuanian virology lab. In this scenario, everything could occur as a totally

THIS IS A HYPOTHETICAL EXAMPLE. NOTHING REPRESENTED BELOW IS KNOWN TO HAVE HAPPENED OR SHOULD EVER BE PURSUED.

1 May 2025

The Russian Ministry of Health reports a new SARS-CoV-2 variant circulating in and around Moscow.

14 May 2025

The WHO confirms a new SARS-CoV-2 variant circulating in Russia, Belarus, and Kazakhstan with increased infectivity.

14 May 2025

Genome sequences are shared with Western repositories (EMBL, NCBI, etc).

15 May 2025

The Chinese Academy of Sciences reports 23 mutations of interest specific to the new variant, distributed across the genome, with 13 of these mutations located in non-coding regions.

agc ctg gcg gtg gcg gtg aaa cgc gcg att aac att taa

16 May 2025

Multiple social media accounts note that the 13 non-coding codons, when translated to single-letter amino acid abbreviations, spell:

SLAVA VKRAINI

17 May 2025

Kremlin declares Russia under biological attack via a synthetic SARS-CoV-2 variant.

18 May 2025

The SVR releases electronic copies of purchase orders showing that a U.S.-based gene synthesis company supplied synthetic SARS-CoV-2 genome fragments encoding these mutations to a Lithuanian virology lab.

19 May 2025

The gene synthesis company in question publicly denies supplying fragments to Lithuania, noting strict adherence to sequence screening best practices for all orders.

20 May 2025

The SVR releases evidence of a Tallinn-based hacker group compromising the gene synthesis company's servers and making changes to sequences after sequence screening.

21 May 2025

The U.S.-based gene synthesis company admits that it does not perform post-synthesis sequence screening to verify the sequences that are ultimately produced. They reaffirm that they did not supply synthetic viral fragments to any customers in Lithuania.

22 May 2025

Russia formally accuses the United States of facilitating a bioengineered attack on Matushka Rossiya (Mother Russia)

FIGURE 5 Unfolding of a hypothetical #FAKEBIO biothreat scenario
Source: Image by Drew Endy.

falsified digital attack, with no actual virus ever having been created, deployed, or detected. Such a scenario could be exploited not just for propaganda purposes but to justify retaliatory actions such as sanctions or direct military action.

Nations could also use biology for counterinsurgency, targeted assassinations, or terror in the name of "regime security." Differences in the DNA sequences of individuals and groups might provide sufficient information to target one person or group and not others, undermining one of President Nixon's three 1969 reasons for abandoning biological weapons work. The possibility of genetic targeting long seemed thankfully hypothetical, but the ongoing development of super-high-fidelity gene-editing systems, developed for therapeutic purposes, forces careful reconsideration.[79] A 2017 Chinese military strategy textbook identified "specific ethnic genetic attacks" (特定种族基因攻击) as a potential offensive bioweapon targeting entire ethnic groups.[80] Political opponents could be targeted with surreptitious biological weapons instead of chemical toxins.[81] Governments could even seek to arm proxies with biological weapons to seed terror in rival nations without direct attribution.

Cultural and political norms helped halt the development, promulgation, and use of bioweapons: Those who would use biology to cause harm were and should still be declared "hostis humani generis," or enemies of all mankind operating outside all rules and norms of law.[82] This framing reflects the intrinsic danger of weaponizing biology and the overwhelming threat bioweapons pose to civilization and society. Such cultural and political norms must themselves be defended. Absent renewal, such norms hold until they fail. Russia, North Korea, and Syria have recently used banned chemical weapons, including VX and Novichok agents, against dissidents without significant lasting repercussions.[83] Experts warn that the ongoing erosion of norms against the use of chemical weapons could spill over to bioweapons.[84]

A world simply researching bioweapons would itself be a world of greater risk. Accidents in laboratories are common.[85] The last person to die of smallpox was Janet Parker in 1978.[86] She was a medical photographer working in a darkroom one floor above a lab studying the virus. The lab working with the virus was rushing to complete research before being shut down; they had already been informed by World Health Organization (WHO) inspectors that their working conditions were unsafe. An air duct connecting the lab to an office next to the darkroom was the presumed route by which the virus got to Ms. Parker. Once sick, and not expecting to be infected with smallpox, she was first treated for chicken pox before dying. Past bioweapons programs are also not free from accidents. In 1979, anthrax spores were accidentally released from a then-secret Soviet bioweapons facility, killing sixty-six people.[87]

Some have reasoned that research with dangerous pathogens could be pushed to a level of operational safety and security such that the benefits outweigh the risks.[88] The US nuclear weapons program suggests otherwise. Despite an extraordinary focus on safety and security, on several occasions the United States has lost nuclear weapons or materials. For example, in 1966, the US military accidentally dropped four hydrogen bombs in Spain.[89] One bomb landed without detonating and was quickly recovered. Two bombs detonated on impact, but luckily, had built-in safeguards to prevent nuclear explosions. The last hydrogen bomb remained missing for nearly four months before it was finally recovered from the Mediterranean Sea. Unlike nuclear weapons, a self-reproducing bioweapon could have impacts that would not be contained to a single point of release.

THE UNITED STATES NO LONGER LEADS THE WORLD IN BIOTECHNOLOGY

Beyond the intentional weaponization of biology by bad actors, losing leadership in biotechnology would add to biosecurity risks.[90]

Imagine computer security if UNIX, iOS, Android, or Windows had been invented outside the United States. What if the Silicon Valley of mid-twenty-first-century biotechnology is in Shenzhen or São Paulo? Falling behind in biotechnology would leave the United States exposed, from agriculture and medicine to economic growth, manufacturing, and national security. Biotechnology leadership is also absolutely required to help preemptively dissuade others who might use biotechnologies to cause harm. World War II was won in part due to scientific leadership with radar, code breaking, computing, and atomic bombs—it's hard to imagine winning a war where another nation can use a technology in which we have fallen behind.[91]

The United States and its allies have worked incredibly hard to remain world leaders in every field of science and technology. It is difficult to imagine what no longer leading in any technology, especially biotechnology, might look like.[92] Yet the United States falling behind becomes more likely should two trends continue. The first is "fear of the fear" of biotechnology.[93] A United States that "rides the brakes" on biotechnology will not lead in biotech going forward. Second, the United States can fall behind by failing to support biotech strategically.[94] Biotechnology offers endless opportunities and positive applications. A democratic system places greater political pressures to fund the most compelling short-term applications (e.g., cure this specific disease now). A centrally controlled authoritarian government can gain strategic advantage by unilaterally directing resources to advance high-leverage foundational capacities that support all applications.[95]

Falling behind in biotechnology would expose any nation to entirely new biological risks. What in the world is a "debilitating peptide attack," as one expert privately warned? Another novel risk could involve a mirror bacteria that "would likely evade many immune mechanisms mediated by chiral molecules, potentially causing lethal infection in humans, animals, and plants."[96] Stated differently, risks increase when we have zero prior knowledge or experience responding to novel potential threats. Never mind all the "normal" challenges associated with developing, manufacturing, and distributing vaccines, diagnostics, or treatments for any known pathogen or toxin. In a worst-case scenario, we may lack the capacity to produce treatments domestically. Imagine being dependent on the goodwill of an adversarial nation for medical countermeasures.

Adversaries believing that we are unprepared as a consequence of not leading in biotechnology would themselves be less deterred—that is, more likely to deploy bioweapons against us. Failure to lead would also contribute to declining economic and geopolitical power. Some estimates suggest that the economic activity derived from biotechnology will increase from 5 percent to 30 percent of the global economy overall, and perhaps up to $30 trillion by 2050.[97] Failure to lead economically will also have outsize impacts on soft power, with others gaining leverage over the "rules of the road," including aspects directly relevant to biosecurity.

ONGOING TRENDS LEADING TO EROSION AND WEAKENING OF PUBLIC HEALTH SYSTEMS

Public health involves all measures that help prevent people from getting sick—everything from water purification and sewage treatment to vaccine campaigns, nutrition, emergency room beds, and urgent care clinics. Public health also includes surveillance, vaccines, diagnostics, and treatments that can be used to identify, prevent, and respond to biological risks impacting people and communities.

Biosecurity and public health go hand in hand. If we lack the capacity to treat those with natural illnesses, then any suffering from a purposeful illness might be missed entirely or mistreated.

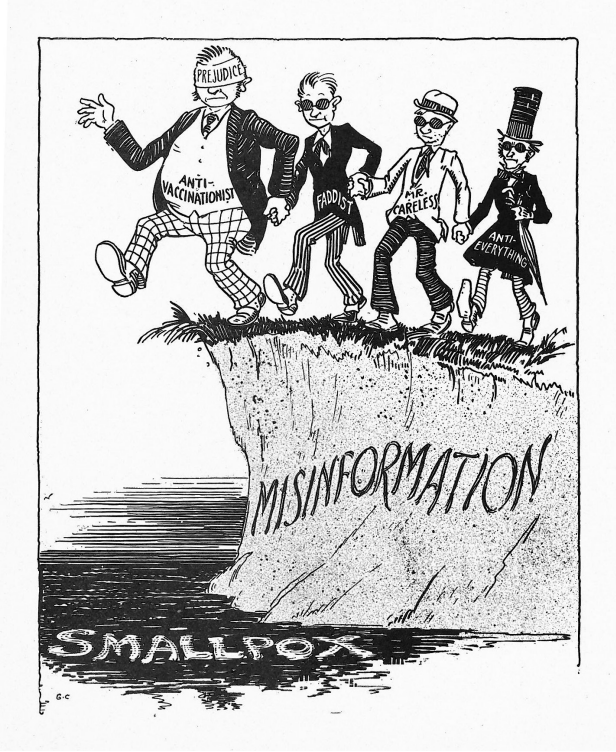


FIGURE 6 A 1930 political cartoon criticizing how the spread of misinformation among the public blinded individuals to the threat of smallpox
Source: *Health in Pictures: A Collection of Cartoons Illustrating the Fundamental Principles of Personal and Public Health* (American Public Health Association, 1930), https://media.snopes.com/2021/05/Health-In-Pictures-Smallpox-Misinformation-Cartoon.pdf.

If there is an inability to deter, stop, or respond to a purposeful biological-based attack, then public health capacities can be overrun.

Consider what must be true for a parent to decide to vaccinate their child during an outbreak. The vaccine must exist, be shown to work via clinical trials, and be available at an accessible location for an affordable price. Critically, the parent must also believe that the vaccine is safe and would provide significant benefit to their child or the community. Stated differently, public health requires capabilities, capacities, and trust.

Misinformation undermines public health (figure 6). False claims that childhood vaccines are linked to autism reduce vaccination rates.[98] Reduced vaccination rates lead to outbreaks, like those in the United States and elsewhere (e.g., Samoa).[99] Misinformation is readily amplified and promulgated, especially during times of crises. A 2021 study found over six hundred SARS-CoV-2 vaccine–related rumors and conspiracy theories across fifty-two countries during the COVID pandemic.[100] Absent strategic efforts to prepare for and counter misinformation, such scenarios will get worse.

Shutting down discussion or government censorship of free speech are rarely effective measures to combat complex biological challenges. As difficult as it may be to carry out educated discussion on these topics, there is no substitute for engaging with the public to educate and foster informed dialogue.

Political polarization leading to factionalism further undermines public health. Unlike individual health, public health requires some baseline sense of belonging to a broader group and a community that agrees on basic principles of scientific expertise and social governance. Without some shared sense of identity, who would seek to suffer the inconvenience or pain of a vaccine jab only to help others?

When political ideologies become intertwined with public health, people can reject expert- or evidence-based advice. Increasing political polarization was linked to greater health risks in the COVID pandemic, shifting trust toward "in-group leaders" rather than doctors and scientists.[101] Confusion, or worse, arises when leaders from competing political parties issue conflicting statements. A 2022 study of 165 European regions found that "when the divide in political trust between supporters and opponents of incumbent governments within societies is high, we observe[d] consistently higher COVID-related excess mortality" during the first wave of the pandemic.[102] At the international level, nationalism

and disagreement further hinder cooperative efforts underlying global public health and biosecurity.

Entrenched economic interests can also undermine public health. Consider avian influenza (i.e., bird flu) strains circulating in the United States in 2024. As required, herds and flocks were sacrificed to help contain the spread.[103] But testing in cows was not initially well established. Because individual cows are relatively expensive compared to chickens, there was reluctance among farmers to test animals and risk sacrificing them.[104] Amid mounting concerns, the US Department of Agriculture (USDA) eventually acted in December 2024 with a federal order to test milk nationwide.[105] By April 2025, at least one person had died of bird influenza in the United States.[106] If the bioeconomy grows as expected, with ever more living systems being used to make essential or valuable materials, then the potential for entrenched economic interests becoming misaligned with public health and biosecurity will increase.[107]

Conflicting interests, politicalization, and attacks on trust are not new. But their ability to undermine public health is at risk of increasing just as trends in biotechnology make risks associated with purposeful misuse worse. Imagine attempting to respond to a biological attack that coincides with a disinformation campaign, on top of widespread misinformation and potential economic losses, all within a highly polarized society supported by healthcare systems winnowed to the bare minimum by market forces.

URBANIZATION, GLOBALIZATION, TRAVEL, AND AGRICULTURE AMPLIFY BIOSECURITY RISKS

Infections require connections. Globalization makes it more likely that infectious diseases will impact more people. Morning medicines are most likely made using active ingredients whose key starting materials were sourced from China or India.[108] Friends arriving from airports took one of more than one hundred thousand commercial flights that navigate the globe each day.[109] Just a few hours of any day show how connected we are.

Over 1.1 billion people traveled internationally in the first nine months of 2024, returning to pre-pandemic levels.[110] When sick people travel, their sickness travels with them. In 2014, a man from Liberia arrived in Texas and was later diagnosed with the United States' first case of Ebola.[111] A year later, another traveler from Liberia touched down at New York's John F. Kennedy International Airport, bringing with him Lassa fever.[112] Annual domestic and international air passenger numbers are expected to increase from roughly nine billion in 2023 to roughly twenty billion in 2042.[113] Expansion in rail travel will also contribute to increased disease transmission risk, with rail passenger traffic expected to double by 2050.[114]

By 2050, around two-thirds of the global population is expected to live in an urban area, up from half today.[115] Cities with a population of over ten million, or "megacities," are expected to increase from forty-four to more than sixty, primarily in Asia and Africa.[116] How cities develop matters. Sanitation, population density, infrastructure, placement of essential services, and more impact disease transmission. Historically, urbanization in low-income countries has contributed to the spread of diseases.[117] Respiratory diseases, including influenza, measles, and tuberculosis, thrive in high-population-density environments. Increased urbanization and population density are correlated with increased rat populations and thus increased risk of rat-borne disease transmission.[118] The growth of megacities will increase infectious disease likelihood if planning does not adapt to address public health and biosecurity challenges.

How goods travel among cities, suburbs, towns, and farmlands impacts biosecurity. DHL's

FIGURE 7 A probiotic facility supplying North America and Europe located on the outskirts of Guadalajara, Mexico
Source: Photo by Drew Endy.

2025 Global Connectedness Tracker assessed that global connectedness "is holding steady at a record high level" based on analysis "of trade, capital, information, and people flows—both worldwide and at the level of individual countries."[119] Global trade was estimated to hit a record $33 trillion in 2024.[120] Nearly a quarter of "the value of all goods and services produced was traded internationally" in 2023. In economic terms, global trade is projected to quadruple by 2050.[121] Trade includes products such as electronics, shoes, and clothes that add little biosecurity risk, but also foods and medicines. Consider potential biosecurity risks associated with probiotic supply chains (figure 7). A well-intentioned probiotic factory that churns out tens of millions of dollars of products could be hijacked to help spread a pathogen or toxin.

Food consumption dependent on international trade has more than doubled since 1995 and is expected to increase going forward.[122] By mid-century, roughly half the world's population "may depend for survival on calories produced oceans away."[123] Growth in food trade increases yet another route for biothreat transmission, whether purposeful or accidental.[124] From 2002 to 2019, there were tens of thousands of cases of salmonella caught by US screening authorities.[125] One 2024 incident involved cinnamon-flavored applesauce sourced from Ecuador that was contaminated with lead, poisoning over four hundred children in the United States.[126] The breadth and diversity of inputs to our food system offer a massive "attack surface" to would-be adversaries.[127] Imagine terrorists spreading a toxin that causes botulism throughout the US milk supply.[128]

Market pressures have favored the adoption of monoculture agriculture, resulting in large-scale, homogeneous populations in plant and animal production. Today, monoculture systems cover 80 percent of the world's arable land, including over four hundred million acres in the United States.[129] The rise of industrial food animal production and Concentrated Animal Feeding Operations (CAFOs) in highly developed nations further favors monoculture production in animals.[130]

Monoculture systems present significant biosecurity risks. Fields or farms containing clonal or near-clonal copies of the same species of plant or animal means that pathogens might spread more rapidly once established.[131] CAFOs used in monoculture animal production have been associated with several zoonotic pathogens.[132] Farming and feeding nearly ten billion people by 2050 is expected to require over 50 percent more food production than today, suggesting that monoculture of both plants and animals is likely to become still more pervasive.[133]

FIGURE 8 Horseshoe crabs are bled at the Charles River Laboratory in Charleston, South Carolina, USA. A compound found in horseshoe crab blood is used to test medicines and medical tools to make sure they are safe for patients

Source: Tom Maloney, Ryan Phelan, and Naira Simmons, "Saving the Horseshoe Crab: A Synthetic Alternative to Horseshoe Crab Blood for Endotoxin Detection," *PLOS Biology* 16, no. 10 (2018): e2006607, https://doi.org/10.1371/journal.pbio.2006607.

BIODIVERSITY AND ECOSYSTEMS ARE DEGRADED OR DESTROYED

Humans need nature. More than half our oxygen comes from plankton and seaweed in the ocean.[134] As much as one out of every three bites of our food was made possible by pollinators such as bees and bats.[135] Bats alone provide services worth between $4 and $50 billion to the United States annually.[136] More than 40 percent of pharmaceutical inputs are still harvested from natural sources.[137] Factors isolated from the blood of endangered horseshoe crabs are used to test the safety of injectable medicines and biomedical implants (figure 8).[138] From our medicines to our food to the air we breathe, human survival is absolutely dependent on other species.

Yet biodiversity is on the decline. Habitat loss, pollution, overharvesting, and climate change are the major factors.[139] Globally, more than one million plant and animal species are under threat of extinction.[140] Sixteen percent of total tree cover has been lost in the last twenty years.[141] Wildlife populations have declined by 70 percent in the past fifty years.[142]

Loss of biodiversity has been shown to increase disease transmission.[143] Biodiversity is thought to reduce disease transmission when infectious agents enter "dead-end hosts" from which they cannot productively replicate.[144] Several studies have found correlations between low bird diversity and greater human risk of West Nile encephalitis in the United States.[145]

Plant biodiversity loss negatively impacts the discovery of drugs, food supplies, and human livelihood.[146] For example, Taxol (paclitaxel) is an essential medicine for treating several cancers. The key starting material for making Taxol was originally derived from the bark of the Pacific yew, a tree found in the forests of the Pacific Northwest.[147]

To some, biodiversity loss is intrinsically immoral and thus motivates action. Island Conservation is a charity whose mission is to eradicate invasive rodents from islands.[148] Invasive rats feed on the eggs and young of endangered birds and reptiles, natural species that transport the majority of island nutrients to and from the sea and contribute to coral and flora health.[149] Given the challenges of manual eradication, Island Conservation and others have been considering the use of gene drives to create bioengineered rats designed to reduce or eliminate invasive rat populations.[150] Similar approaches are being considered for European rabbits, which are invasive to Australia.[151] While these efforts are well intended, the possibility of a "population collapse gene drive" being used to modulate mammalian populations raises concerns. Could a gene drive targeting European rabbits accidentally escape Australia and eliminate rabbits from their native Europe?[152] A planet with increasing species loss will also be a world of increasingly desperate actors seeking to leverage biotechnology to intervene in diverse environments.[153]

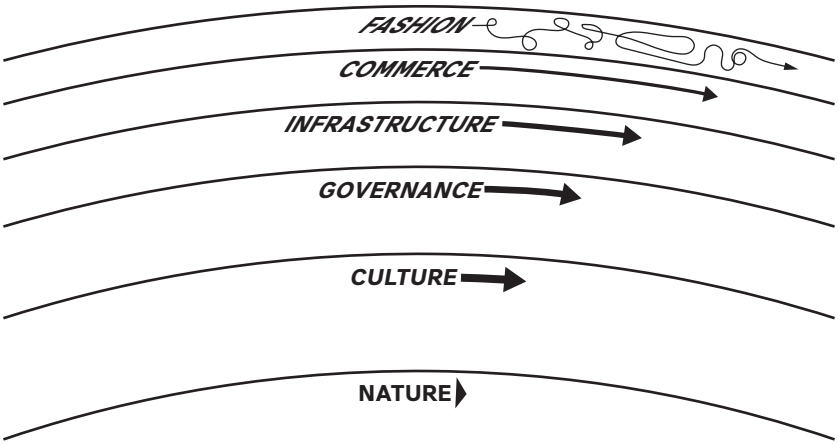


FIGURE 9 Stewart Brand's framing of the six layers of society and their respective paces of change through time
Source: Stewart Brand, *The Clock of the Long Now: Time and Responsibility* (Basic Books, 1999).

SOCIETAL TRENDS THAT WORSEN BIOSECURITY

In 1999, Stewart Brand elaborated his pace layers framework (figure 9).[154] Brand describes a functioning society across six characteristic layers: nature, culture, governance, infrastructure, commerce, and fashion. The layers are stacked one upon another, with nature at the bottom and fashion at the top. The pace of change increases from bottom to top; nature and culture are slow to change, while commerce moves quickly and fashion is fleeting. If and when the layers shift out of alignment and become imbalanced, calamities can ensue. Biosecurity requires that all six layers are working well individually and in combination.

Which layers experienced or contributed to the COVID pandemic? All layers. Coronaviruses first arose from nature. A culture of science seeking to understand studies coronavirus biology. Our governance framework for research with viruses created ambiguity regarding pandemic origins. Public health infrastructure was quickly saturated as the virus spread. Strained manufacturing infrastructure and offshore commercial supply chains led to rationing of needed equipment and supplies. Wearing masks was in or out of fashion depending on cultural identity and government regulation. And so on.

Biosecurity trends involving biodiversity loss (nature), political partisanship (governance), cities and travel (infrastructure), and globalization (commerce) have already been mentioned. Additional aspects to note include passivity—normalizing the notion that biology just happens to us (culture), incentivization and exploitation of crisis to entrench power (governance), and reduction

DEFINITION

Gene drive: "A type of genetic engineering technique that modifies genes so that they (the genes) don't follow the typical rules of heredity. Gene drives dramatically increase the likelihood that a particular suite of genes will be passed onto the next generation, allowing the genes to rapidly spread through a population and override natural selection."

Donavyn Coffey, "What Is a Gene Drive?," LiveScience, April 17, 2020, https://www.livescience.com/gene-drive.html.

of public health capacities (infrastructure and governance).

A holistic approach to biosecurity must be mindful of activities and trends spanning all layers and the secondary impacts that can arise when the layers slip out of alignment. A biological incident that impacts workers integral to fertilizer production could cause regional hunger or starvation.[155] An epidemic that stops law enforcement officers from serving could lead to an uptick in crime and sporadic collapse of civil society. Our ecological, infrastructure, and governance systems form a network of civilization, which is simultaneously resilient yet increasingly difficult to govern and secure.

CONCLUSION

Biosecurity has long posed challenging and largely unsolved problems. Current trends make clear that biosecurity will become more challenging and involve ever more significant worst-case scenarios. Technologies including AI and distributed biomanufacturing suggest futures in which anyone anywhere will gain the capacity to source any toxin or pathogen. Nation-states could reembrace biological weapons programs, raising the risks of lab accidents and the likelihood of purposeful misuse. The United States, a long-standing leader in biotechnology, may soon become a strong second or third. Worsening ecological decay and biodiversity loss will increasingly incentivize crisis actors. Public health organizations are being undermined by misinformation, disinformation, and political factionalism, all as the layers of our society become more intertwined in ways that, by default, contribute to risk and reduce our ability to prepare and respond.

We lay out these trends and worst-case scenarios to inform and motivate action. It is not too late to outmaneuver possible bad paths. We must work to secure biology. But doing so requires that we clearly understand and acknowledge the trends at hand and ahead of us. We must develop our best ideas and organize them into strategies that can be turned into sustained actions sufficient to secure the future.

2. Using Biology to Secure Biology

"I want to consider the preparations that were made before war broke out. If we were short of tanks, aeroplanes, and tractors, it was mainly because we had put our not inexhaustible supplies of money and labor into concrete. . . . We had been taught to put our whole trust in the Maginot."

—Marc Bloch, Strange Defeat

INTRODUCTION

In 2001 the United States was surprised by an anthrax attack. A scramble ensued. One outcome was the creation of the National Biodefense Analysis and Countermeasures Center, "a one-of-a-kind facility dedicated to defending the nation against biological threats."[156] In 2009 swine influenza (H1N1) emerged.[157] The United States rushed to develop vaccines but the virus still infected about sixty million and killed roughly twelve thousand Americans.[158] From 2014 to 2016 an Ebola outbreak in West Africa killed more than ten thousand people and infected eleven in the United States.[159] By early 2020 SARS-CoV-2 was well established in the United States. The 2002 SARS-CoV-1 and 2012 MERS outbreaks had previously raised alarms regarding coronaviruses, but the United States first met the COVID-19 pandemic with mask shortages, poor communication strategies, and inaccurate test kits.[160] The United States has long aspired to transcend a "react and forget" cycle when it comes to biosecurity. In practice, however, the nation scrambles in response to a recurring parade of biological threats, argues internally while forgetting how bad the last crisis was, and prays for no future pandemics, all while the next one inevitably develops.[161]

Historically, American casualties from infectious disease are about sevenfold greater than from war. There is no security domain other than biology for which the United States largely waits for the next bad thing to happen before taking decisive action. When appropriately tasked, supported, staffed, and led, the United States creates the best defenses in the world.[162] Given that we expect biosecurity threats to become more frequent and dangerous, now is the time to transition to a biosecurity strategy characterized by sustained vigilance and ambition. We must deter rational actors via denial of objectives. We must

DEFINITION

Medical countermeasures (MCMs) traditionally include diagnostics, medicines, and vaccines that help prevent, detect, or respond to biological threats.

Lawrence O. Gostin, Lisa Brown, Shalini Singaravelu, and Matthew Masiello, eds., *Future State of Smallpox Medical Countermeasures* (National Academies Press, 2024), xiii, https://nap.nationalacademies.org/read/27652/chapter/1.

TABLE 1 KEY BIOSECURITY DEPARTMENTS AND AGENCIES

Department/Agency	Core Biosecurity Responsibilities	Subgroup
Department of State (DOS)[a]	Partners with allies and international organizations to minimize the risk of infectious diseases to Americans at home and abroad by funding global health programs; lead agency involved in the Biological Weapons Convention (BWC).[b]	
Environmental Protection Agency (EPA)[c]	Protects human and environmental health during bioincidents.	
Department of Health and Human Services (HHS)[d]	Invests in medical countermeasures and research to respond to biothreats; leads response to public health emergencies; establishes and regulates biosafety policies.	ASPR[e]; CDC[f]; NIH[g]; ARPA-H[h]; FDA[i]
Department of Energy (DOE)[j]	Funds basic research and harnesses lessons learned from nuclear security to strengthen biodefense.[k]	Z Division[l]
Department of Defense (DOD)[m]	Develops and maintains biological defense capabilities for the US military; invests in innovative technological defense solutions; partners with allies to reduce global bioweapons risks.[n]	CBDP[o]; DARPA[p]; DTRA[q]
Department of Agriculture (USDA)[r]	Inspects plants, animals, and foods for potential biological threats.	APHIS[s]; Select Agent Program[t]
Department of Commerce (DOC)[u]	Implements export controls on potential dual-use biotechnologies to prevent dangerous misuse.	
National Science Foundation (NSF)[v]	Supports fundamental research and education in science and engineering, including research to combat bioterrorism.[w]	
Department of Homeland Security (DHS)[x]	Secures the nation from biothreats by strengthening preparedness, resilience, and counterterrorism efforts; invests in R&D for MCMs, early warning/detection systems, and threat characterization.	BioWatch[y]

Notes: Key federal departments and agencies that invest in and coordinate biosecurity responsibilities, including subgroups that fall under their governance; accurate as of January 2025

Source: Chart by Raj Patel and Rhea Jain.

make the potential practical consequences of any irrational actors insignificant. Doing so will also make natural infectious diseases operationally obsolete, a dividend whose domestic economic benefits could approach $1 trillion annually.

Where to start? During the Trojan War the ancient Greeks, after a decade of failed siege, feigned retreat and left behind a massive wooden horse as a false gift of surrender. Hidden inside were elite soldiers who, once within Troy's walls, emerged at night to open the gates for the returning Greek army. Troy fell not because of a direct assault, but because its defenses assumed the threat would come from outside. Today, in biosecurity, we do not yet have sufficient towers or walls worth guarding. "Only" needing to worry about fantastical biological Trojan horses—toxic peptides in

TABLE 1 (*Continued*)

a. "About the US Department of State," United States Department of State, accessed May 24, 2025, https://www.state.gov/about/; b. "Office of Chemical and Biological Weapons Affairs," US Department of State, accessed May 24, 2025, https://www.state.gov/bureaus-offices/under-secretary-for-arms-control-and-international-security-affairs/bureau-of-arms-control-deterrence-and-stability/office-of-chemical-and-biological-weapons-affairs/; c. "Our Mission and What We Do," US Environmental Protection Agency, accessed March 26, 2025, https://www.epa.gov/aboutepa/our-mission-and-what-we-do; d. "About HHS," US Department of Health and Human Services, accessed March 26, 2025, https://www.hhs.gov/about/index.html; e. "ASPR: Administration for Strategic Preparedness and Response," Office of the Assistant Secretary for Preparedness and Response (ASPR), US Department of Health and Human Services, accessed March 26, 2025, https://aspr.hhs.gov/Pages/Home.aspx; f. "About CDC," Centers for Disease Control and Prevention, accessed March 26, 2025, https://www.cdc.gov/about/cdc/index.html; g. "About NIH," National Institutes of Health, accessed March 26, 2025, https://www.nih.gov/about-nih; h. "About ARPA-H," Advanced Research Projects Agency for Health (ARPA-H), May 20, 2025, https://arpa-h.gov/; i. Home page, Office of the Commissioner, US Food and Drug Administration (FDA), May 22, 2025, https://www.fda.gov/; j. "Energy," US Department of Energy, accessed March 26, 2025, https://www.energy.gov/; k. "President's FY23 NNSA Budget Enables 'Responsive and Responsible' Nuclear Security Efforts," US Department of Energy, March 2022, https://www.energy.gov/nnsa/articles/presidents-fy23-nnsa-budget-enables-responsive-and-responsible-nuclear-security; l. Michael Collins and Josh Meyer, "What's the 'Z Division'? A Secret Team of Scientists Searches for Answers on COVID-19's Origins," *USA Today*, March 1, 2023, https://www.usatoday.com/story/news/politics/2023/03/01/z-division-secret-team-scientists-investigated-covid-19-origins/11364009002/; m. "About," US Department of Defense, accessed March 26, 2025, https://www.defense.gov/About/; n. "Cooperative Threat Reduction Directorate," Defense Threat Reduction Agency (DTRA), accessed March 26, 2025, https://www.dtra.mil/About/Mission/Cooperative-Threat-Reduction/; o. "Chemical, Biological, Radiological, and Nuclear Defense," Office of the Secretary of Defense, accessed March 26, 2025, https://www.acq.osd.mil/ncbdp/cbd/; and "DOD Releases Chemical and Biological Defense Program Enterprise Strategy," US Department of Defense, accessed March 25, 2025, https://www.defense.gov/News/Releases/Release/Article/4010749/dod-releases-chemical-and-biological-defense-program-enterprise-strategy/; p. Home page, Defense Advanced Research Projects Agency (DARPA), accessed March 26, 2025, https://www.darpa.mil; q. Home page, Defense Threat Reduction Agency (DTRA), accessed March 26, 2025, https://www.dtra.mil/; r. "About USDA," US Department of Agriculture, accessed March 26, 2025, https://www.usda.gov/about-usda/general-information/our-agency; s. Home page, Animal and Plant Health Inspection Service (APHIS), US Department of Agriculture, accessed March 26, 2025, https://www.aphis.usda.gov/; t. "Biennial Review of the List of Select Agents and Toxins," Centers for Disease Control and Prevention (CDC), accessed March 26, 2025, https://www.selectagents.gov/; u. Home page, US Department of Commerce, accessed March 26, 2025, https://www.commerce.gov; v. "About NSF," National Science Foundation, accessed March 26, 2025, https://www.nsf.gov/about; w. Tara Kirk Sell and Matthew Watson, "Federal Agency Biodefense Funding, FY2013–FY2014," *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science* 11, no. 3 (2013): 196–216, https://pmc.ncbi.nlm.nih.gov/articles/PMC3778993/; x. "Mission," US Department of Homeland Security, accessed March 26, 2025, https://www.dhs.gov/mission; y. *BioWatch and Public Health Surveillance: Evaluating Systems for the Early Detection of Biological Threats: Abbreviated Version*, Institute of Medicine (US) and National Research Council (US) Committee on Effectiveness of National Biosurveillance Systems (National Academies Press, 2011), https://www.ncbi.nlm.nih.gov/books/NBK219704/.

imported probiotics or botulinum in domestic milk—would be an improvement given our current circumstances.

To secure biology really, we must consider new systems, strategies, and practices. We must anticipate needing to counter threats that will be increasingly novel, distributed, and difficult to predict. Such systems should include real-time, runtime intelligence; rapid and local production of medical countermeasures; and a suite of policies that reduce or eliminate as many threats as possible from ever occurring. Let us start by undertaking a frank assessment of our current capabilities.

PILLARS OF BIOSECURITY AS PRACTICED TODAY

The US federal government invests in biosecurity. The Council on Strategic Risks (CSR) noted that in fiscal year 2023 the US federal government

spent nearly $28 billion on biodefense.[163] CSR's definition is expansive and includes public health, MCMs, and biodefense investments, closely matching our definition of biosecurity.[164] Biosecurity responsibilities span multiple agencies. According to an April 2024 report from the Bipartisan Commission on Biodefense, biodefense responsibilities alone are distributed across "fifteen federal departments, nine independent agencies, and one independent institution."[165] Many federal entities are involved (table 1).

Presidential administrations have long recognized the importance of federal action on biosecurity. In 2004, President George W. Bush issued HSPD-10, a presidential directive on "Biodefense for the 21st Century."[166] In 2009, President Barack Obama signed his own directive, releasing the "National Strategy for Countering Biological Threats."[167] These periodic directives came to be called National Biodefense Strategies. A 2018 National Biodefense Strategy was advanced by the first Trump administration.[168] A 2022 National Biodefense Strategy was developed by the Biden administration.[169] Each biodefense strategy identifies core pillars of biodefense including threat awareness, prevention and protection, surveillance and detection, and recovery and response.

Recent reforms have addressed some existing gaps in the US federal government's biosecurity portfolio. In 2019, the DOD established biotechnology as an enterprise priority.[170] In 2021, Congress created the National Security Commission on Emerging Biotechnology (NSCEB), tasking the commission broadly with reviewing how advances in biotechnology will impact national defense.[171] In 2022, Congress established the Office of Pandemic Preparedness and Response Policy (OPPR) at the White House to strengthen public health capabilities for detecting and mitigating future pandemics.[172] In 2023, the DOD took up the mantle of biosecurity, releasing a *Biodefense Posture Review* (*BPR*).[173] Key *BPR* priorities included to "fully assess the biothreat landscape through 2035"; to "clarify biodefense missions, priorities, roles, responsibilities, authorities, and the capabilities needed to enable biodefense"; and to "ensure biodefense is routinely included in DOD training, exercises, and doctrine." One key reform from the first *BPR* was the establishment of a Biodefense Council to implement key *BPR* improvements and facilitate greater cooperation among federal stakeholders working on biodefense.

The Biden administration's National Security Memorandum 15 launched a National Biodefense Strategy and Implementation Plan that envisioned "a world free from catastrophic biological incidents" and, per a January 2025 report, a "coordinated, whole-of-government effort to prepare for biothreats."[174] In the *2023 Biodefense Posture Review*, Deputy Secretary of Defense Kathleen Hicks wrote, "I am confident that DoD, along with our counterparts throughout the US government and our allies and partners around the world, will continue to act boldly to meet the biological threats and pandemic challenges of this decisive decade."[175]

Yet the United States failed to prepare for and initially respond to SARS-CoV-2 and remains underprepared to deal with future biological threats. A Global Health Security Index report from 2021 found that each of the 195 countries analyzed, including the United States, "remain[s] dangerously unprepared for meeting future epidemic and pandemic threats."[176] A December 2022 report from the US Senate Committee on Homeland Security and Governmental Affairs found that "many of the problems identified as part of the initial federal response to SARS-CoV-2 are longstanding and remain unaddressed," including "insufficient funding across multiple administrations" and "conflicting authorities and overlapping roles between federal agencies."[177] The report also found that "public health agencies, and the federal government as a whole, lack sufficient global biodefense surveillance capabilities to identify and track emerging infectious disease

DEFINITION

The National Security Commission on Emerging Biotechnology (NSCEB), established by Congress in 2021, is chartered with the responsibility of examining the intersection of emerging biotechnology and US national security. As part of its charter, the commission released its final report, *Charting the Future of Biotechnology*, in April 2025.

Home page, National Security Commission on Emerging Biotechnology (NSCEB), accessed May 19, 2025, https://www.biotech.senate.gov/; and *Charting the Future of Biotechnology*, NSCEB, accessed May 19, 2025, https://www.biotech.senate.gov/final-report/chapters/.

threats." In short, the United States is still struggling to realize its biosecurity aspirations.

Securing and winning any battle is impossible without proven, battle-ready technologies and equipment. An even better strategy would be to meet threats with overwhelming force, as practical. Domain-specific capacities are also essential. Securing software requires software. Securing electronics requires electronics. Securing biology really will require biotechnology. Because biotechnology has been and remains an emerging technology, we have not always had the biosecurity capacities we would wish for. Yet as biotechnology advances, we can leverage key advances to realize significant improvements to biosecurity.

The decades-old BioWatch program, based on 1980s biotechnology, could transition to more recent DARPA-led innovations.[178] The National Wastewater Surveillance System (NWSS) is leveraging improvements in DNA sequencing to indirectly monitor for infectious diseases, including COVID and influenza, among approximately half the US population.[179] The CDC's Traveler-Based Genomic Surveillance (TGS) program tests toilets from international aircraft to help detect biothreats early.[180] But these advances are just "snowflakes on the tip of an iceberg." Much more can and must be done.

USING EMERGING BIOTECHNOLOGIES TO SECURE BIOLOGY

Emerging biotechnologies can help solve conventional biosecurity needs including surveillance, vaccines, diagnostics, and treatments.[181] By using biology to observe biology, we can instrument the living world, making observation and diagnosis much easier. By using biology to treat biology, we can enable a reliable and resilient supply of therapies when and where they are needed. And so on. We can also leverage biotechnology to reduce biological threats and realize positive benefits. What if egg-laying chickens could be safely bioengineered so that they never caught the flu? As biology becomes a general-purpose technology, we must leverage biology to secure biology.

SURVEILLANCE

A future with increasing and increasingly novel biological threats demands greatly improved biosurveillance capabilities. SARS-CoV-2 may have been circulating for two months before the first human cases were identified in Wuhan, China, in December 2019.[182] Detecting a pandemic as it overwhelms clinics is like detecting a nuclear weapon by its blast shock wave.[183] We must become capable of sustained monitoring and surveillance of potential biothreats in real time. Our goal should be to detect circulating pathogens prior to the onset of symptoms and clinical presentation.

Beyond today's sensors and wastewater monitoring, securing biology requires institutionalizing

DEFINITIONS

Surveillance involves tools and systems to detect or monitor pathogens in the environment or within populations before they cause widespread harm.

Vaccines train the immune system to fight off specific diseases before humans, plants, or animals get sick.

Diagnostics are methods for identifying diseases quickly and accurately (e.g., influenza or COVID tests).

Treatments are medicines or therapies such as antiviral drugs or antibody infusions that help people recover from illnesses or manage symptoms.

the capacity within the United States to surveil for pathogens at the biomolecular level. The cost of genomic sequencing has dropped—from roughly $100 million per human genome in 2001 to around $600 in 2022—making real-time, untargeted metagenomic sequencing more affordable.[184] For biosecurity, DNA sequencing represents a paradigm shift comparable to the advent of satellite imagery and geospatial intelligence (GEOINT) during the Cold War. Persistent and pervasive observation of potential biothreats by sequencing could form the foundation of biotic intelligence, a concept and capacity called BIOINT.[185] One group, the Nucleic Acid Observatory, is already developing computational tools and surveillance methods capable of detecting pathogens that may evade conventional detection systems.[186] Going further, anonymized analysis of antibody repertoires from routine blood draws would provide powerful and complementary signals indicating when and where people's immune systems have been exposed to particular pathogens.[187]

A qualitative upgrade in biosurveillance capabilities will be realized when biology itself becomes bioengineered to help with surveillance. Researchers have already explored engineering plants and common insects to detect land mines, toxic contaminants, or plant viruses, triggering visible alerts.[188] Adapting such technologies for biosurveillance is a natural progression. Imagine a houseplant or mouthwash that alerts you when you are spreading influenza. Microbes could be deployed in wastewater or soil, glowing in response to DNA from infectious agents of greatest concern.[189] Animals could serve as biosecurity sentinels; oysters or mussels could signal waterborne pathogens.[190] Aquarium fish can be bioengineered to glow when their immune systems are stressed.[191] By bioengineering sensors into organisms, we could create a "biosecurity of things" comprising a distributed, embedded, and continuous monitoring network. Remote-sensing technologies, including drones and satellites, could amplify the power of this network. Our goal should be to never be surprised by the lurking presence or unexpected arrival of any infectious agent or biological threat.

VACCINES

The rapid development of messenger RNA (mRNA) vaccines for SARS-CoV-2 showcased how emerging biotechnologies can help secure public health more quickly and efficiently than past technologies. The success of Pfizer-BioNTech's and Moderna's SARS-CoV-2 vaccines was enabled by discoveries in foundational science and driven by synthetic biology.[192] Unlike with traditional vaccines, mRNA technology allows researchers to test hundreds of potential antigen targets quickly, streamlining the process from sequence identification to clinical trials.[193] Despite these advancements, it still took nearly a year for the first SARS-CoV-2 vaccines to be rolled out. While many have endorsed the goal of being able to make and deliver vaccines in one hundred days

or less, we are not there yet.[194] Emerging biotechnologies can help.

Many vaccines require continuous refrigeration or freezing prior to use to remain effective, dramatically increasing the complexity of vaccination campaigns. In June 2021, when the United States announced plans to donate Pfizer's COVID vaccine to about one hundred countries, cold-chain requirements made doing so much harder. Sierra Leone reportedly had only one freezer operating that was capable of storing the vaccine at the proper temperature in the entire country.[195] The freezer was already being used to keep an Ebola vaccine cold. Even when freezers are available facilities may lack reliable electricity to keep vaccines cold.[196]

Cell-free, freeze-dried systems can bypass this cold-chain requirement. Dry, shelf-stable biocompounds can be turned back into viable vaccines when and where needed by adding water.[197] One company has begun clinical trials for vaccines using cell-free, freeze-dried methods. Sixty vaccines have been identified that could be improved using a cell-free approach, including vaccines for tetanus and diphtheria.[198] Eliminating cold-chain requirements alone could increase vaccine coverage two- to threefold worldwide, reshaping global health and pandemic preparedness.[199]

DEFINITION

Cell-free systems are made by extracting cytoplasm from cells, either as bulk extract or by purifying and reconstituting specific biomolecules. Once made, cell-free systems maintain their biochemical activity and are capable of making nucleic acids and proteins, including as needed for producing infectious disease medical countermeasures.

Daniel Siegal-Gaskins, Zoltan A. Tuza, Jongmin Kim, Vincent Noireaux, and Richard M. Murray, "Gene Circuit Performance Characterization and Resource Usage in a Cell-Free 'Breadboard,'" *ACS Synthetic Biology* 3, no. 6 (2014): 416–25, https://doi.org/10.1021/sb400203p.

Synthetic biology is also redefining what can serve as a vaccine in the first place. Bioengineers recently demonstrated that bacteria found naturally on skin can be engineered to express tumor antigens, effectively training the immune system to recognize and attack melanoma.[200] Imagine a living skin cream that offers vaccination against skin cancer—no syringes or needles required. Imagine if this technique could be applied to other diseases and infections. Twenty-five years from now, people may be able to immunize themselves against biosecurity threats not with a needle but via a moisturizing lotion.

Going further, the very things that infect us may become "vaccines." Salmonella causes over one million infections in the United States every year yet may provide a pathway for vaccinating people against diseases such as the flu.[201] In mouse studies, an ingestible salmonella vaccine conferred robust immunity for the flu; the bacteria had first been "defanged" so as not to cause disease.

What if mosquitoes could vaccinate people against malaria? In 2024, researchers reported reprogramming the parasite that causes malaria to stop developing shortly after entering the human liver, preventing the parasite from infecting red blood cells.[202] The arrested development triggers an immune response that enables the body to recognize and combat future malaria infections. Such an approach could help eliminate approximately 250 million infections and about six hundred thousand deaths from malaria each year.[203]

Researchers have even developed an innovative approach to vaccine development called synthetic

attenuated virus engineering, or SAVE. The idea is to automatically recode the DNA of a natural virus to make an attenuated variant that can be used to create immunity.[204] SAVE combines the most ancient form of vaccination with modern synthetic biology tools. Computer algorithms identify and replace commonly used DNA code for rarely used sequences. The resulting virus particle is still the same, but the SAVE-encoded virus has a greatly reduced ability to infect cells. Researchers have successfully applied SAVE techniques to the influenza virus in animal studies.[205]

Biotechnology-enabled improvements to vaccines can revolutionize how we approach immunization and help secure biology going forward.

DIAGNOSTICS

Infectious disease diagnostics help form the front line of biosecurity defenses. If diagnostic capacity is insufficient, then people, leaders, and doctors are working in the dark. Early during the COVID pandemic, testing failures—including a US test with a 33 percent error rate due to faulty reagents—led to delays and misdiagnoses, and contributed to the pandemic's rapid spread.[206] During the 2014–2016 Ebola outbreak in West Africa, testing bottlenecks due to centralized labs meant infected individuals waited for up to six days for test results, allowing the virus to spread unchecked.[207] Biosecurity really requires distributed, abundant, and resilient diagnostic capacities. Pervasive, embedded, and decentralized diagnostics made possible by advances in biotechnology can provide real-time detection, improving outbreak response and accelerating treatments.

Pathogens themselves are self-documenting. What does this mean? Inside every pathogen are DNA or RNA molecules unique to, and encoding, that specific pathogen. By amplifying these molecules from a sample, we can more reliably identify whether pathogens are present, and which ones. Polymerase chain reaction (PCR) is a 1970s-era approach for making many copies of target DNA molecules. In the 1980s, researchers learned how to use a DNA-copying enzyme that does not fall apart at high temperatures. This allowed thermocyclers—machines that shift between cooler and hotter temperatures—to quickly make many copies of DNA molecules found in a sample. But thermocyclers are expensive and require electricity to operate.

Later, a method for making copies of DNA molecules that does not require temperature changes was invented. The method is loop-mediated isothermal amplification, or LAMP.[208] LAMP operates at a fixed temperature, offering a rapid and cost-effective approach to pathogen detection. LAMP has already been used to detect a wide range of pathogens and can be deployed via freeze-dried, shelf-stable reagents.[209] Both PCR and LAMP are examples of using biotechnology to detect biology. Much more is possible.

Any parent should be able to tell within minutes whether their child's sniffle is a common cold or something worse. Paper-based, low-cost pathogen diagnostics activate when a sample and water are added—like a pregnancy test.[210] If a pathogen is present, the color changes. Paper-based diagnostics are highly portable and affordable, and require no specialized equipment, making them ideal for widespread use.[211] Ongoing improvements enable testing for multiple diseases simultaneously. Ultimately, infectious disease diagnostics should become household items that are ready and available for use, including when times are normal.

But why should we have to wait for a diagnosis at all? What if our bodies could tell us directly, in real time, whether we are infected, and with what? One 2020 project explored the idea of bioengineering friendly sentinel bacteria to live in our

sinuses.[212] The bacteria would take up genetic material from any pathogens naturally present in the environment and change the color of nasal mucus depending on whether a pathogen is present and, if so, which strain—bright orange mucus for the flu, bright purple mucus for coronavirus, and so on. No need to sample and wait. This would be embedded, real-time, run-time infectious disease diagnostics. Similar approaches are being explored for monitoring skin pH and blood glucose levels.[213] Unlike conventional test kits that must be made in factories and processed in labs, living bacteria sentinels can make themselves, once bioengineered. Such innovations could transform frontline diagnostics, making real-time pathogen detection faster, simpler, and pervasive.

TREATMENTS

The WHO estimates that one in three people globally do not have access to essential medicines.[214] Some diseases lack treatments entirely or evolve in ways that make existing treatments obsolete.[215] Whenever we fail in our ability to treat disease, we accrue exposure to, and become increasingly vulnerable to, biosecurity risks. Our ongoing reliance on centralized manufacturing and stockpiles of medical countermeasures has clear limitations, from fragile supply chains to high costs to inequitable access.[216] Emerging biotechnologies could revolutionize how we discover, produce, and distribute treatments, enabling on-demand production of existing and novel medicines to complement traditional stockpile-based approaches.

Small-molecule drugs help form the backbone of modern medicine—everything from antibiotics to antivirals. Synthetic biology promises decentralized and agile manufacturing of small-molecule medicines.[217] Imagine if drugs could be produced in the amounts needed, when and where needed.

High-throughput chemistry, AI, and synthetic biology are transforming the discovery of new medicines. Instead of focusing only on the binding of candidate drug molecules to single proteins, teams can now better understand the entire cellular mechanisms modulating disease.[218] Researchers can test thousands of drug interactions at once by tagging molecules or biological components with unique DNA "barcodes."[219] The resulting datasets, representing subtle biological effects across large numbers of experiments, help fuel AI-driven drug discovery.

DEFINITIONS

Small-molecule drugs are medicines that can enter cells easily. Most small-molecule drugs can be administered orally and make up the majority of marketed drugs, from those for pain and allergy relief to antibiotics.

Biologics, short for biological drugs, are biomolecules that are generally bigger and more complex than small molecules and must be given via injection or infusion. Monoclonal antibodies for treating COVID infection or heart disease are biologics.

"Small-Molecule Drug," National Cancer Institute, NCI Dictionary of Cancer Terms, accessed March 26, 2025, https://www.cancer.gov/publications/dictionaries/cancer-terms/def/small-molecule-drug; "A Big Future for Small Molecules: Targeting the Undruggable," AstraZeneca, accessed March 26, 2025, https://www.astrazeneca.com/r-d/next-generation-therapeutics/small-molecule.html; Michelle W. Y. Southey and Michael Brunavs, "Introduction to Small Molecule Drug Discovery and Preclinical Development," *Frontiers in Drug Discovery* 3 (November 30, 2023): 1314077, https://doi.org/10.3389/fddsv.2023.1314077; and "Understanding Biologic and Biosimilar Drugs," American Cancer Society, Cancer Action Network, July 27, 2018, https://www.fightcancer.org/policy-resources/understanding-biologic-and-biosimilar-drugs.

Antibodies produced by our immune system naturally help fight disease. By bioengineering antibodies outside the body, we can more aggressively treat and cure diseases. When President Donald Trump caught SARS-CoV-2 in October 2020, his treatment was accelerated using a cocktail of monoclonal antibodies.[220]

Infants too young to be vaccinated against respiratory syncytial virus (RSV) can now be protected via bioengineered antibodies.[221] When combined with maternal mRNA vaccination during pregnancy, such treatments reduced RSV-associated hospitalizations in infants under six months by over 70 percent during their first season of use in the United States.[222] Imagine a future in which preformulated antibody treatments covering flu, RSV, SARS-CoV-2, and other seasonal illnesses are available each winter, offering protection or potential cures when needed.[223] For bioengineered antibodies to reach their fullest potential, dramatic reductions in cost and increased scale of manufacturing must be realized.[224]

Advances in AI and high-performance computing can make bioengineered antibodies even more useful. Lawrence Livermore National Laboratory's Generative Unconstrained Intelligent Drug Engineering (GUIDE) program has demonstrated how AI-driven simulations can rapidly redesign antibodies, restoring their effectiveness against evolving viral variants while predicting mutations to maintain long-term efficacy.[225] Computational approaches significantly reduce development time and costs, promising just-in-time therapeutic deployment.

Llamas—the South American pack animal—naturally produce a simpler type of antibodies. When repurposed, llama-derived "nanobodies" offer smaller, more stable, and easier-to-produce molecules capable of binding disease targets.[226] Nanobodies can tolerate extreme heat and pH, making them ideal for alternative delivery methods, including as inhalable therapeutics that have shown efficacy in treating asthma and SARS-CoV-2.[227] By targeting the parts of viruses that are common across viral strains, nanobodies can remain effective despite viral mutations, making them valuable stopgap therapies if and when a variant escapes an established vaccine.[228] Coupled with AI-driven antibody design, nanobody research could further enable ultrafast, cost-effective responses to infectious diseases, again reducing delays between outbreak and treatment. Imagine an antibody cocktail administered through an inhaler if and whenever needed, either in support of anticipatory protection or in response to an emerging threat.

The best treatments are moot if they cannot be produced, transported, and made available when and where needed. Advances in whole-cell synthetic biology are promising to disrupt how medicines are manufactured, akin to how chemical synthesis (1800s) and recombinant DNA (1980s) revolutionized medicine manufacturing. Bioengineered yeast can now brew sophisticated small-molecule medicines in metric ton amounts.[229] As medicinal precursors become bio-makeable, we can change how and when medicines are made or made available.[230] Critically, bio-based production methods could offer faster, more agile, or more affordable approaches to making medicines.[231]

Pushed to a logical extreme, biomanufacturing methods could enable real-time and local production of whatever medicines might be needed. DARPA's Pharmacy on Demand and Biologically-Derived Medicines on Demand programs developed miniaturized platforms that could produce therapeutic agents in response to specific threats.[232] The technology can already produce proteins administered in response to radiation exposure, requiring just a few hours to make the biologics and avoiding the need for a cold chain.[233] Such devices could ultimately

enable highly sophisticated and local responses to biosecurity threats; imagine carrying an entire biofactory in a small briefcase directly to an incident, giving treatment to those affected as fast as possible.[234] Chicken eggs, historically used in influenza vaccine manufacture, could be adapted to produce many more molecules.[235] Ultimately, we can imagine the emergence of consumer devices, realizing for biotechnology what the personal computer did for computing. Imagine a kitchen countertop appliance—the personal biomaker—that could be programmed to make whatever medicines are needed, in the home and on demand.

Emerging biotechnologies have the potential to revolutionize how we monitor, prevent, diagnose, and treat disease. We must leverage these possibilities to imagine best-case-scenario capabilities that help make infectious diseases and biosecurity risks operationally obsolete. US leadership in these technologies is vital, from keeping Americans healthy to preventing outbreaks elsewhere from ever reaching our shores. Such emerging biotechnologies can also form the backbone of a resilient biosecurity network that dissuades any and all from pursuing bioattacks.[236]

Secondary impacts of embracing biotechnology to secure biology would include helping to drive broader biotechnology leadership, including for economic opportunity and political soft power. Securing biology with biotechnology would also harness and renew the best of American innovation and ingenuity.

CONCLUSION

Implicit in our urgency to explore leveraging biotechnology to secure biology is a fundamental view of the living world: that natural living systems form a sort of open distributed network. Organisms naturally reproduce and move about, often distributing and sharing genetic information among themselves. When such sharing causes illness, we label it infection, epidemic, or pandemic. Humans are increasingly capable of adding bioengineered information to the natural flow and exchange of genetic information. We must therefore anticipate that, in the future, anyone, anywhere could introduce any genetic content that they can access or imagine into such flows and exchanges. Viewed this way, the question of biosecurity becomes, in part, how can we secure an open and distributed network of living things?

Lessons from the ongoing experience of securing computer networks are relevant. Securing computers requires both centralized and decentralized capabilities. Individual computer owners and users must be capable of knowing when something is wrong and empowered to take action. Centralized coordination of computer threat surveillance, vulnerability detection, and vulnerability mitigation is also essential. A zero-trust mindset—that no person or machine on the network can be trusted—becomes relevant. Security must exist everywhere, to some extent, for our networks to be secure.

Complementing traditional and centralized biosecurity capacities with fully distributed capabilities challenges our instincts and assumptions. People gravitate toward central authority and resources in times of crisis, especially in matters involving health or medicine. For fully distributed biosecurity capacities to be welcomed and operationally useful, those who depend on such capabilities will need to gain a familiarity with and trust in such systems that can only be realized via hands-on experience.

Consider those who were concerned about or outright refused vaccines during the COVID-19 pandemic. Could emerging biotechnologies make a difference going forward, helping even those who might otherwise shun biosecurity

capabilities? What if vaccines became akin to a special holiday dinner, like Thanksgiving? Families who wish could make their own vaccines at home using the best available ingredients sourced locally.[237] Potential concerns regarding embedded wireless tracking chips would be avoided entirely by people knowing firsthand that they simply did not include a wireless chip in their at-home vaccine recipe.[238] The feasibility of such capabilities relies not only on technological advancements, but on widespread bioliteracy along with advances in biometrology—measurement tools and standards that help guarantee anyone actually making their own vaccine creates a safe and useful one.[239] How far might we be willing to go to secure biology?

3. How Far Are We Willing to Go?

INTRODUCTION

In late 2018 a delegation of US scientists and policymakers flew to Hong Kong for the Second International Summit on Human Genome Editing. Upon landing they were surprised to learn that a Chinese scientist, He Jiankui, had announced he had edited human embryos with CRISPR, resulting in genetically engineered girls with supposed resistance to human immunodeficiency virus (HIV).[240] Jiankui's edits were to the girls' germline, meaning any of their children would also inherit the changes. Jiankui's experiment shocked the world and prompted outrage. Over one hundred Chinese scientists signed a statement calling Jiankui's actions "crazy."[241] Dr. Francis Collins, then-director of the US National Institutes of Health (NIH), said the NIH was "deeply concerned about the work" and that the experiment had "been carried out so irresponsibly."[242] Other critics highlighted more efficient and ethical ways to protect against HIV.[243] Jiankui was soon sentenced to three years in prison, although he has since been released.[244]

What if we temporarily set aside the profound ethical and safety issues (e.g., consent, approval, transparency) that plagued Jiankui's experiment? Would we ever promote human genome editing to ensure pathogen resistance and biosecurity more broadly?[245] What if such technologies worked nearly perfectly? What if a virus more deadly than SARS-CoV-2 was circulating? Would we do whatever is necessary, including human genome editing, to protect our future children? Imagine a world so fraught with biothreats that everyone—from parents to policymakers—confronts similar questions, not only about genome engineering but also about other beyond-the-frontier biotechnologies. How far might a nation be willing to go to reduce, avoid, or eliminate the risk of intentional harms from biology?

This collision of biotechnology, governance, and ethics is not new. In 1901, doctors and police raided Little Italy in New York City, forcibly vaccinating residents for smallpox.[246] *The New York Times* reported that "infected children [were] torn from shrieking mothers" and that vaccinators "kicked down the door" to one home.[247] Similar raids took place throughout New York and Boston. The resulting outcry resulted in *Jacobson v. Massachusetts*, a 1905 US Supreme Court case. The court ruled in favor of using police power for forced public health vaccination campaigns.[248]

Twenty-five years ago, few were wondering how AI, genome editing and construction, and synthetic cells might promise or threaten to transform daily life, geopolitics, sustainability, and society. Yet here we are. The UK's Wellcome Trust just announced that they are unilaterally taking the first steps toward creating entirely synthetic human genomes.[249] What is lurking within the

next twenty-five years of biotechnology possibilities that might inspire or inform approaches to biosecurity?

EVALUATING BEYOND-FRONTIER BIOTECHNOLOGIES

In considering such futures we must be mindful of both technological possibilities and cultural acceptability. To evaluate beyond-frontier biotechnology approaches to biosecurity we will use both technology and societal readiness levels.

Technology readiness levels (TRLs) are a well-established tool for assessing the maturity of an emerging technology (figure 10).[250] TRLs 1–3 represent new ideas and scientific concepts that need exploration. TRLs 4–6 involve evaluating new technologies in relevant working environments. TRLs 7–9 combine components, establish full working models, and deliver successful technologies ready for widespread deployment.

Consider airplanes. TRL 1 is Leonardo da Vinci's sketches for flying machines. The engineering was lacking, but the idea was born.[251] TRLs 2–5

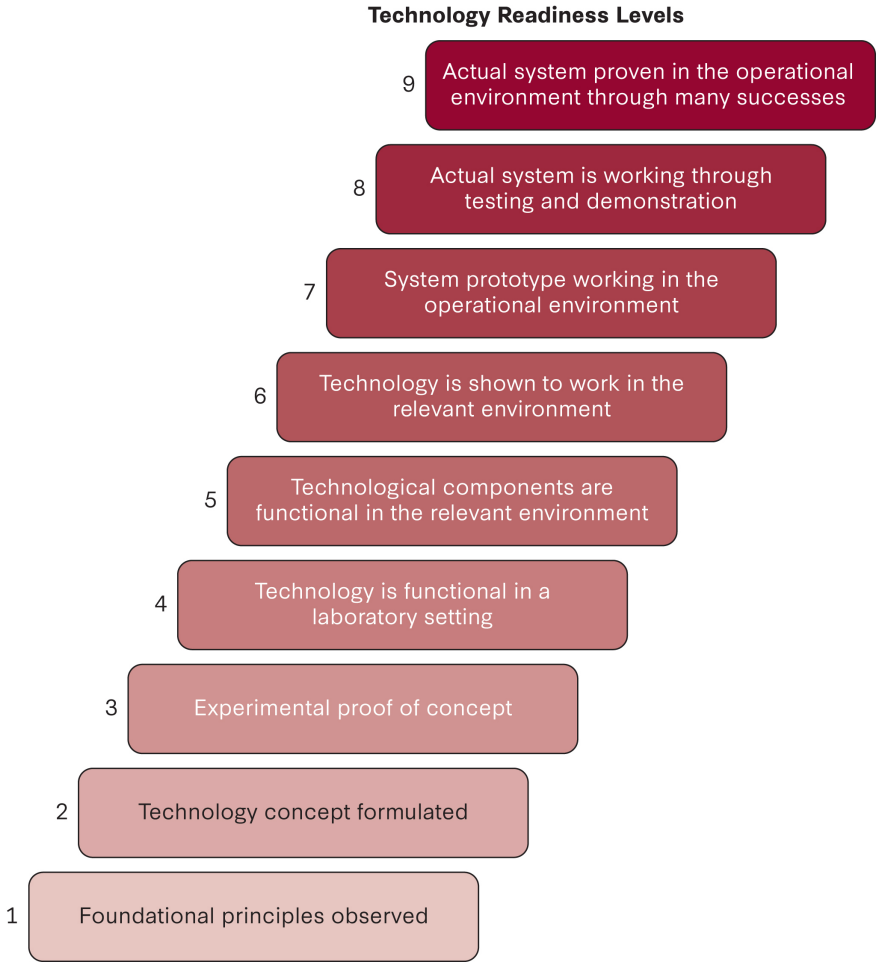


FIGURE 10 Levels of technology readiness from 1 to 9, with 1 being the least ready and 9 being fully mature and reliably deployed

Source: Adapted from Catherine G. Manning, "Technology Readiness Levels," NASA, September 27, 2023, https://www.nasa.gov/directorates/somd/space-communications-navigation-program/technology-readiness-levels/. Image by Raj Patel.

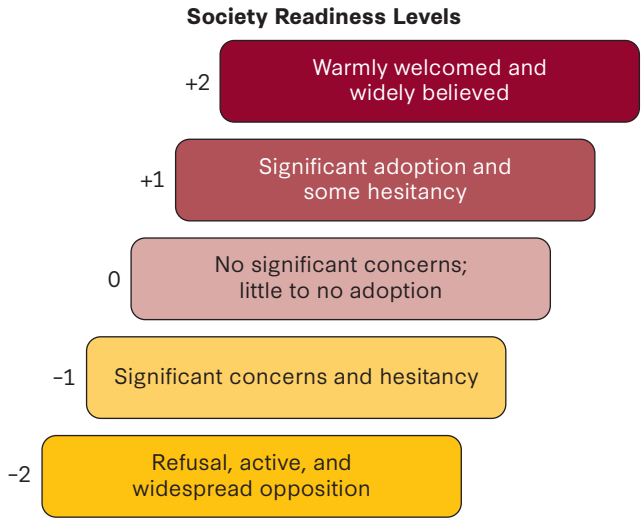


FIGURE 11 Levels of societal readiness from –2 to +2. Negative numbers represent opposition and positive numbers represent approval. An SRL of zero represents relative societal neutrality. SRLs are used by European companies such as the Innovation Fund in Denmark
Source: Image by Raj Patel.

include the Wright brothers' tests of individual systems—thrust and lift—needed for flight.[252] Combining these functions led to the *Wright Flyer* aircraft's first flight at Kitty Hawk, representing TRL 6.[253] TRL 7 includes near-final prototypes of World War I aircraft.[254] TRL 9 includes most of general, commercial, and military aviation today.[255]

Technological readiness is not the only metric that matters. Societal readiness can be even more important. Consider artificial wombs. In 2017, researchers reported that lamb embryos could be grown in plastic bags.[256] By 2023, US regulators were reportedly considering human trials for artificial wombs.[257] Ethical concerns, however, have slowed further development.[258] Consideration of ethics and appropriateness continues.[259]

To formalize consideration of broader aspects of emerging biotechnologies, we will use societal readiness levels (SRLs), following our own definition. Our SRLs span five levels, from –2 to +2, reflecting cultural readiness for an emerging biotechnology: SRL –2 represents significant public opposition; SRL –1 involves concerns; SRL 0 is a neutral stance; SRL 1 represents acceptance with some hesitancy; and SRL 2 is widely acceptable and believed to be good (figure 11). Human cloning is SRL –2, an idea with widespread opposition.[260] Some vaccines are SRL 1, widely used, yet hesitancy is real.[261] Most antibiotics used to treat deadly infections are SRL 2.

SRLs and TRLs can be correlated or mutually reinforcing. A technology that works well may have an easier time gaining acceptance, and vice versa. Self-driving cars are gaining ground in San Francisco, Phoenix, and elsewhere as the technology improves.[262] Herein we estimate SRLs against the backdrop of an "average American" cultural context, recognizing the limitations of doing so; SRLs may change depending on the group(s) engaged or impacted. Finally, we note that in exploring the potential impacts of frontier biotechnologies on biosecurity we are not endorsing any idea, per se; rather, we are only raising the possibility that such technologies may one day be needed if we otherwise fail to secure biology.

BEYOND-FRONTIER BIOTECHNOLOGIES PRESENTING FOR ETHICAL CONSIDERATION

ENVIRONMENTAL INTERVENTIONS

In the 1920s Galveston, Texas, declared "war on rats."[263] Officials created ordinances requiring that buildings be made of concrete or raised eighteen inches or more, all to stop the spread of bubonic plague. In the 1940s the United States drained wetlands and deployed an early synthetic insecticide (DDT) to fight mosquito-borne diseases including typhus and malaria, a practice later banned due to unintended ecological costs.[264] Might we further change insect, plant, and animal populations or wild environments to secure biology going forward?

Gene drives are a bioengineering tool for greatly increasing the chance that offspring in sexually reproducing populations all have the same trait. Target Malaria is one project that has been working toward gene-drive deployment for reducing disease-transmitting mosquitoes in Africa.[265] Significant opposition to gene drives has impacted Target Malaria's plans.[266] Field trials in Africa and the United States using non-gene-drive mosquitoes bioengineered to produce offspring less likely to reproduce have been more positively received and have shown success in temporarily reducing mosquito populations.[267] One practical issue is that non-gene-drive mosquitoes must be grown and deployed over and over again, whereas treatment with a gene-drive mosquito might need to occur only once or rarely.

Mice Against Ticks is a community-driven ecological engineering project taking a different approach.[268] Instead of collapsing mouse populations with a gene drive, the idea is to bioengineer mice to be resistant to the bacterium that causes Lyme disease. Ticks feeding on the bioengineered mice will be less likely to transmit Lyme disease to humans.[269] Initial trials may occur on islands off the New England coast harboring the highest rates of Lyme disease. One goal is to limit bioengineered gene flow among wild mouse populations on the mainland.[270]

As another approach, large-scale vaccination of wild animal populations could reshape biosecurity and public health risks. Zoonotic spillover—when a pathogen jumps from animals to humans—has driven many deadly outbreaks.[271] Most emerging infectious diseases originate in wildlife, with urbanization and biodiversity loss accelerating spillover risks.[272] Vaccines are already widely used with domesticated livestock and animals.[273] What if high-risk species, from bats to pangolins, could be vaccinated against diseases before transmission to humans ever occurred?

Wild-animal vaccination campaigns typically work via catch-and-release or by dispersing vaccine-laced bait. Self-spreading vaccines offer an alternative. By promulgating immunity from one individual to another, self-spreading vaccines can immunize entire populations.[274] In 2001, researchers inoculated rabbits on a Spanish island with a vaccine for rabbit hemorrhagic disease. Inoculated rabbits transmitted the vaccine to others, thereby self-immunizing half the rabbit population.[275] In 2017, researchers tested topical rabies vaccines for vampire bats, finding that oral vaccines spread through grooming could increase population immunity more than twofold compared to catch-and-release vaccination.[276] Proactive disease prevention, including by vaccinating high-biosecurity-risk animal populations using emerging biotechnologies, might help secure biology.

Bioengineered mosquito populations could be widely deployed now to combat insect-borne diseases, if needed. Self-spreading vaccines may soon undergo controlled field trials to immunize wildlife against zoonotic pathogens. Within fifteen years, such vaccines could be integrated into global disease prevention strategies, curbing

zoonotic spillovers before they reach human populations.[277] On similar timescales, leveraging biotechnology for conservation biology could revive or restore key species that help buffer against zoonotic spillovers.[278] Longer-term possibilities stretch the imagination: prey species bioengineered to immunize entire food chains, creating pervasive barriers against zoonotic threats.

Gene drives have been tested in mammals, and insect-based test experiments are well documented.[279] Gene drives are poised to transition from experimental proof of concept to validation in field trials, but societal readiness is limiting. Self-exhausting gene drives that propagate for only a handful of generations before vanishing promise greater control.[280] Self-spreading vaccines are a less mature approach.[281] Overall, we assess TRL 5 to 6 for gene drives and TRL 3 to 4 for self-spreading vaccines.

Public perception and policy readiness for biotechnology-led environmental interventions vary. Gene drives have faced regulatory and ethical pushback, especially regarding potential ecological risks and governance challenges.[282] One scientist warned that gene drives could be a "genetic atom bomb."[283] Countries differ in their regulatory stances toward gene drives, and questions of responsibility remain unclear.[284] In 2023, Oxitec withdrew its permit application for release of genetically engineered mosquitoes in California.[285] Less attention has been given to self-spreading vaccines. Overall, we assess SRL –2 to –1 for gene drives and SRL –1 for self-spreading vaccines.

GAIN OF FUNCTION

In 2011 researchers were studying how highly lethal bird influenza might evolve to better spread among mammals. By infecting ferrets with a mutated virus, including in cages separated by air gaps, they selected for changes enabling the virus to spread more easily through air. Just five genetic changes allowed bird influenza to become "airborne."[286] The research created confusion, concern, and controversy. Forty influenza researchers announced a self-imposed moratorium on such work, only to lift it a year later.[287] The US government halted funding for such research in 2014.[288] But in 2017, US funding restarted subject to an updated governance framework.[289] In 2025, US research funding paused again, pending approval via a further revised oversight policy.[290] Some scientists argue that studying viral evolution helps prepare for future outbreaks. Critics warn of accidental or intentional release.[291]

Before 2010, "gain of function" was a general term for any experiment that gives an organism new or enhanced attributes.[292] During the 2011–2012 bird flu debates, the concept of "gain-of-function research of concern" (GOFROC) was coined to specify studies that increase pandemic risk. Despite the new terminology, most labs still called research "gain of function" (GoF) even if there was no pandemic potential.[293] The disconnect between policy and practice created confusion, with oversight bodies and researchers deploying different definitions in grant reviews and biosafety frameworks.[294] The Center for Security and Emerging Technology found that common techniques, such as growing viruses in cell cultures for vaccine development, are frequently lumped together as GoF, despite posing minimal novel risk.[295]

In February 2020, Swiss scientists seeking to fight the pandemic rebuilt SARS-CoV-2 from scratch before the first case arrived in Switzerland.[296] Computer models can now help scientists predict which mutations are most likely to enhance pathogen transmission or immune escape.[297] Generative biology tools allow researchers to assess millions of mutations at once, refining our understanding of viral evolution.[298] Taken together, emerging biotechnologies increasingly allow scientists to map and study potential virus variants so as to preemptively develop countermeasures. Imagine

DEFINITIONS

Gain-of-function (GoF) research involves changing organisms, most typically via direct (i.e., introduced) or indirect (i.e., evolved) genetic changes, in attempts to enhance or acquire new biological functions and observe what behaviors or phenotypes are possible or can emerge.

Computational and systems biology uses software and computers to represent and simulate biological organisms or to help interpret data, often on a very large scale.

"Global Pandemics: Gain-of-Function Research of Concern," congress.gov, accessed April 25, 2025, https://www.congress.gov/crs-product/IF12021; and "Computational Biology," National Library of Medicine, accessed April 25, 2025, https://www.ncbi.nlm.nih.gov/mesh?Cmd=DetailsSearch&Db=mesh&Term=%22Computational+Biology%22%5BMeSH+Terms%5D.

forecasting dominant mutations and future-proofing vaccines before outbreaks even occur.

Machine learning and computational biology are starting to make routine the identification and prediction of genetic mutations leading to GoF changes.[299] High-throughput laboratories allow rapid experimental testing of variants of interest. Researchers can now simulate millions of potential mutations, synthesize selected variants, test them in the lab, and iterate faster than ever before. Overall, we assess TRL 6 to 8 for computational and high-throughput experimentation with GoF mutants.

The COVID pandemic increased awareness and shifted opinion on GoF research. Because building viruses from scratch is now routine in research settings, people can reasonably wonder whether any pandemic comes from nature or a lab. Given heightened regulatory responses and increased public skepticism, we assess SRL –1 for GoF research with live and intact pathogens and SRL –2 for GoF research with pandemic-potential pathogens.[300]

NONHERITABLE INTERVENTIONS

Nonheritable interventions—ways of protecting people without changing their DNA—are among the earliest foundations of public health. In the 1700s, doctors noticed that those infected with cowpox did not get smallpox.[301] Later, by purposely exposing people to a weakened form of the virus, first-generation smallpox vaccines sought to develop immune protection without causing disease. The human immune system maintains this protection in long-lived memory cells, ready to react if the wild virus appears.[302] Throughout the twentieth century, scientists developed live-attenuated vaccines for measles, mumps, and rubella—combined in the MMR vaccine—as well as for chicken pox, yellow fever, and tuberculosis.[303] Such vaccines represent a historical use of nonheritable interventions for public health and biosecurity purposes.

Human artificial chromosomes (HACs) are DNA bioengineered to act like natural chromosomes inside human cells.[304] HACs allow scientists to introduce many new genes and complex genetic instructions at once.[305] Ongoing research is addressing key hurdles in HAC technology, improving both the construction and reliable delivery of HACs into human cells.[306] Bioengineered HACs could potentially carry an entire genetically encoded "biodefense suite."[307] Imagine a HAC enabling continuous production of antibodies or antiviral molecules throughout a person's life, reducing the need for vaccines and booster shots, or a HAC encoding gene-editing system targeting all known families of intracellular pathogens.[308] Such thinking leads to the idea of "biosecurity at birth." Parents

DEFINITIONS

Nonheritable interventions are medical or environmental actions that protect individuals from diseases but do not change people's genetic information. Such changes are typically confined to the treated individual via their somatic cells (i.e., skin, muscle, bone) and are not transmitted to offspring.

Heritable interventions, also known as germline editing, involve making changes to the genetic material of reproductive cells such as eggs, sperm, or early embryos. The resulting changes are inherited by future generations.

National Academy of Medicine, National Academy of Sciences, The Royal Society, and International Commission on the Clinical Use of Human Germline Genome Editing, *Heritable Human Genome Editing* (National Academies Press, 2020), https://doi.org/10.17226/25665.

using reproductive-health clinics could elect to have bioengineered HACs added to early-stage embryos. Such HACs could be further bioengineered to remain within somatic cells such that nothing would be inherited by future generations. Each generation would receive updated HACs encoding protection for any new biosecurity threats.

HACs remain a nascent technology. Laboratory studies have introduced HACs carrying human genes into animal cells to produce human antibodies and integrate large human gene fragments into mice.[309] The use of extensively bioengineered HACs for biosecurity has not been attempted. Overall, we assess TRL 2 to 4 for the use of HACs in biosecurity.

The addition of genetic material to human embryos, even if nonheritable, would raise significant questions and concerns.[310] If other solutions are working well (e.g., vaccines) then demand for such an approach would be negligible to nonexistent. Overall, we assess SRL –1 for the use of human artificial chromosomes in biosecurity.

HERITABLE INTERVENTIONS

What about heritable changes to the human genome itself? From the historical infanticide of twins among the Ibibio and the Efik, to twentieth-century eugenics programs in America, Sweden, and Germany, to China's one-child policy, people have long acted in ways that purposefully sought to impact or indirectly impacted human populations.[311] The primary legacy of such past practices is not genetic but cultural. Looming within today's debates on genetic screening, embryo selection, and heritable gene editing are profound normative and ethical questions.[312]

More recently, scientists and medical doctors have returned to an old observation: The blood of a pregnant woman contains material naturally shed from the fetus.[313] Today, a blood draw followed by DNA sequencing can allow determination of some genetic aspects of the future child, from biological sex to Down syndrome. Such methods, known as noninvasive prenatal diagnosis (NIPD), have become routine in some regions.[314] NIPD-enabled genetic counseling can thus influence decisions by future parents on whether to continue a pregnancy based on genetic findings, a subtle and indirect method of sculpting the human genome.

Recent studies have demonstrated the potential of inserting genes encoding pathogen-specific antibodies directly into cells, allowing for the continuous production of neutralizing antibodies.[315] While such studies have primarily focused on somatic cells, the concept could, in principle,

be extended to germline modifications to confer heritable immunity against specific infectious diseases at a population level. Future biosecurity applications could also involve engineering heritable genetic resistance in livestock populations to prevent agricultural outbreaks from spilling over to humans, impacting food security, or disrupting the economy.[316]

In 2020 John Ratcliffe wrote: "US intelligence shows that China has even conducted human testing on members of the People's Liberation Army in hope of developing soldiers with biologically enhanced capabilities."[317] If advanced, such work would most likely be pursued on a nonheritable basis but, if proven effective, could theoretically transition into heritable interventions. Traits of initial interest could include disease and toxin resistance and modified dietary requirements or metabolic capabilities. However, as one 2024 RAND Corporation study noted, "It is unlikely that genomic enhancement of the warfighter will be realistic within the next five years, when scientists can only just now . . . cure single-locus diseases."[318]

NIPD works for supporting decision making for simple genetic traits during pregnancy. However, making heritable edits to the human genome is still an early-stage emerging technology. We assess TRL 7 to 9 for NIPD, with the primary limitations being cost, availability, and lack of utility for complex genetic traits. We assess TRL 4 for human germline engineering, as challenges including precision, off-target effects, and long-term consequences remain to be resolved.[319]

Several countries explicitly ban human germline engineering and scientists have called for a global moratorium on its use.[320] The United States effectively has a de facto ban, as public funds cannot be used to fund such research. The US Food and Drug Administration (FDA) will also not approve clinical trials even for privately funded research.[321] However, public opinion on human germline engineering is not entirely fixed. A 2017 US National Academies group cautiously endorsed germline modifications to prevent serious diseases when no reasonable alternative exists.[322] The Third International Summit on Human Genome Editing signaled growing, if cautious, interest.[323] Overall, we assess SRL –1 for human germline engineering and SRL 2 for NIPD.

CONCLUSION

The frontiers of biotechnology offer many options for imagining new ways of securing biology, spanning a range of technology (figure 12) and societal (figure 13) readiness levels. We hope to never need to seriously consider making real some of the ideas introduced above. The development and adoption of such technologies may only become necessary if our worst-case scenarios unfold—if we fail to secure biology with better policies and more practical approaches that are accessible today and over the near term.

Being aware of such ideas is itself important for securing biology. Imagining that bad actors could leverage gene drives designed to wipe out regional-scale pollinators can help us prevent or prepare for such actions, or for one who bioengineers drug resistance into tick-borne bacterial illnesses, or for GoF research that is weaponized by a nation to create virus variants for which only they hold a treatment or vaccine. And so on.

At the same time, we note the possibility that simply imagining and sharing such ideas makes them more likely to be pursued. Technologies become true when people make them true, and doing so starts with dreaming.[324] We urge researchers, readers, policymakers, and the

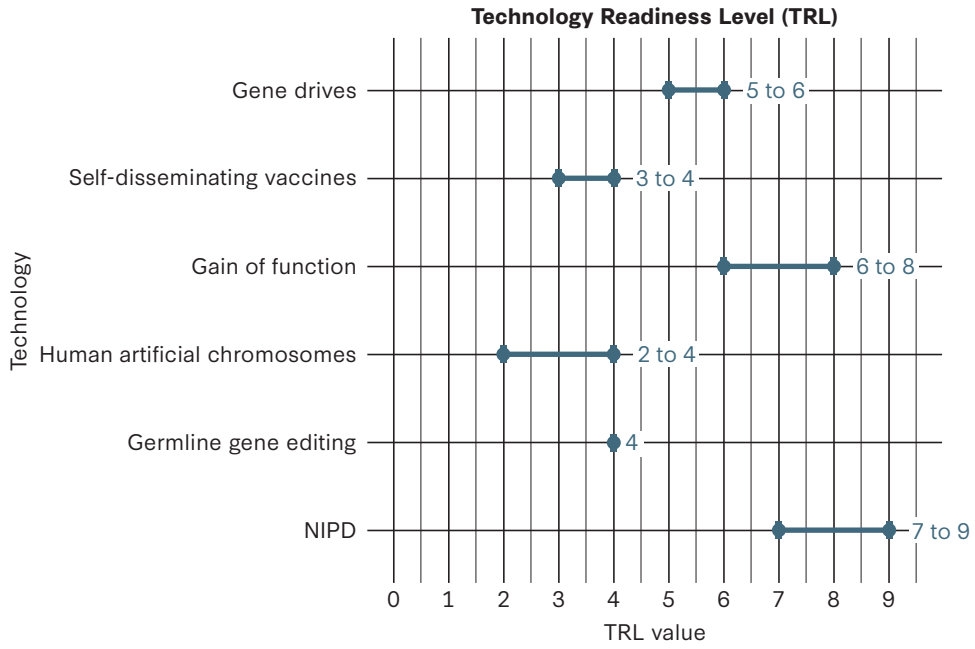


FIGURE 12 Estimated TRLs for six biotechnologies: gene drives, self-disseminating vaccines, gain-of-function research, human artificial chromosomes, germline gene editing, and noninvasive prenatal diagnosis (NIPD)
Source: Image by Raj Patel.

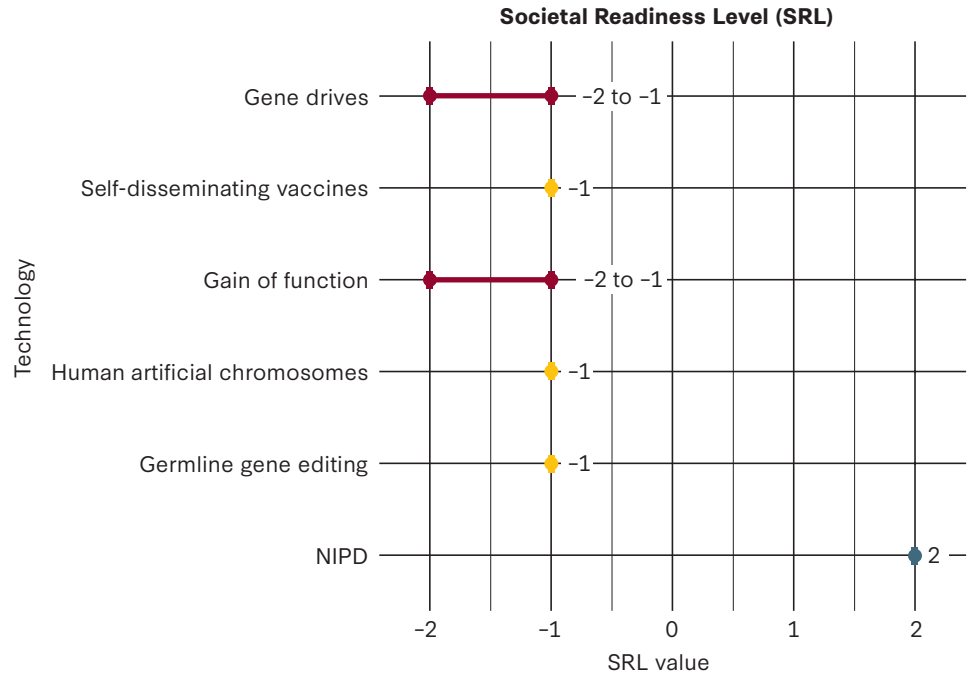


FIGURE 13 Assessed societal readiness levels (SRLs) for the same six biotechnologies
Source: Image by Raj Patel.

public to be mindful of potential information hazards and to approach exploration of beyond-frontier ideas and work with caution.[325]

Securing biology with biotechnology ultimately depends on our ability to advance innovations that mitigate risks without destabilizing bio-security. Beyond-frontier technologies may hold tremendous promise for human health, but their potential development and application must be guided by principles of transparency, safety, and the well-being of nature along with that of future generations. Proactive risk assessments and the development of robust governance frameworks, both nationally and internationally, can help ensure that such approaches, if ever needed, are harnessed in ways that benefit humanity as a whole and mitigate concerns early.

4. Twenty-First-Century Biosecurity Blueprint

INTRODUCTION

A strategy for securing biology must unfold over time. We propose three stages. Stage 1 focuses on immediate actions to be taken within the next one thousand days to reduce risk and improve intelligence. Stage 2 extends through 2030 and prioritizes developing and deploying next-generation capabilities along with the policies and institutions needed to sustain them. Recommendations associated with Stages 1 and 2 are urgent; the actions proposed in Stage 2 require longer lead times for effective implementation. Stage 3 organizes thinking for capacities that may never be needed but, if required, would be most useful by or before 2040.

Each proposed action is flagged accordingly (Stage 1, 2, or 3). Taken together, they comprise and offer a holistic strategy for securing biology in perpetuity. The recommendations themselves are written with the United States in mind but can be adopted elsewhere as appropriate. Some specific details are meant to be illustrative rather than prescriptive, as options exist for best accomplishing certain goals.

POLICY RECOMMENDATIONS

1 SEEING BEHIND THE MOLECULAR CURTAIN

RECOMMENDATIONS

1A: Organize and task biological intelligence (BIOINT) gathering as a unified, cross-agency, multimodality biosurveillance effort whose mission is to ensure that we are never surprised by biological threats (Stage 1).

1B: Jump-start BIOINT using tools we already have—metagenomic sequencing, wastewater surveillance—while responsibly sunsetting legacy systems (Stage 1).

1C: Integrate new measurement and surveillance modalities (Stage 2).

1D: Develop, deploy, and integrate pervasive living sensors—plants, microbes, and animals—to detect threats in real time (Stage 3).

At the core of biosecurity is intelligence. Lacking intelligence, we can only react. Our current biosurveillance systems are fragmented and slow. We need real-time, threat-agnostic systems for detecting unusual biological activity anywhere.[326] An organization focused on biological intelligence (BIOINT) is needed to unify and expand existing efforts into a coordinated network.[327] The goal of BIOINT is to create a future in which we are never surprised by the emergence of a biological threat—no mystery pathogens, no unexplained outbreaks, just immediate, layered awareness. Getting there requires breaking free from DNA-only detection, using every modality at our disposal, and updating key governance frameworks.

BIOINT should start with persistent, untargeted metagenomic sequencing across environments—air, water, crops, animals, and people. Real-time sampling of DNA is already feasible and affordable. We should deploy DNA sequencing widely. BIOINT should integrate geospatial, ecological, health, and travel data through close coordination with agencies including DOD, the Department of Health and Human Services (HHS), USDA, and the Department of Homeland Security (DHS). Data streams should feed into intelligent systems capable of flagging known risks and highlighting unknown ones.[328] BIOINT can begin by upgrading legacy infrastructure, overhauling the BioWatch program, expanding new detection programs such as Sigma+, and scaling wastewater monitoring.[329]

Not all biothreats offer easily detectable genomic footprints. Some pathogens may be missed by sequencing alone. By analyzing antibody repertoires from routine blood draws, BIOINT could detect what has been infecting people—even when direct DNA signatures are hard to find. For example, during routine blood draws, patients could opt in to BIOINT by donating a small portion of their draw to an anonymized pool. Threat monitoring can occur via high-throughput antigen-testing systems capable of spotting early, localized patterns of exposure.[330] Immune-based surveillance would complement nucleic acid–based methods, offering a clearer view of what pathogens are spreading, and where and when.

BIOINT could extend beyond DNA, RNA, and antibodies. The leap, if needed, would be to living organisms—plants, microbes, and animals—deployed as pervasive sensors, as previously described. Governments and others should support advancing pervasive and persistent biosensing capabilities to TRL 7 so that they are poised for manufacturing and deployment at scale if ever needed.

2 DISTRUST AND BIOAUDIT

Biotechnology will continue to advance and proliferate.[331] As access to biotechnology expands, our systems for trust and accountability must keep pace. Missing is a scalable, flexible system of oversight that is itself trusted, ensuring safety and security without unduly burdening innovation and commerce. “Bioaudits” solve this puzzle.

Modeled on financial audits, bioaudits are independent, third-party evaluations of biosafety, biosecurity, and dual-use risks. Bioaudits work to enforce rules and establish trust. As with finance, as biotechnologies become pervasive we need

RECOMMENDATIONS

2A: Create and launch bioaudits (Stage 1).

2B: Develop certification standards for bioaudits (Stage 2).

2C: Provide for federal oversight of bioaudits (Stage 2).

2D: Promote global adoption of bioaudit norms (Stage 2).

DEFINITION

Biotrust includes believing that others are using or will use biology and biotechnology in ways that are ethical and responsible. Biotrust encompasses trust in institutions, researchers, and technologies related to biology.

visible standards and systems that presume that even well-intentioned actors can get things wrong. Bioaudits offer a way to formalize distrust by catching problems early, certifying safety, and showing the public that responsibility and stewardship are not optional.

Biotechnology is far from the first widely used technology that can be used for good or ill. Money transformed trade, enabled cooperation across cultures, and helped build empires. But money also introduced severe and unevenly distributed risks, including theft, fraud, money laundering, and the financing of violence and terrorism.[332] The Bible warns that "the love of money is a root of all kinds of evil," a belief the O'Jays elaborated on in their 1973 hit song, "For the Love of Money."[333] Money is also a continually evolving technology, generating new opportunities for misuse, greed, and exploitation.[334]

Societies developed institutions and tools to address the persistent skepticism inherent in financial transactions. Few leave cash unattended, offer loans without considering creditworthiness, or trust institutions solely on goodwill. From simple receipts offered when buying groceries to comprehensive annual audits of corporations, our financial systems recognize mutual distrust as the default condition.

Central to managing mutual distrust is a system of third-party accountability culminating in independent financial audits. Rather than expecting people to blindly trust actors and entities, societies empower and require auditors to scrutinize how organizations handle transactions involving money. Independent firms review books, processes, and controls, issuing reports that signal whether an organization can be trusted.[335]

Financial audit reports have become a cornerstone of trust in the corporate world. In the United States, all publicly traded companies must undergo audits annually.[336] Even private companies often choose audits to reassure investors.[337] Trust in finance does not rest on the idea that institutions are honest. Rather, trust arises only because we assume institutions and individuals might be dishonest. By formalizing and responding to distrust via audits, society has realized a structure by which oversight creates confidence.

Biosafety audits can do for biotechnology what financial audits do for commerce: enable trust, incentivize responsible behavior, and identify risks before they escalate. Here's how: Professional third-party bioauditors would review university labs, biotechnology companies, and government facilities for biosafety and biosecurity gaps, dual-use concerns, and operational compliance. Reviews would occur under confidentiality agreements. New firms or existing audit firms would work with the biosafety and biosecurity community to establish and pilot bioaudits in practice.

Financial auditors are themselves bound by strict standards—and bioauditors should be held to the same level of accountability.[338] Lawmakers should establish safeguards to ensure that bioauditors remain independent from the entities they review. A certification process akin to the CPA credential—requiring bioauditors to demonstrate education, experience, and specialized training in biosafety and biosecurity protocols—should be established.

Congress should take a further step by creating an independent oversight body modeled on the Public Company Accounting Oversight Board (PCAOB), which regulates financial auditors. A Bioaudit Oversight Board would set standards, inspect bioauditors, register bioaudit firms, and enforce compliance. Under this system, bioaudit firms would operate under clear standards, face rigorous oversight, and be held legally accountable for violations. Firms caught falsifying reports or leaking sensitive data would risk losing their licenses—ensuring accountability and confidentiality during the bioaudit process and protecting public trust.

The financial sector offers a clear model for how bioaudits can scale globally. The PCAOB inspects thousands of audit firms—many outside the United States—through formal partnerships with regulators in twenty countries and enforcement coordination with over one hundred others.[339] When Deloitte China let clients write their own audit work, the PCAOB caught the violation and issued a $20 million fine.[340] The system works because accountability travels across borders. A bioaudit system could function the same way: Auditors could be held to shared global standards, carry liability insurance, and be subject to third-party review.[341] Intellectual property concerns would be managed by contractual confidentiality, making enforcement a legal—not geopolitical—issue.

3 BUILDING A GOVERNANCE REGIME FOR DANGEROUS PATHOGENS

Where did COVID come from—lab or market? We may never know. Some have spent more time debating COVID's origins than fighting it. Never again. Tracing the origins of any pandemic must become easy. Our existing policies derive from a time when building viruses was not yet routine. We must change how we govern research with dangerous and potentially dangerous biological materials.

RECOMMENDATIONS

3A: Disallow research on pandemic-potential pathogens by default (Stage 1).

3B: Create and support a multilateral review-and-approval process enabling narrowly scoped research with pandemic-potential pathogens (Stage 1).

3C: Track and eliminate remaining inventories of pandemic-potential pathogens (Stage 1).

3D: Increase penalties for possession of, or intent to possess, pandemic-potential pathogens (Stage 1).

When our understanding of viruses was limited, prioritizing research made sense. Today, the pendulum has swung the other way. We know enough to build pandemic-level threats. Many could do so. For the most dangerous pandemic-potential pathogens, we should adopt a "default-no" research policy. All research should be disallowed by default. Only if work with live pandemic-potential pathogens is absolutely needed to improve diagnostics, treatments, or vaccines might permission to conduct research be granted. We already work this way with smallpox.[342] We need to apply the same logic to any pathogens at risk of causing a pandemic. Such a list might expand beyond smallpox to include human or human-adjacent coronaviruses, influenza, and Nipah virus, to start.

Some research will be essential. A multilateral review process modeled on smallpox governance should be used to decide whether and when specific projects can proceed.[343] Those deciding whether work should be allowed must be sufficiently independent from those conducting any such work. Research must only occur in a small number of participating laboratories that

themselves are subject to multilateral inspections. Research results must be shared with all. Such an approach has allowed essential research with smallpox to continue. Tecovirimat (TPOXX), the first FDA-approved smallpox treatment, now also used against emerging threats such as mpox, was developed this way.[344]

A "default-no" regime works best if we reduce the number of labs working with pandemic-potential pathogens to a minimally viable level. We have done this before. In the 1970s the WHO compiled a global inventory of smallpox research, traced every lab working with the virus, and coordinated with national health authorities to contain and eliminate remaining stocks.[345] Stocks of live pandemic-potential pathogens should be eliminated from all but the small number of well-known participating laboratories subject to multilateral inspection and research review.

US law already makes it illegal to possess smallpox, with penalties of up to $2 million and twenty-five years to life in prison.[346] Similar penalties should apply to other pandemic-potential pathogens, increasing existing penalties associated with the Select Agent Program.[347] No one should be allowed access to pandemic-potential pathogens outside of the "default-no," multilateral review and multilateral inspection framework.

4 WORKING WITH ALLIES AND ADVERSARIES

RECOMMENDATIONS

4A: Keep biological weapons off the table (Stage 1).

4B: Modernize and resource the Biological Weapons Convention (BWC) (Stages 1 & 2).

4C: Couple the BWC with bioaudits (Stage 2).

Preventing the use of biological weapons demands global coordination. Nations must navigate their differences and work toward this shared goal. Such a call is not wishful thinking but rather a pragmatic appeal to shared survival guided by history. When the risk of nuclear war became real, Cold War powers faced a hard truth: No one wins a nuclear conflict.[348] We need the same renewed clarity and commitment for biology going forward. Governments must take an all-hands approach in renewing and redoubling resourcing, posture, actions, and mission in support of de-escalating geopolitical rhetoric and reducing or eliminating nation-state-level bioweapons programs.

The Biological Weapons Convention anchors global coordination against bioweapons. But fifty years since its inception the BWC has only four permanent staff and an annual budget of less than $2 million—less than that of a typical McDonald's franchise.[349] The agency enforcing the Chemical Weapons Convention (CWC) has a roughly $91 million budget and five hundred staff.[350] The BWC also lacks verification and enforcement mechanisms. Voluntary self-reporting through confidence-building measures (CBMs) exists, but these reports are too often missing or incomplete.[351] Over 40 percent of signatory countries have never submitted a single report.[352] Attempts to fix the weaknesses of the BWC have failed for decades due to concerns over industrial espionage, among other issues.[353]

The BWC must be brought into the twenty-first century. Funding and staffing should be increased at least tenfold. New staff should be assigned to three core missions. First, connect the BWC's mission to national and, as appropriate, international BIOINT biosurveillance and intelligence programs. Second, help promulgate and legitimize bioaudits among BWC signatory countries. By endorsing common standards, the BWC could bridge the gap between voluntary domestic audits and

international verification—building trust without requiring treaty revisions. Third, review and, as needed, update global definitions of what counts as a biological weapon.[354] Without up-to-date definitions red lines risk becoming blurry.

Bioaudits at the national level can help with bioweapons at an international level. Unlike historical inspection programs, bioaudits do not require direct state-level engagement or treaty revisions. Instead, bioaudits rely on enforceable contracts, legal liability, and third-party certification—tools that already work in other high-stakes domains. Countries should voluntarily opt in to a BWC-endorsed registry of certified bioauditing firms, each operating under strict standards and protected by confidentiality agreements.

Bioaudits should feed into CBMs, allowing nations to show compliance with the BWC without risking industrial espionage or political entanglement. Nations would select their preferred method of verification: unverified, self-verified, or multilaterally verified. We anticipate that most countries will choose to be self-verified, grounded in a domestic bioaudit program. Nations without a bioaudit program could make unverified pledges or pursue multilateral verification of compliance. While a stronger enforcement mechanism is preferable, a name-and-shame approach to countries in partial compliance or noncompliance with CBMs would be an important step forward.

5 USING BIOLOGY TO SECURE BIOLOGY

Biosecurity victory requires deterrence by denial—deterring an adversary from attacking by making it apparent and unlikely that their attack would succeed. Would-be adversaries must conclude that any bioattack would fail. Irrational actions must be met with operational resilience at all levels. Achieving such capabilities for biology requires leveraging biology itself. We must develop, leverage, and deploy world-leading capacities in emerging biotechnology to help secure biology.

RECOMMENDATIONS

5A: Organize, create, and resource a National Biosecurity Institute (NBSI) to lead and coordinate development of emerging biotechnologies as needed to secure biology (Stages 1 & 2).

5B: Deploy financial instruments stabilizing and amplifying private sector contributions to biosecurity (Stage 1).

5C: Entrench and sustain a perpetual Operation Warp Speed (Stage 1).

We recommend creating a National Biosecurity Institute (NBSI) whose top-line mission is to leverage emerging biotechnologies to help secure biology. Ongoing breakthroughs must be translated into new medical countermeasures (MCMs) fast enough to counter today's threats and protect against next-generation threats before they emerge. In the United States, the NBSI should (1) have the authority to establish national priorities, requirements, and government-wide strategy for advancing biotechnology to secure biology, (2) establish and manage joint programs across departments and agencies, (3) be supported by staff drawn from across the US government, and (4) conduct its work in an unclassified manner to the greatest extent possible to permit outreach and participation by US industry and academic researchers, and in support of geopolitical and public trust.

To secure biology, we must turbocharge the translation of discoveries and innovations from lab to practice. We must also ensure that early-stage private enterprise grows into resilient, onshore,

and profitable companies operating at the scales required. An emerging biotechnology investment fund modeled after In-Q-Tel's B.Next group or recommendation 2.2a from the 2025 NSCEB report is needed for early-stage translation.[355] Downstream capital is also needed to ensure that early-stage companies can access resources as needed to build factories and other capacities required to provide the materials needed to make biosecurity real. The DOD Office of Strategic Capital is one such mechanism, but resources must be made available and actually deployed for biotechnology, not only for other equally high-priority technology domains. Tax-free bonds and other state-level mechanisms should also be leveraged.[356]

Markets are missing for many MCMs absent a crisis. MCM innovation is itself too dependent on unpredictable surges of boom-then-bust emergency funding.[357] We need enduring government-led, public-private capacities inspired by Operation Warp Speed (OWS), ready for immediate action.[358] All other domains of security maintain and sustain vigilant defense systems, from manufacturing to deployment. Deterrence by denial for biosecurity requires the same. One dividend would be to help eliminate naturally recurring infectious diseases, saving the United States up to $1 trillion annually in direct and indirect costs.

6 GOVERNING AT THE SPEED OF BIOLOGY

Bad actors do not wait for regulatory approval. Good actors must. Those seeking to misuse biology will do so regardless of red tape. Those working to use biology for good face a fragmented, risk-averse oversight system that slows down defense. To use biology to secure biology, regulators will need to move at the speed of innovation, not bureaucracy. Doing so requires new institutional muscle throughout the government.

RECOMMENDATIONS

6A: Establish a National Biotechnology Coordination Office (NBCO) (Stage 1).

6B: Create and resource a Biotechnology Governance Office (BGO) (Stages 1 & 2).

We strongly endorse the NSCEB recommendation to establish a National Biotechnology Coordination Office (NBCO) within the Executive Office of the President.[359] The NBCO would coordinate policy and direct funding to keep US biotechnology competitive and innovation focused. To build cross-agency expertise, the NBCO should adopt a "joint-duty" model where staff rotate into the office from key agencies including DHS, HHS, the Department of Commerce (DOC), DOD, the Department of Energy (DOE), and USDA. Joint-duty rotations would help create a new generation of "bionative" civil servants trained to navigate and connect the full biotech ecosystem.[360] The NBCO would also serve as the central coordinating hub for the NBSI as well as for a new office called the Biotechnology Governance Office (BGO).

Coordination alone will be insufficient. We also need an office to govern modern biotechnology at speed. We recommend creating the BGO to fill this gap. Building on NSCEB recommendation 4.4a, the BGO would cut through regulatory gridlock, streamline biotech approvals, and write clear rules for emerging tools.[361] The BGO would manage licensing, operate regulatory sandboxes, and help oversee high-risk pathogen research with the authority to pause dangerous projects if necessary. The BGO's goal should be to cut red tape while raising the bar on safety, security, and public trust.

The BGO must also be able to commission and support testing of new biotechnologies under

controlled conditions as needed to best inform policy.[362] During COVID, Emergency Use Authorizations (EUAs)—special permissions given by the government to allow the use of MCMs during an emergency even if they haven't gone through all the usual testing—often arrived too late.[363] To effectively deploy tools before a crisis escalates, the BGO should create EUA-like approval pathways for nonemergency use.[364] The BGO should also fast-track low-risk diagnostics by updating the Centers for Medicare & Medicaid Services' Clinical Laboratory Improvement Amendment (CLIA) rules that have kept tests stuck in regulatory limbo.[365] Finally, the BGO should help unify oversight under a national bioaudit framework, replacing patchwork rules with consistent and clear standards.[366]

Oversight must evolve alongside the technologies it governs. The BGO should take the lead in designing governance systems for frontier tools such as gene drives and self-spreading vaccines. Such breakthroughs could transform global health and biosecurity but come with major potential risks.[367] We need new governance systems designed to help manage emerging biotechnologies. Implementing such systems necessarily means funding research into biological fail-safes and self-limiting mechanisms, enforcing clear standards for risk assessment and containment, and mandating robust postdeployment monitoring.[368]

Together, the NBSI, NBCO, and BGO could form a coordinated federal architecture for modern biosecurity. The NBSI leads on development and deployment of biotechnologies to secure biology. The BGO ensures that governance keeps pace with emerging technologies, leads oversight, and resolves ambiguities via focused research. The NBCO sits at the center, resolving conflicts, coordinating national strategy, and ensuring that the whole system moves together.

7 STRENGTHENING OUR DIGITAL BIODEFENSES

RECOMMENDATIONS

DNA SYNTHESIS

7A: Make strategic investments in DNA construction to guarantee global leadership (Stage 1).

7B: Incorporate DNA sequence screening into bioaudit frameworks (Stage 1).

7C: Develop and deploy decentralized, privacy-preserving DNA sequence screening (Stage 2).

AI X BIO

7D: Coordinate strategic investments in AI for biotech to guarantee global leadership (Stage 1).

7E: Determine whether AI is more likely to aid in threat detection or threat generation (Stage 1).

7F: Develop digital "research assistants" to enhance safety, security, and bioaudits (Stage 2).

7G: Develop and deploy AI across all layers of biosecurity infrastructure, as appropriate (Stage 2).

DNA Synthesis

As DNA synthesis continues to improve and becomes more widely used, who can make which DNA sequences becomes more important than ever. Sequence screening checks digital DNA code before the DNA gets made. In 2010, the United States recommended that DNA providers

screen both their customers and the sequences they order to stop bad actors from making dangerous viruses or toxins.[369] But this system has gaps, and full coverage may be unrealistic or counterproductive.

Security starts with competitiveness. If US companies are not the world leaders in building DNA, then users will order DNA elsewhere. In a global market, researchers and companies will migrate to jurisdictions with fewer restrictions and better tools, further undermining security and competitiveness. If policymakers believe DNA sequence screening is important, then they must also act to lead in synthesis technology. The United States must coordinate investment in next-generation DNA synthesis technologies. Such work could be spearheaded by the NBCO and take the form of a Strategic DNA Initiative, informed in part by the US Strategic Computing Initiative.[370]

DNA sequence screening systems should be paired with bioaudits. Audit trails and reports should affirm publicly who has not ordered dangerous sequences without exposing proprietary designs. Doing so broadens the reach of sequence screening, enabling third parties and the public to learn who is not doing risky work. The United States should begin prototyping a bioaudit-linked DNA sequence screening framework now.

Sequence screening as currently practiced creates centralized burdens on those operating DNA synthesizers, often early-revenue startups or, at best, modestly profitable companies. Centralized screening also creates a longer-term hypothetical risk involving potential censorship of who can build what DNA. We need a better approach that scans for danger without slowing down discovery, innovation, and entrepreneurship, or hindering freedom.

One solution would be to develop and deploy decentralized, privacy-preserving DNA sequence screening systems that are operated by users of DNA synthesis. Imagine you enter a circular cave that, to pass through, requires unlocking a door deep inside the cave. For reasons of privacy or security you do not wish to reveal how you unlock the door, only that you can do so. If you enter the cave in one direction and reappear from the other, then you have indirectly proven that you can unlock the door without sharing how you did so. This is the starting logic behind zero-knowledge proofs.[371] Applied to biosecurity, zero-knowledge proofs could allow researchers and others to demonstrate that they have not ordered anything dangerous without revealing the exact DNA sequences they are working with. This kind of system could also help safeguard intellectual property and reduce regulatory friction. The United States should invest in building and testing privacy-preserving and decentralized DNA screening tools now.

All the while, we must remember that DNA sequence screening is like airport security screening. The Transportation Security Administration (TSA) does not catch every threat, but it contributes to trust and reduces liability.[372] No one believes TSA screening alone is enough—we also rely on airport fences, air marshals, no-fly lists, and ID checks. Such overlapping defenses contribute to a "Swiss cheese" model of security, helping stop threats that might slip through any individual vulnerability.[373] Today, the global community risks placing too much faith in DNA sequence screening alone, as if checking all computer code could by itself stop misuse of software. In reality, biosecurity requires lab audits, biosurveillance, threat modeling, real enforcement, and everything else.

AI x Bio

The United States must remain at the forefront of using AI in biotechnology. Leadership is not only about driving innovation; it is about setting global standards for safe, secure, and responsible use. Guaranteeing the United States as the world

leader requires sustained federal investment, creating and dedicating large language laboratories (LLLs) to safely generate and handle high-quality biological data at the scales required.[374]

As with DNA synthesis, the NBCO should coordinate investments to ensure leadership in AI for biotechnology. A key biosecurity research priority should be to assess whether AI is more likely to aid in the detection or generation of dangerous biological functions. Restated, which is easier: prompting an LLM to design a novel, harmful biomolecular function or using AI to detect one that has never been seen before?[375] If analysis and detection remain ahead of generation, then AI, properly deployed, could provide a powerful biosecurity advantage. But if generating threats becomes just as easy, the balance shifts, giving malicious actors a dangerous edge. Understanding this balance will shape downstream governance decisions, including risk management and funding priorities, and should be a day-one priority project for the BGO.

We also recommend developing and deploying LLM-based assistants to support researchers.[376] Such tools can increase productivity and safety within research workflows.[377] Linkage to institutional auditing systems can help by flagging safety risks. At the national level, we should embed AI capabilities across biosurveillance, sequence screening, and medical countermeasure design. AI systems can also flag novel viral threats in environmental samples and help accelerate antibody development for viral variants, with AI facilitating faster responses to threats we didn't know to look for.[378] Moreover, as DNA synthesis becomes cheaper and more accessible, smarter AI-based screening systems will be essential to detect dangerous sequences before they are made. Practically doing so requires continuous investment to ensure that our defense capabilities stay ahead of the ability to generate novel biological threats.

8 SECURING OUR AIR

RECOMMENDATIONS

8A: Perform a comprehensive economic analysis of the costs and benefits of implementing national indoor air quality standards (Stage 1).

8B: Prototype national air quality standards for infectious disease control (Stage 2).

8C: Implement air quality standards in high-leverage spaces (Stages 2 & 3).

8D: Require air quality standards more broadly, if needed (Stage 3).

One of the most effective ways to fight infectious disease is to assure clean drinking water. In 1908 Jersey City, New Jersey, became the first US city to continuously add small amounts of chlorine to its water supply.[379] Clean water saves lives by killing harmful germs like those causing typhoid fever, effectively cutting typhoid rates by 99 percent within one hundred years.[380] Today, municipal water systems must meet strict rules to ensure that dangerous microbes are not piped to people's homes, schools, and places of work.[381] But what about pathogens in the air we breathe? While there are standards and guidelines for treating air to reduce risks from airborne pathogens in select settings, there are no enforceable federal standards or regulations based on absolute amounts of airborne pathogens, as with water.

It is past time to treat air like we treat water by setting standards to control airborne pathogens. We have the tools to do so. Basic steps include regulating airflow, using high-quality filters such as HEPA, and maintaining proper humidity levels.[382] Dry air allows virus-laden aerosols to stay airborne longer, while moderate humidity

(40 to 60 percent) can reduce transmission.[383] Ventilation ensures that fresh air dilutes indoor contaminants, and filters remove particles before they recirculate. A promising addition is far-UVC light.[384] Recent research suggests that this type of ultraviolet light can destroy viruses and bacteria in air without harming people. Unlike ventilation or filters, far-UVC works continuously in occupied rooms, inactivating pathogens before they spread. Far-UVC might thus provide always-on protection—a potentially critical defense against highly contagious diseases such as measles, influenza, or future pandemic threats.[385]

A national economic public health analysis of air quality standards should be conducted. The analysis should include an assessment of what spaces would provide the highest leverage in terms of reducing disease transmission (e.g., schools). Should the results be compelling, enforceable, absolute concentration-based standards should be developed for the settings where risk is high and public benefits clear. Implementation could follow. If needed, air quality standards could eventually expand to cover all new construction or be applied across public buildings, with appropriate lead times.

9 PROMOTE BIOLITERACY AND REWARD BIOSECURITY LEADERSHIP

RECOMMENDATIONS

9A: Improve policymakers' knowledge and leadership capabilities in biology and biosecurity (Stages 1 & 2).

9B: Recognize and reward biosecurity service and leadership more broadly (Stage 1).

9C: Integrate a national "labrary" network into biosecurity preparedness (Stages 1 & 2).

Improving biosecurity requires informed decision makers. Yet many policymakers lack the training, tools, and confidence to engage meaningfully with emerging biotechnologies. Scientists often present biology as too complex for nonexperts, unintentionally sidelining those who hold the power to act. But biology is no longer a niche scientific issue; biology is a strategic domain that is central to national security and beyond.

The number of high-consequence decisions tied to biology is rising faster than the number of bioliterate leaders. We are in the gap period where biotechnology has become strategically important faster than bionative professionals are arriving into positions of influence. Leaders everywhere, not only in dedicated science and technology offices, must be equipped to understand, advise, and act on biotechnology-related issues directly.

Governments should normalize biotechnology and biosecurity briefings as a core part of governance. As in Cold War–era nuclear orientation sessions, every incoming member of Congress and agency head should be offered a biotechnology briefing.[386] Those outside of government also have a role to play. Targeted biosecurity "boot camps" put on by think tanks or academic centers can help teach emerging biotechnologies, security risks, and regulatory frameworks to nonscientists.[387]

Beyond educating current policymakers, Washington should step up recruitment of those with biology expertise. Every congressional committee that touches national security, intelligence, health, or science should include professionals with a biology or biotechnology background.[388] By supporting policymakers with trusted advisors fluent in biotechnology we can enable better, faster, and more confident decision making.

Congress must also improve its infrastructure to match biotechnology's growing strategic

DEFINITION

Bioliteracy imbues people with an understanding and ability to confidently engage with biology as a strategic domain.

"Bioliteracy for the Age of Biology," National Security Commission on Emerging Biotechnology, working paper, February 2024, https://www.biotech.senate.gov/wp-content/uploads/2024/02/NSCEB_Bioliteracy_WP.pdf.

importance. We recommend establishing a dedicated Subcommittee on Biotechnology under the House Committee on Science, Space, and Technology.[389] This body would serve as a focal point for hearings, oversight, and legislative development.

Biosecurity will not succeed on policy leadership alone. Securing biology requires a cultural shift—a shared ethos that makes safety and responsibility a collective priority. Think about how we treat the power grid—it is protected not just by regulation but by widespread agreement that it must not fail. We defend energy because we depend on it. Biology lacks this cultural gravity, in part because we do not treat biosecurity leadership as though it matters. The professionals in these roles often face blame, harassment, and termination.[390] Recognition is rare and inconsistent.[391] We need to cultivate and empower a new generation of biosecurity leaders—inside and outside of government—who view biosecurity not just as a job but as a calling.

If we want a robust biosecurity workforce, we must make service in biosecurity respected and aspirational. Like our military service members, biosecurity practitioners and leaders provide a shield around American families—silently protecting them from biological threats.[392] We should recognize them for the work they do. Such recognition could look like the honors that General Gustave Perna earned for his work leading Operation Warp Speed (OWS) but can also manifest at the state and local levels.[393] Honors and recognition could be awarded for all service contributing to biosecurity, including pandemic preparedness and response, diagnostics innovation, public health logistics, and so on.[394]

Beyond better recognition for existing biosecurity heroes, we must inspire the next generation so that when children are asked what they wish to be when they grow up, "biosecurity expert" and "bionaut" join the ranks of "firefighter," "astronaut," and "soldier." Doing so might involve hosting "public health games" in schools, adding biosecurity floats to Fourth of July parades, or public engagement campaigns such as "All Vote No Play"—but for biosecurity.[395]

Local bioliteracy is also key. We support calls for a national "labrary" network: local, community-based biology labs run by certified "labrarians" serving as trusted stewards of education, diagnostics, and early-warning systems.[396] In the next thousand days, a dozen labraries should be created in every state. By 2030, this number should grow to several dozen in each state. With credentialing, safety standards, and transparent governance, professionally staffed community biolabs will serve as trusted nodes in a decentralized biosecurity network.[397]

CONCLUSION

Biology is shaping the twenty-first century—for better or worse. Whether biology expands as a tool for healing or harm depends on what we do now to help biology help us. The blueprint offered above offers proof that the necessary architecture, incentives, and cultural shifts needed to secure biology are imaginable and achievable. No plan or strategy is perfect or resists adjustment in a changing reality. Yet having, sharing, and improving strategies is essential. Biosecurity threats are real and increasing. The tools for securing biology exist or can be made real soon enough to matter. We should get to work now before the next crisis.

5. Biosecurity Victory

The world is changing. Our approach to biosecurity must evolve. We should expect to enter an era of near unlimited-access biotechnology. Most people in most places will eventually have the capacity to make nearly any toxin or pathogen. Almost all will have zero interest in doing so. Some eventually will.

Meanwhile, advancements in AI and synthetic biology are lowering barriers for designing novel toxins and pathogens. Social, political, and other trends may exacerbate the consequences of biological incidents. Conflicts and eroding norms against biological weapons may nudge nations toward Stupidly Assured Destruction (S.A.D.) by dangerously expanding their arsenals with modern biological capabilities.

In the years to come we will face more intentional, natural, and accidental biothreats than at any point in human history. We already know from the COVID-19 pandemic that our existing systems are not up to the task.

But biology is not just a source of biosecurity risks. Biotechnology properly advanced will form our best biodefenses. Affordable DNA sequencing begins to unlock biological intelligence (BIOINT). Engineered plants and animals can form embedded real-time biosurveillance systems. Advancements in vaccines can transcend cold-chain and supply chain challenges. Paper-based and embedded diagnostics can make rapid identification of pathogens possible before they spread. Brewing medicines, personalized treatments, and antibody technologies can enable local and on-demand production of therapeutics.

Effective biosecurity demands effective governance. Implementing such governance requires updating and streamlining regulatory frameworks to address twenty-first-century threats and technologies; improving interagency coordination across governments; investing in biotechnologies to pioneer the solutions of the future; establishing systems that promote biotrust among scientists, policymakers, and the public; upgrading governance for research on dangerous pathogens; and advancing biosecurity leadership inside and outside of government. Most critically, the sequence of implementation matters. Stabilizing actions such as BIOINT must happen first.

Much of what is needed falls squarely within the mandate of government. Just as national security is a public duty, governments must lead on ensuring biological security. As such, many of the solutions advanced here will need to utilize precious public treasure. We expect that a strategic, future-focused biosecurity program like the one laid out here would cost the US federal government no more than $40 billion annually while generating up to $1 trillion annually in direct and indirect public and economic benefits. Compare

that to the $95 billion per year that the United States is expected to spend to operate, maintain, and upgrade its nuclear arsenal over the next ten years.[398]

Public investments in biosecurity will also deliver benefits beyond human health. The history of DOD-driven innovations shows that strategic investments can transform industries. For example, ARPANET, a precursor to the internet, was developed by what later became DARPA to connect universities and allow multiple computers to communicate over a shared network.[399] Strategic biosecurity spending should stimulate development of a BIONET enabling distributed manufacturing resilience. When weighing the costs of biosecurity investments against the costs of biosecurity failures and economic returns of advancing biotechnology, biosecurity funding is likely one of the most efficient allocations of public resources available to policymakers.

Without leadership and action we risk a grim future—one in which humanity is increasingly threatened by biology, in which biotechnology is used to harm rather than help, all while we remain at war with biology. Marc Bloch, in *Strange Defeat*, warned of the risks of failing to adapt to changing conditions, saying: "History is, in its essentials, the science of change. By examining how and why yesterday differed from the day before, it can reach conclusions that will enable it to foresee how tomorrow will differ from yesterday."[400] Just as 1920s France trusted concrete over innovation, we cannot afford to double down on the solutions of the past. We must anticipate the future, dream up new solutions, and adapt fast enough to protect humanity from evolving biological threats.

We can make a world in which we are safe from preventable biological harms. We can make a world in which COVID-19 is the last pandemic humanity ever faces. We can create frameworks for managing distrust in the development and deployment of biotechnologies. We should all be confident that the powerful tools of twenty-first-century biotechnology are being wisely developed and responsibly deployed.

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BIO-STRATEGIES AND LEADERSHIP FELLOWS, STAFF, AND STUDENT RESEARCH ASSISTANTS

Vassilis Andrea Alexopoulos

Lindsey Armeen

Britney Bennett

Ken Bernard

Tanner Braman

Alex Cessna

Drew Endy

Eric Heng

Josh Hodges

Rhea Jain

Rick Johnson

Jackie Johnstone

Audrey Jung

Riya Karumanchi

Mike Kuiken

Sarah Moront

Raj Patel

Tanner Pulice

Jack Shumway

Emily Clise Tully

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Steve Luby

David Magnus

Zack McGahey

Piers Millett

Tara O'Toole

Jassi Pannu

Govind Rao

Andrew Snyder-Beattie

Victor Tang

Ryan Tully

Crystal Watson

Ian Watson

Andy Weber

Jaime Yassif

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ABOUT THE AUTHORS

DREW ENDY

Drew Endy is the Martin Family University Faculty Fellow in Undergraduate Education (bioengineering) and science and senior fellow (courtesy) at the Hoover Institution. Drew helped start two gene-synthesis companies, advises global biosecurity bodies, and serves on key WHO and NASEM committees. He has helped launch undergraduate majors in bioengineering at MIT and Stanford, and cofounded an international genetic engineering "Olympics."

SARAH MORONT

Sarah Moront is a senior research program manager with the Hoover Institution's Bio-Strategies and Leadership Initiative. Prior to joining Hoover, she was the deputy policy director for a presidential campaign and policy organization for several years. Earlier in her career, she served in the Peace Corps in the South Pacific. She attended the University of Virginia.

VASSILIS ANDREA ALEXOPOULOS

Vassilis Andrea Alexopoulos is an incoming master's student at Stanford, studying electrical engineering and biology. He has engineered cryopreservation systems, built autonomous underwater vehicles for marine monitoring, and designed novel health sensors. His work encompasses biosecurity policy, emerging tech, and technology governance.

RAJ PATEL

Raj Patel is an undergraduate bioengineering student at Stanford University working in the Gray Laboratory to investigate E3 ubiquitin ligase mechanisms for cancer degradation. He is passionate about advancing biotechnologies to improve public health and intends to pursue a career in medicine.

RHEA JAIN

Rhea Jain is a rising junior majoring in human biology with a concentration in biosecurity and global health. Her work bridges biotechnology, law, and policy. Beyond Hoover, she researches climate change with Stanford's Existential Risks Initiative, leads Stanford's Bioethics Bowl team, and coaches high school debate. She plans to pursue a career in biosecurity law and policy.

BRITNEY BENNETT

Britney Bennett is a rising senior at Stanford majoring in biomedical computation on the simulation track. She works as a research assistant for the Bio-Strategies and Leadership Initiative and is passionate about the intersection of biology, technology, and policy. Driven by interdisciplinary research, she plans to pursue a PhD in global or environmental health in the future.

SYNOPSIS

Current trends make clear that biosecurity will become much more challenging over the next several years. We must act strategically to secure biology—before it becomes a general-purpose technology. Drawing on decades of experience and the knowledge of dozens of subject matter experts, *Biosecurity Really* offers a forward-looking analysis of how global trends and technologies are reshaping the biosecurity landscape, and actionable steps we can take to respond.

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Hoover Institution, Stanford University
434 Galvez Mall
Stanford, CA 94305-6003
650-723-1754

Hoover Institution in Washington
1399 New York Avenue NW, Suite 500
Washington, DC 20005
202-760-3200

HOOVER INSTITUTION