EXECUTIVE OFFICE OF THE PRESIDENT
PRESIDENT'S COUNCIL OF ADVISORS ON SCIENCE AND TECHNOLOGY
WASHINGTON, D.C. 20502

November 2016

Dear Mr. President,

Advanced biotechnology offers the promise of transforming the way the world produces food and portable fuels, protects the environment, and treats disease.[1] The power of biotechnology has been growing at an exponential rate over the past several decades, driven by intense efforts in academia and the private sector aimed at both fundamental research and commercial applications.[2] The United States is the clear world leader, but biotechnological knowledge and skills are broadly distributed across many developed and developing nations.

While the ongoing growth of biotechnology is a great boon for society, it also holds serious potential for destructive use by both states and technically-competent individuals with access to modern laboratory facilities.[3] As the security challenges evolve rapidly with technological advances, it is important that the Federal Government's own thinking about how to protect the Nation keeps pace.

Since 2001, the U.S. Government has spent billions of dollars annually to protect the Nation against both intentional biological attacks and emerging infectious diseases, and much has been accomplished.[4] But, molecular biologists, microbiologists, and virologists can look ahead and anticipate that the nature of biological threats will change substantially over the coming years—in ways both predictable and unpredictable. The U.S. Government's past ways of thinking and organizing to meet biological threats need to change to reflect and address this rapidly-developing landscape.

We, your President's Council of Advisors on Science and Technology (PCAST), urge you to take immediate action to ensure that the Nation has the ability to meet these challenges. In this letter, we recommend measures aimed at decreasing the probability and impact of a future biological attack against the United States. Our recommendations are divided into actions with near-, medium-, and long-term goals. All of these actions should be undertaken now to ensure that the capabilities will be ready when needed.

An important overarching observation is that there is significant overlap between some of the steps needed to protect the Nation from intentional biological attack and those needed to protect against natural outbreaks of new and emerging infectious diseases—including with respect to disease surveillance, response, and recovery. We highlight potential synergies between efforts directed at these goals.

I. Biotechnology and Biological Threats: The New Landscape

The Federal Government's approach to defending against intentional biological threats over the past two decades has centered around a list of "select agents," consisting of a particularly dangerous subset of the known human and agricultural pathogens. The *Public Health Security and Bioterrorism Preparedness and Response Act of 2002*, together with the *Agricultural Bioterrorism Protection Act of 2002*, require the Department of Health and Human Services (HHS) and the United States Department of Agriculture

(USDA), respectively, to establish and regulate lists of biological agents that have the potential to pose a severe threat to public health and safety (HHS) or animal and plant health and safety (USDA).[5] The laws require HHS and USDA to periodically review, update, and publish these lists. Together, the lists currently include about 60 pathogens, along with approximately 10 toxins. The Government's defensive research related to potential biological weapons has largely focused on these agents, and it has developed and stockpiled medical countermeasures (MCMs) for a subset of them. In addition, Government-funded research with the most dangerous of these agents receives special scrutiny if it could significantly increase the risk that these agents would pose if misused, for example by increasing their virulence, transmissibility, or ability to overcome vaccines or therapeutics.[6]

These defensive efforts have been valuable and should be continued. Yet their adequacy is increasingly challenged by advances in biotechnology.

Advances in biotechnology

Over the past decade, the scientific community has been developing increasingly sophisticated "second-generation methods" for biological engineering, driven by applications such as fundamental research, improving human health, and enhancing agriculture.

The first generation of biotechnology included such tasks as transferring a "recombinant" gene from one organism to another. That approach has been used for such purposes as manufacturing large amounts of a therapeutic protein (e.g., insulin) in microorganisms, producing plants that are resistant to certain pests, creating mouse models of human diseases, and early efforts at gene therapy.

While powerful, these technologies have had important limitations—for example, (1) the procedures for assembling recombinant genes were time-consuming; (2) the available regulatory-control sequences were limited; (3) targeting genetic modifications to specific locations in the genome of a living cell required complex procedures; and (4) delivering DNA to specific cell types was often challenging.

Increasingly, however, biotechnologists have been finding ways to overcome these limitations, based on advances such as:

- **Massively parallel DNA synthesis**. It is now possible to assemble large stretches of any desired DNA sequence, by synthesizing many thousands of short DNA fragments on microchips and using biochemical methods to assemble them together in the right order. Using this approach, scientists can readily create DNA molecules that encode scores of genes, or entire viruses.

- **Improved knowledge of gene regulation**. Biologists are gaining much greater knowledge about the natural regulatory sequences that cause a gene to be expressed in particular cell types and under particular conditions. In addition, they are developing methods to create synthetic regulatory sequences that are activated by specific signals.

- **Genome-editing and -targeting technologies**. The discovery that microbes have a natural system, called CRISPR,[7] that can target a protein to any desired DNA sequence has stimulated tremendous activity in biotechnology. Scientists quickly showed that the CRISPR system can be

adapted to work in the cells of many organisms—including humans, animals, and plants. Scientists can now cause virtually any DNA sequence of interest to be cut (genome cleavage), modified to a new sequence (genome editing), or bound by a regulatory protein (gene activation or repression). Moreover, the process is rapid and efficient: genetic engineering that previously required many months or years can now be performed in days or weeks.

- **Gene delivery**. After initial challenges with human gene therapy, there has been revived interest and growing success in using the approach to treat some rare genetic diseases. The progress is due in part to steady improvements in vectors (such as viruses) for delivering genetic material to specific cell types.

More broadly, biotechnologists are increasingly adopting an "engineering mindset"—thinking in terms of developing collections of modular parts that can be reliably assembled into working biological circuits that carry out desired behaviors. More powerful and efficient methods for genetic engineering are increasingly a part of routine practice across the biotechnology enterprise.

At the same time, basic, biomedical, and agricultural scientists are learning much about natural biological circuits—including how pathogens hijack such circuits to cause disease in their hosts and how these circuits may be perturbed to treat diseases.

Potential for intentional misuse

The developments described above, and many others, hold great promise for medicine and agriculture in the coming decades. As is often the case with technology, they also harbor the potential for misuse.

Relatively straightforward examples of misuse would include the modification of pathogens to overcome existing immunity or to be resistant to available drugs. Such possibilities are not far-fetched: (1) a research team reported in 2001 that insertion of a gene affecting the immune system into the mousepox virus—the rodent analog to the human smallpox virus—enabled the virus to kill mice that were immune to the normal virus;[8] and (2) scientists have identified genetic changes in many highly virulent pathogens that confer resistance to first-line therapeutic drugs.[9] Notably, such small modifications were feasible even with "first-generation" biotechnology methods.

A more complex example would be to try to use CRISPR technology to create viruses that can cut, modify, repress, or activate a host gene so as to disrupt an important cellular function.

While it is not hard to conceive of such ideas, it should be emphasized that creating a truly novel and effective pathogen is unlikely to be simple. Effective pathogens typically have carefully tuned mechanisms to solve a variety of biological challenges—including overcoming host defense systems and, for contagious organisms, spreading efficiently between hosts. Despite these challenges, the risks are real and will only grow as biotechnology becomes more sophisticated in the years ahead.

Importantly, biothreats differ in significant ways from nuclear or chemical threats in that the initial creation of biologically engineered organisms requires much more modest resources and smaller facilities

that cannot be readily distinguished from ordinary research labs. Work undertaken with malevolent intent is thus harder to distinguish from work undertaken for benevolent purposes.

A deliberate biological attack could also differ in important ways from a naturally-occurring disease outbreak or accidental release. A well-executed intentional attack could, for example, begin with near-simultaneous release of a biological agent in multiple, geographically dispersed areas to reach the greatest number of individuals as quickly as possible; moroever, a pathogen might be deliberately modified to affect its spread or to be resistant to current preparedness and response capabilities.

Implications for biodefense strategy

PCAST focused on five key components that must be part of a comprehensive biodefense strategy: (1) scientific analysis of the scope of the problem; (2) intelligence gathering to detect activity by potential adversaries; (3) biosurveillance to detect the presence of biothreats; (4) development of effective medical countermeasures to protect against biothreats; and (5) leadership and organization.

In view of the rapid advances in biotechnologies, a biodefense strategy must prepare not only for *known* biological agents, but also for a much wider array of novel and ever-changing biological threats that may be impossible to fully anticipate; moreover, even attacks involving known pathogens may not follow scenarios devised during the Cold War (e.g., an aerosol dispersion of anthrax spores) because biotechnologies may lead to new paths for dissemination.

The first challenge is to maintain awareness and understanding of technological capabilities and their impact on offense and defense.

Much responsibility to provide threat awareness and understanding lies with the Intelligence Community (IC)—through (1) scientific knowledge of what is possible and (2) identification of potential attackers and acquisition of a better understanding of their motivations, intentions, and capabilities. The IC's task is made more difficult by a number of factors, including an ever-expanding and ever-changing array of possible options for an adversary, the modest resources and abilities needed to use these technologies, and the small footprint that their laboratory use presents.

In the best case, a biological attack would be prevented through enhanced threat awareness and deterrence and/or interdiction. However, it is possible that a well-planned, well-executed attack might go unnoticed for days or weeks. The ability of the United States to escape serious consequences will depend on effective detection (biosurveillance), response (such as medical countermeasures), and recovery capabilities.

The challenges are considerable. Whereas biosurveillance in the past could focus primarily on a list of known biothreats, the challenge ahead will be to detect novel biothreats reliably (for example, by using technologies such as genome sequencing). With respect to medical countermeasures, the challenge of being prepared for novel threats is even greater. The research, development, clinical trials, and distribution planning required to develop vaccines or drugs against a specific infectious agent currently requires many years, often more than a decade. As ongoing advances in biotechnology continue to add to risks

of misuse, it will be important to create new approaches for producing medical countermeasures much more rapidly.

In formulating biodefense strategy, it is important to recognize that efforts to control biotechnological knowledge by imposing wide-ranging security classification will be neither *effective*, because scientific expertise is too widely disseminated across nations, nor *desirable*, because such restrictions are likely to interfere with fulfilling the promise of biotechnology for improving human health and welfare. Indeed, as discussed below, a vibrant and open scientific research community developing novel solutions will be a critical part of the Nation's biodefense against both human-made and naturally-occurring pathogens.

Finally, we note that it is critically important that the U.S. Government and the scientific community continue to discourage the development or use of biological weapons through all available means and channels.

Naturally-occurring biological threats

While it is essential to have an effective strategy for defense against deliberate biological threats, the Nation and the world will continue to face naturally-occurring infectious diseases.

Over the past decade, the world has seen the increasing emergence of naturally-occurring infectious diseases such as SARS, H1N1 influenza, MERS, Ebola hemorrhagic fever, and Zika fever. These outbreaks often reflect changes in hosts and environment such as urbanization, movement of people, and changes in the climate and land use, as well as ongoing evolution in the pathogens, including adaptations to growth in their non-human host organisms. These natural outbreaks have been harmful to human life and have caused substantial economic disruption.

Defense against intentional biological attack shares some key features with the defense against new and emerging naturally-occurring outbreaks—particularly, with respect to biosurveillance (both require similar capabilities to detect and monitor the spread of unanticipated organisms); need for medical countermeasures (in both cases, effective vaccines and drugs may be lacking and would need to be developed more rapidly than currently possible); attention to logistics (where an outbreak could outpace the ability even to distribute stockpiles of existing medical countermeasures); consideration of the overall challenge of rapidly mobilizing public health resources, and the emergency response capabilities needed in the event that the functioning of public and private infrastructure is compromised by a large scale health crisis.

Accordingly, efforts to protect against new and emerging infectious diseases, which arise on a regular basis and represent a key medical and humanitarian threat, also provide a critical testing ground for approaches to detect and respond to potential deliberate biothreats. PCAST favors maximal coordination between biodefense efforts directed at deliberate and naturally-occurring threats.

II. Organization of the Government's Efforts

The complexity of the effort necessary to prepare for and respond to possible attacks and/or naturally occurring disease outbreaks is considerable. Preparation and response draws on resources, policies, and

programs of numerous Federal entities including the Departments of Agriculture, Defense, Justice, State, Homeland Security, and Health and Human Services; the Environmental Protection Agency; and various science-funding agencies. Moreover, it depends on effective coordination among those agencies. Response planning demands substantial preparedness work in advance of a crisis (e.g., pandemic flu planning and medical countermeasure development) as well as work in direct response to a crisis (e.g., 2001 anthrax response, 2009 H1N1 influenza pandemic response, 2014 Ebola response, and ongoing Zika response).

A number of White House studies and directives have addressed these issues—most notably *Defense of United States Agriculture and Food* (2004), Homeland Security Presidential Directive 10 (HSPD-10) *National Policy for Biodefense* (2004), *National Strategy for Pandemic Influenza* (2005), *Medical Countermeasures Against Weapons of Mass Destruction* (2006), and *National Strategy for Countering Biological Threats* (2009)—but all are increasingly out of date, especially in light of ongoing rapid advances in biotechnology. Among them, HSPD-10 endures as the framework for biodefense with the most concrete goals and objectives articulating government biodefense priorities.[10] While HSPD-10 has explicit requirements for periodic review and for updates on progress to be provided to the White House, the last time its implementation was examined was in 2008.[11]

Since 2001, the United States has invested billions of dollars and undertaken substantial work to prepare for and respond to deliberate biological attacks and natural disease outbreaks. While the Nation has much to show for these efforts, PCAST believes that it is necessary to rethink the overall organizational structure for anticipating, preparing for, and responding to biological threats. With respect to planning and preparation, many of the efforts have been distributed among individual departments and Federal agencies—sometimes without optimal coordination, mechanisms to evaluate progress, or adequate focus on and accountability for long-term strategic goals. The Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) is an example of an interagency coordination structure that has addressed the development of medical countermeasures for naturally occurring and human-made biological threats (as well as chemical, radiological, and nuclear threats). But there has been no adequate standing structure for coordination and oversight over the entire biodefense enterprise. PCAST met with White House officials who have responsibilities for biosecurity issues. Practically all of them had to divide their time among many other responsibilities, many of which have a day-to-day urgency that preparing for potential future biological attacks does not.

With respect to infectious disease outbreaks, there have been four unusually threatening, naturally occurring, infectious disease outbreaks in the past decade (SARS, H1N1, Ebola, and Zika). In each case, the President has had to designate a White House official to provide required oversight and coordination of the operational response. For SARS, H1N1, and Zika, the efforts have been led by the Assistant to the President for Homeland Security and Counterterrorism (John Brennan in the first two cases, Lisa Monaco in the third case). In the case of Ebola, the President appointed a full-time White House coordinator (Ron Klain). Notably, Klain has recently written (based on his experience) that "the next President should put a coordinating unit together *before* an outbreak begins."[12]

PCAST concludes that the current organizational structure will not ensure that the United States has the leadership that is necessary to anticipate, prepare for, and respond to the entire evolving landscape of biological threats enabled by the rapid advance of biotechnology. A more robust leadership and process is needed to (1) coordinate and oversee situational awareness of ongoing developments in the life sciences; (2) maintain institutional memory of lessons learned from past crises; (3) devise, articulate, and maintain a national strategy to address the interconnected problems of defense against attack and response to disease outbreaks, especially in light of rapid advances in biotechnology; and (4) hold agencies, including the IC, accountable for progress under this strategy.

PCAST recommends below an appropriate new White House-led interagency mechanism (Recommendation 1). This mechanism would not supplant lower-level existing entities that currently operate to harmonize department and agency activities in various specific aspects of biodefense (such as PHEMCE). Rather, with appropriate dedicated White House staff, the mechanism would facilitate White House leadership and coordination over, and the accountability of, the entire biodefense enterprise.[13]

III. Threat Assessment

In the course of this study, PCAST received briefings from and had conversations with many current and former members of the Intelligence Community. Based on these discussions, PCAST has developed a set of recommendations that we believe would increase the effectiveness of that community in anticipating and preventing biological attack. These recommendations concerning threat assessment are presented in the classified annex to this report.

IV. Biosurveillance

Biosurveillance has long been recognized as a critical component of an overarching biosecurity framework for both natural disease outbreaks and intentional attacks with biological weapons. In 1996, the White House released Presidential Decision Directive NSTC-7, *Addressing the Threat of Emerging Infectious Disease*, which focused on improving disease surveillance, prevention, and response for emerging infectious disease. Following the anthrax attacks in 2001, and with the specter of an H5N1 pandemic influenza outbreak, the White House in 2004 established the President's Bio-Surveillance Program Initiative. Subsequently, the White House has issued numerous directives and strategies to further enhance disease surveillance, detection, diagnosis, and reporting.

In the 2004 HSPD-10 *National Policy for Biodefense*, the White House reinforced the need for a national bioawareness system to permit the recognition of a biological attack at the earliest possible moment. In the 2007 HSPD-21 *Public Health and Medical Preparedness*, the White House formally defined biosurveillance as "the process of active data-gathering with appropriate analysis and interpretation of biosphere data that might relate to disease activity and threats to human or animal health—whether infectious, toxic, metabolic, or otherwise, and regardless of intentional or natural origin—in order to achieve early warning of health threats, early detection of health events, and overall situational awareness of disease activity." This definition has guided PCAST's analysis and recommendations in this report. HSPD-21 directed the U.S. Government to develop a nationwide, robust, and integrated biosurveillance capability, with connections to international disease-surveillance systems, in order to provide early warning and ongoing characterization of disease outbreaks in near-real time.

A central element of the envisioned biosurveillance system was an epidemiologic-surveillance system to monitor human disease activity across populations. That system would identify specific disease incidence and prevalence in heterogeneous populations and environments and would possess sufficient flexibility to tailor analyses to new syndromes and emerging diseases. The 2009 Presidential Policy Directive 2 (PPD-2), *National Strategy for Countering Biological Threats*, called specifically for government biosurveillance to include integration with international health organizations. In 2012 and 2013, the White House released two additional, complementary documents calling for specific biosurveillance actions, *National Strategy for Biosurveillance*[14] and *National Biosurveillance Science and Technology Roadmap*,[15] respectively. The *National Strategy for Biosurveillance* calls for the Federal Government, acting across all levels of government (including state, territorial, tribal, and local) and with private sector partners, to: (1) integrate capabilities, including combining human, animal, and plant health data in what is now termed a "One Health" approach; (2) build capacity, including development and use of point-of-care diagnostics; (3) foster innovation, including new detection and health information exchange approaches; and (4) strengthen partnerships domestically and internationally.

PCAST endorses the overall goals of past White House efforts on biosurveillance, including the more recent emphasis on "One Health." To be successful, national biosurveillance efforts must be well-coordinated by the Federal Government. Biosurveillance efforts at the Federal, state, and local levels should be compiled and examined, with redundant or ineffective efforts proposed for elimination. Gaps in capability should be analyzed and addressed, including analysis of feasibility and resource requirements.

PCAST itself has previously identified some focuses for improving the Nation's biosurveillance capabilities. In its 2014 *Report to the President on Combating Antibiotic Resistance*, PCAST recommended strengthening state and local public health infrastructure for surveillance and response, together with establishing a national capability for pathogen surveillance based on genome analysis.[16] PCAST also estimated costs for the various components of each of these recommended steps.[17] Most of those earlier recommendations are directly relevant to the broad purpose of protection against naturally occurring disease or intentional biological attack, and PCAST reiterates their importance here.

Briefly, the Nation needs a robust national capability for surveillance of human, animal, and plant pathogens that integrates environmental, epidemiological, and clinical information with genomic sequence data and analysis on a routine basis. The goal should be to obtain—through sampling strategies appropriate to different situations and tasks—sufficient genomic, environmental, clinical, and epidemiological data to be able to:

- improve and accelerate the detection of biological pathogens—whether known organisms, new or emerging natural pathogens, or human-made agents—by monitoring relevant cases, including "fevers of unknown origin";

- provide an understanding of the genetic diversity of the pathogen causing the outbreak, which is important for faster initiation of vaccine development;

- provide information about the origin and spread of an outbreak; and

- quickly determine whether and how any given organism has been engineered or modified, and with what plausible consequences.

As noted in PCAST's 2014 report, the capability should include: (1) a national laboratory network for pathogen surveillance, including strong efforts on genomic sequencing of pathogens based on the study of cultured clinical strains, as well as of DNA and RNA extracted directly from clinical samples (using the techniques of metagenomics); (2) a reference collection of genome sequences from diverse pathogen isolates and an appropriately accessible database; (3) development of appropriate computational methods and tools; and (4) surveillance efforts in diverse settings, including the human population and agriculture. Because the clinical relevance of microbial isolates and sequences from a case of disease is sometimes not clear, surveillance programs should consider complementing a microbial sequencing approach with one that examines at the same time the detailed features of the host immune response; genomic technologies enable this latter approach, as well.

PCAST notes that many of these objectives are being undertaken by the Centers for Disease Control and Prevention's (CDC) Advanced Molecular Detection Program (AMD), which Congress first funded in 2014. By March 2016, AMD funds were supporting Next Generation Sequencing (NGS) capacity development in 32 states, among other projects.[18] PCAST supports the continuation and expansion of this program. To maximize its public health benefit, data generated by the program should be made promptly available to the scientific community, without delays for publication. PCAST also recognizes the importance of the National Animal Health Laboratory Network, overseen by the U.S. Department of Agriculture.[19]

In addition to efforts within the United States, there is a need to dramatically strengthen international disease-surveillance efforts[20] to (1) provide early warning about outbreaks of human disease, including through genomic analysis of cases including fevers of unknown origin; (2) bolster public-health capacity of other countries to assess their domestic outbreaks; (3) monitor zoonotic disease outbreaks, as well as important animal reservoirs where important zoonotic infectious disease agents reside, to predict future human disease threats; (4) maintain situational awareness during ongoing epidemics to facilitate response; and (5) fulfill U.S. obligations under the International Health Regulations[21] to assist other countries in developing the capacity to detect and respond to outbreaks of international concern. In addition, efforts should be made to develop programs to address international biosurveillance in agriculture.

Building on the work of the Global Health Security Agenda, the Federal Government should take active steps to ensure that such biosurveillance capabilities are widely available in both the United States and key countries around the globe. Within the array of U.S. Government agencies involved in international disease surveillance, there should be two homes for this effort. The first is within the Global Disease Detection Centers within the CDC's Global Disease Detection (GDD) program; among their other missions, these state-of-the-art regional centers detect and respond to emerging infectious diseases.[22] The second is within the appropriate international facilities of the Department of Defense's (DoD) Global Emerging Infections Surveillance and Response System (GEIS), for example the Naval Medical Research Units, whose mission is to identify infectious disease threats of military and public-health importance, in order to protect the health of the force.[23] Some of the needed biosurveillance capacity can be built within existing laboratories, centers, and international partnerships.[24]

Strengthening the international biosurveillance system will also require addressing various international rules that affect sharing of biological samples and epidemiological and clinical data during outbreak surveillance and response.

VI. Medical Countermeasures

Medical countermeasures (MCMs) are critical aspects of the response to biological agents, whether natural or human-made. Here, we focus on two different kinds of MCMs: (1) measures such as vaccines and immunobiologicals, including antibodies, that provide immune protection against pathogens and (2) therapeutic drugs that kill or inhibit reproduction of pathogenic fungi, bacteria, or viruses (antimicrobials: for bacteria, called antibiotics; for viruses, called antivirals).

No other country has devoted as much government attention and investment to developing and deploying MCMs as the United States. Despite this national effort, the development of MCMs against new biological agents presents considerable challenges. While MCMs against some biological agents exist and are present in the Strategic National Stockpile, an intelligent and capable adversary may increasingly be able to employ biological agents for which MCMs do not currently exist or have not been stockpiled.

The fundamental challenge is that developing MCMs against novel biological agents and producing sufficient quantities of these MCMs currently takes far too long.

In the most favorable case, a proven "recipe" exists for producing a vaccine against a biological agent. An example is the development of vaccines against strains of the influenza virus. Pharmaceutical companies each year produce a seasonal influenza vaccine based on the viral variants that an expert advisory committee to the Food and Drug Administration (FDA) concludes are likely to be circulating in the population during the coming flu season.[25] The U.S. Government conducts significant work to prepare for potentially more severe influenza outbreaks by, for example, stockpiling vaccines against the dangerous strains H5N1 and H7N9, funding basic and applied research, and supporting vaccine and drug development by private biotechnology and pharmaceutical companies. Nonetheless, it is challenging for these efforts, as currently configured, to respond rapidly to surprises and emergencies. Even in the case of the 2009 H1N1 influenza virus—an influenza strain for which considerable response architecture was already in place—the time between the declaration of an urgent need for a vaccine and the availability of the first, limited doses of vaccine was 26 weeks, which was 8 weeks after the start of the second wave of the pandemic in the United States.[26] In less favorable cases, a vaccine developer may have to rely only on analogies to related agents or may have little or no direct precedent on which to draw, further delaying the response.

Despite recent improvements, analysis by U.S. Government agencies confirms that the pace of vaccine development and deployment remains too slow to materially affect the outcome of most plausible attacks.[27]

Developing therapeutics is even more challenging. Such therapeutics are typically "small-molecule drugs," each with its own properties. The drug-development process involves designing a specific cellular assay to test whether a chemical inhibits an important function of the infectious agent; testing hun-

dreds of thousands of chemicals to find a subset with the desired biological activity; modifying these initial hits to improve their potency, efficacy, and safety; studying the molecules in animals; undertaking human clinical trials; filing for regulatory approval; and scaling up manufacturing. All told, the process can take many years—and often more than a decade. While continued traditional drug development against known infectious agents is critical, it is clear that it is not suitable for creating a truly novel drug on a rapid timescale for a novel biological agent.

PCAST has previously prepared several reports with recommendations relevant to improved development of MCMs.

- The 2010 PCAST report *Reengineering the Influenza Vaccine Production Enterprise to Meet the Challenges of Pandemic Influenza* recommended a number of steps that could be taken over the coming decade to shorten the time required to provide influenza vaccine to the entire U.S. population. By moving fully to recombinant technology and optimizing the process, it should be possible to reduce the timeline for vaccine production to about 12 weeks.[28]

- The 2012 PCAST report *Propelling Innovation in Drug Discovery, Development, and Evaluation* examined a number of the issues that have slowed the development of therapeutic drugs, including development of MCMs against emerging diseases.[29] The recommendations in this report included scientific investments in improving the drug discovery process, provision of additional positive economic incentives to increase the pace of private sector drug discovery and development, and changes in the regulatory processes by which drugs are approved for human use.

- The 2014 PCAST report *Combating Antibiotic Resistance* addressed ways to increase the pace of development of new antibiotics.[30] This report recommended a number of measures, including investment in new scientific approaches to antibiotic development, the establishment of a robust national infrastructure to support clinical trials with new antibiotics, increased economic incentives for developing urgently needed antibiotics, and the development of new regulatory pathways to evaluate antibiotics.

In addition to these PCAST efforts, a 2010 review of the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) called for significant new investment in new public-private partnerships with pharmaceutical companies, in FDA regulatory science, and other initiatives.[31] Some of these new investments have been put into place and have increased national response capabilities, but PCAST finds that further investment is needed, as discussed below.

Going forward, it will be critical to focus increasingly on developing and refining *platform technologies*—that is, well-established, general approaches that can be reliably and rapidly applied to new pathogens by "dropping in" specific information about the organism. Just as rapid advances in biotechnology have increased the risk of misuse by bad actors, they have expanded the tools available to protect the public.

The most straightforward example of a technology platform is the current capability for developing influenza vaccines, whereby a virus can be rapidly sequenced, and specific protein antigens can be designed directly from the genetic sequence of a viral strain, produced by recombinant DNA technologies

in existing scientific and manufacturing facilities, and formulated into safe and effective vaccines. In the case of influenza vaccines, the main focus should be on shortening the time from initial detection to vaccine release to the public.

It is critical, however, that capabilities to rapidly produce products that confer immune-based protection be: (1) broadened to include many more classes of biological agents, including those most likely to require countermeasures in the medium term; and (2) extended to include a wide range of existing and novel technological approaches. Examples of novel technological approaches include developing "universal" vaccines that provide protection against a wide range of variant strains of a pathogen, using antigens expressed by RNA and nucleic acid analogs to stimulate protective immunity against specific protein targets on a pathogen, and conferring short-term "passive" immunity via engineered antibodies and immune cells to provide rapid protection when natural immune responses are too slow or insufficient.

The Federal Government should set the goal that, within 10 years, not more than 6 months will be required to design, develop, manufacture, clinically test, and license vaccines and antibodies against many types of pathogens. This goal will require substantial progress in science, technology, and production. While recognizing that this goal is ambitious, PCAST believes that achieving it is an important objective for both response and deterrence. For infectious organisms that might be reasonably anticipated to lead to sudden epidemic spread that could threaten the U.S. population or U.S. interests overseas, the United States should have pre-tested vaccine candidates through safety and immunogenicity studies in humans. A robust start for these initiatives, based on established technologies, is likely to cost at least $250 million per year. Substantial additional funding will be needed to test and develop novel technology platforms with the potential for greater speed and reliability, such as new kinds of engineered antibodies and RNA-based vaccine delivery.

Developing platform technologies to create therapeutics is even more challenging. As noted above, the development of small-molecule drugs is tedious, slow, and idiosyncratic. With a view toward the longer term, the Nation should launch now active research programs to develop entirely new kinds of technology that can be reliably and rapidly "programmed" in a general manner to inhibit a pathogen of concern. (This example illustrates that the same emerging biotechnologies that may pose risks also have the potential to provide the tools to develop new types of countermeasures.[32]) While developing such "over-the-horizon" approaches represents an ambitious challenge, their potential generality makes them compelling goals for biodefense against both natural and engineered pathogens.

Scientific advances will need to be matched by ongoing advances in "regulatory science," so that there are rapid paths for effective review and approval of new MCMs produced by platform technologies. The Food and Drug Administration has taken an important initial step with its MCM Initiative,[33] whereby a manufacturing process for a new vaccine that is near-identical to a previous manufacturing process can be rapidly approved.

VII. Need for a Public Health Emergency Response Fund

One common element in biodefense preparedness against deliberately deployed human-made biological agents and naturally-occurring infectious-disease outbreaks is the need to respond rapidly. Despite the

reorganization of the Federal Government in the period following the September 11th terrorist attacks and the linkage of public health and preparedness, the Nation still lacks a sustainable, reliable way rapidly to fund a response to epidemic emergencies.

Substantial funding is typically appropriated for epidemic response, but often only well into the course of the outbreak. Eventually, Congress appropriated $7.7 billion for 2009 H1N1 influenza and $5.5 billion for Ebola. But the delays can be long and can impede local and Federal action. The Obama Administration first requested emergency supplemental funding for the Zika response from Congress in February 2016, but Congress only appropriated the funds necessary to respond at the end of September, as part of the Continuing Resolution needed to prevent the U.S. Government from shutting down.[34]

Clearly, the Nation needs a new approach to enable rapid public health response to disease-outbreak emergencies that does not require starting from scratch in each case. The Disaster Relief Fund (DRF) for the Federal Emergency Management Agency (FEMA) provides a good model.

The Stafford Emergency Relief and Disaster Assistance Act authorizes the President to issue declarations for incidents ranging from destructive, large-scale disasters to more routine, less damaging events. Declarations trigger Federal assistance in the forms of various response and recovery programs to state, local, and tribal governments. FEMA's Disaster Relief Fund (DRF) is the primary funding source for disaster response and recovery. Funds from the DRF are used to pay for ongoing recovery projects from disasters occurring in previous fiscal years, to meet current emergency requirements, and as a reserve to pay for unanticipated incidents. The DRF is funded annually and is a "no-year" account, meaning that unused funds from the previous fiscal year (if available) are carried over to the next fiscal year. In general, when the balance of the DRF becomes low, Congress provides additional funding through both annual and supplemental appropriations to replenish the account.

The Federal Government provides significant funding to state and local governments each year for emergency and major disasters. Even in years having relatively few major disasters, it is not uncommon for the Federal Government to annually appropriate between $2 billion and $6 billion to help pay for recovery projects.[35] FEMA provides a monthly report on the DRF. As of May 31, 2016, the total balance was $5.8 billion.[36]

In PCAST's judgment, a Public Health Emergency Response Fund is needed and should have a floor of $2 billion.[37] This would allow mobilization of a large-scale Federal response to an acute infectious disease event, including public health interventions by the CDC, emergency response capabilities overseen by the HHS Assistant Secretary for Preparedness and Response (ASPR) or the Department of Agriculture, scientific research by the Biomedical Advanced Research and Development Authority (BARDA) and the National Institutes of Health (NIH),[38] regulatory activities by the Food and Drug Administration, and global response by the Department of Defense and the U.S. Agency for International Development. While this floor level is unlikely to fund an entire response to an infectious disease emergency, it would allow a rapid start of the response. Such a fund should, analogously to FEMA's Disaster Relief Fund, consist of funds that carry over across years and can be replenished by routine and emergency appropriations. It is important to emphasize that these funds are for *emergency* response. They would not take the place of ongoing—and, as called for in this report, increased—funding for scientific and medical research and development for biothreat detection and countermeasures.

The availability of funds under the Public Health Emergency Response Fund should be contingent upon the express authorization of the President or the joint declaration of the Secretaries of HHS and DHS, to prevent drawing down the fund for routine operations.

VIII. PCAST's Recommendations

PCAST divides its recommendations into actions aimed at near-, medium-, and long-term objectives. In all cases, work should begin now to ensure that the various measures will be in place by the time the Nation needs them.

In addition to the recommendations below, PCAST has made recommendations pertaining to threat awareness in the classified annex to this letter report.

Near-Term Recommendations

RECOMMENDATION 1. The President should create a new interagency entity charged with planning, coordination, and oversight of national biodefense activities across the Intelligence Community and the Departments of Defense (DoD), Homeland Security (DHS), Health and Human Services (HHS), and Agriculture. The entity should be co-led by the Assistant to the President for Homeland Security and Counterterrorism, the Assistant to the President for Science and Technology, and the Chair of the Domestic Policy Council. The entity should have senior-level representation from all of the indicated agencies, including from within HHS, the Centers for Disease Control and Prevention (CDC), the Biomedical Advanced Research Projects Administration (BARDA), and the National Institutes of Health (NIH). The entity should be charged with:

a. Developing, within six months, a national biodefense strategy—including short-, medium-, and long-term components—to anticipate, prepare for, and respond to all issues that arise as biotechnology continues to advance;
b. Preparing thereafter annual public updates (with a classified annex) to the President that describe progress toward achieving the strategy and update the strategy as necessary;
c. Overseeing execution of the national biodefense strategy and holding agencies accountable for progress;
d. Guiding requirements and taskings of the Intelligence Community (IC) and holding the IC accountable for adequate collection and analysis of current and future biological threats to the United States and for other activities of the IC that might mitigate these threats; and
e. Ensuring coordination of efforts against new and emerging infectious diseases, antibiotic resistance, and intentional biothreats—including through the development of biosurveillance systems and the new medical-countermeasures.

RECOMMENDATION 2. The President should request that Congress establish a Public Health Emergency Response Fund of at least $2 billion. The fund would support mobilization of rapid Federal responses to serious, rapidly emerging natural or intentional infectious-disease events, including public health interventions (by CDC), scientific research (by BARDA and NIH), regulatory activities (by FDA), and global response (by DoD, CDC, and the U.S. Agency for International Development).

a. The Emergency Response Fund should, analogously to Federal Emergency Management Agency's (FEMA) Disaster Relief Fund, consist of funds that carry over across years and can be replenished by routine and emergency appropriations.
b. Access to funds should be contingent upon the express authorization of the President or the joint agreement of the secretaries of HHS and DHS.

Medium-Term Recommendations

RECOMMENDATION 3. As part of its national biodefense strategy, the White House should act to substantially strengthen Federal, state and local public health infrastructure for disease surveillance, as well as promote a stronger international system of disease surveillance. The surveillance capacity should include:

a. Laboratory networks in the United States and abroad with the capability for early detection and rapid monitoring of both human-made and natural emerging infectious agents in public health, agricultural, and wildlife settings.
b. The ability to routinely and rapidly employ advanced biological tools—including rapid diagnostic tests, large-scale genome sequencing and analysis, and new approaches to monitor the host immune system—for systematic evaluation of possible cases, including those presenting simply as "fevers of unknown origin" or "severe acute respiratory infections."

RECOMMENDATION 4. The White House should set the following ambitious ten-year goals with appropriate funding (of at least $250 million per year) for medical countermeasures preparedness. The Secretary of Health and Human Services and the Secretary of Defense should report annually to the White House about progress and impediments to reaching these goals:

a. For infectious organisms for which there exist effective approaches to creating vaccines, the United States should have the ability to accomplish, within a six-month period, the complete development, manufacture, clinical testing, and licensure of a vaccine. For pandemic influenza, the goal should be 3 to 4 months to vaccine deployment.
b. For infectious organisms that might be reasonably anticipated to lead to sudden epidemic spread that could threaten the U.S. population or U.S. interests overseas, the United States should have pre-tested vaccine candidates through safety and immunogenicity studies.

RECOMMENDATION 5. The United States should set as a national priority the identification and development of additional classes of broad-spectrum antibiotic and antiviral drugs. Building on progress already made pursuant to the President's Executive Order on Combating Antibiotic Resistant Bacteria, and the corresponding National Strategy and National Action Plan, the United States should fully implement PCAST's recommendations from its 2014 report *Combating Antibiotic Resistance* related to antibiotic development, as well as the analogous strategies for antiviral development:

a. Expand fundamental research relevant to developing antibiotics for human healthcare and other approaches to treating bacterial infections
b. Establish a robust national infrastructure to support clinical trials of new antibiotics
c. Strengthen and expand the dedicated existing regulatory efforts for MCMs and develop new regulatory pathways to evaluate urgently needed antibiotics; and
d. Significantly increase economic incentives for developing urgently needed antibiotics.

The United States should also support the development of platform technologies for rapid production of therapeutics and preventative medicines (examples include specific immunobiologicals such as engineered antibodies, emerging nanomedicines that elicit specific and desired immune responses, and chemically modified nucleic acids with peptide adjuvants) to neutralize and block infectious organisms of natural origin or agents of biological attack.

Long-Term Recommendation

RECOMMENDATION 6. The Departments of Defense, Health and Human Services, and other government agencies should promote vigorous basic and applied research efforts in academic, industrial and government laboratories with the goal of developing new types of countermeasures. These countermeasures should be rapidly and easily modified to target, safely and effectively, specific human-made and naturally-occurring pathogens. The delivery of approved countermeasures should be within days after the an agent's detection and characterization.

HHS and DoD should receive new funding of $75M per year for four years to lay the foundation of this initiative. Funding for relevant agencies within HHS and DoD should then ramp up to a steady-state of at least $250M per year.

Examples of such rapid countermeasures might include approaches that: target infectious agents based on their genomes; employ optimized and tested vectors to deliver other nucleic acid-based anti-pathogen approaches to a wide range of specific human cell types; activate the immune system against classes of pathogens; target host pathways required by pathogens; rely on antigens expressed by RNA and nucleic acid analogs to stimulate protective immunity against specific pathogen epitopes; or provide immunity via antibodies and immune cells engineered to recognize pathogen-specific epitopes.

Sincerely,

The President's Council of Advisors on Science and Technology

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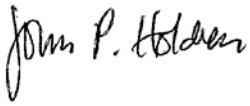
John P. Holdren



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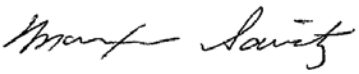

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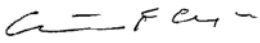

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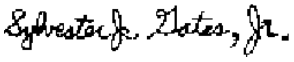

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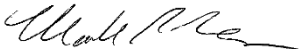

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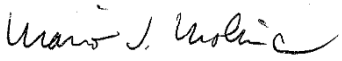

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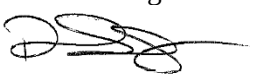

[1] See: The National Academies, "Globalization, Biosecurity, and the Future of the Life Sciences," April 2006 nationalacademies.org/hmd/reports/2006/globalization-biosecurity-and-the-future-of-the-life-sciences.aspx; Carlson, R., "Causes and consequences of bioeconomic proliferation: Implications for U.S. physical and economic security," Department of Homeland Security, 2012; and Carlson, R., *Biology is Technology: The Promise, Peril and New Business of Engineering Life*, Harvard University Press, 2011.

[2] Carlson, R., "The pace and proliferation of biological technologies," *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science*, 2003 1(3) p. 203-214; Carlson, R., "Estimating the biotech sector's contribution to the U.S. economy," *Nature Biotechnology*, 2016 Mar, 34(3) p. 247-255.

[3] For example, in 2015 a World Health Organization (WHO) Scientific Working Group on Synthetic Biology and Variola Virus and Smallpox determined that a "skilled laboratory technician or undergraduate student with experience of working with viruses" would be able to generate variola virus from the widely available genomic sequence in "as little as three months". Importantly, this Working Group concluded that "there will always be the potential to recreate variola virus and therefore the risk of smallpox happening again can never be eradicated." The Independent Advisory Group on Public Health Implications of Synthetic Biology Technology Related to Smallpox, WHO, 2015.

[4] Sell, T.K., Watson, M., "Federal Agency Biodefense Funding, FY2013-FY2014," *Biosecurity and Bioterrorism : Biodefense Strategy, Practice, and Science,* 2013 Sep, 11(3) p. 196–216.

[5] See: www.selectagents.gov/SelectAgentsandToxins.html.

[6] See: www.phe.gov/s3/dualuse/Pages/default.aspx and www.phe.gov/s3/dualuse/Pages/InstitutionalOversight.aspx. Note that the institutional policy not only covers all government-funded research but it also covers non-government-funded research performed at institutions that receive any U.S. Government funding for life sciences research.

[7] Clustered regularly interspaced short palindromic repeats (CRISPR).

[8] Jackson, R.J., Ramsay, A.J., Christensen, C.D., Beaton S., Beaton, S., Hall, D.F., Ramshaw, I.A., "Expression of mouse interleukin-4 by a recombinant ectromelia virus suppresses cytolytic lymphocyte responses and overcomes genetic resistance to mousepox," *Journal of Virology*, 2001 Feb, 75(3), p. 1205-1210.

[9] See, for example: Damon, I.K., Damaso, C.R., McFadden, G., "Are We There Yet? The Smallpox Research Agenda Using Variola Virus," *PLoS Pathogens*, 2014 May, 10(5), and Duraffour, S., Lorenzo, M.M., Zoller, G., Topalis, D., Grosenbach, D., Hruby, D.E., Andrei, G., Blasco, R., Meyer, H., Snoeck, R., "ST-246 is a key antiviral to inhibit the viral F13L phospholipase, one of the essential protiens for orthopoxvirus wrapping," *Journal of Antimicrobial Chemotherapy*, 2015 May, 70(5) p. 1367-1380.

[10] The White House, National Security Presidential Directive NSPD-33/Homeland Security Presidential Directive HSPD-10, "National Policy for Biodefense (U)," April 21, 2004 (document classified). The White House released the white paper "Biodefense for the 21st Century" to accompany HSPD-10. See: 2001-2009.state.gov/t/isn/rls/fs/32000.htm.

[11] Joint Homeland Security Council and National Security Council Deputies Committee Meeting Discussion Paper on Bio Preparedness (U), March 3, 2008, p. 2 (document classified).

[12] See: Ronald Klain, "Confronting the Pandemic Threat," *Democracy Journal* (Spring 2016), No. 40, democracyjournal.org/magazine/40/confronting-the-pandemic-threat.

[13] PCAST recognizes the importance of agricultural biodefense and includes the Department of Agriculture among those agencies that play important biodefense roles. However, this report focuses on selected topics in the defense of human health, and PCAST was unable to pursue agricultural issues in detail.

[14] See: National Strategy for Biosurveillance, July 2012. www.whitehouse.gov/sites/default/files/National_Strategy_for_Biosurveillance_July_2012.pdf.

[15] See: National Biosurveillance Science and Technology Roadmap, June 2013. www.whitehouse.gov/sites/default/files/microsites/ostp/biosurveillance_roadmap_2013.pdf.

[16] See: PCAST report *Combating Antibiotic Resistance*, released September 2014. www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast_amr_jan2015.pdf.

[17] For a total of $190M per year.

[18] See: www.cdc.gov/amd.

[19] See: www.nahln.org.

[20] See: Center for Biosecurity of UPMC, "International Disease Surveillance: United States Government Goals and Paths Forward," June 2010. www.dtic.mil/dtic/tr/fulltext/u2/a528990.pdf.

[21] See: www.who.int/topics/international_health_regulations/en.

[22] See: www.cdc.gov/globalhealth/healthprotection/gdd/where-we-work.html.

[23] See: health.mil/Military-Health-Topics/Health-Readiness/Armed-Forces-Health-Surveillance-Branch/Global-Emerging-Infections-Surveillance-and-Response/GEIS-Partners.
[24] For example, GEIS is already establishing a Next Generation Sequencing (NGS) and Bioinformatics Consortium, which will bring GEIS partners together to achieve a harmonized approach to NGS and bioinformatics. It is important to have NGS capability in the country where samples are being collected to save the time required for transportation back to the United States, and because in many cases partner countries will not allow samples or isolates to be transferred to the United States. In such cases there must be at least forward NGS capacity, with the ability to send data back to the United States for bioinformatics. This Consortium initiative is estimated to require an additional $5 million in funding annually to ensure its success.
[25] See: Centers for Disease Control and Prevention, "Selecting Viruses for the Seasonal Infuenza Vaccine," www.cdc.gov/flu/about/season/vaccine-selection.htm.
[26] See: PCAST report *Reengineering the Influenza Vaccine Production Enterprise to Meet the Challenges of Pandemic Influenza*, released August 2010. www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST-Influenza-Vaccinology-Report.pdf.
[27] Defense Advanced Research Projects Agency, Biological Technologies Office, briefing to PCAST working group, November 17, 2015.
[28] See: PCAST report *Reengineering the Influenza Vaccine Production Enterprise to Meet the Challenges of Pandemic Influenza*, released August 2010. www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST-Influenza-Vaccinology-Report.pdf.
[29] See: PCAST report *Propelling Innovation in Drug Discovery, Development, and Evaluation*, released September 2012. www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-fda-final.pdf.
[30] See: PCAST report *Combating Antibiotic Resistance*, released September 2014. www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast_amr_jan2015.pdf.
[31] U.S. Department of Health and Human Services, Assistant Secretary for Preparedness and Response, "The Public Health Emergency Medical Countermeasures Enterprise Review: Transforming the Enterprise to Meet Long-Range National Needs," August 2010. www.medicalcountermeasures.gov/media/1138/mcmreviewfinalcover-508.pdf.
[32] This dilemma helps explain the attention given by the U.S. Government to so-called "Dual Use Research of Concern," or research motivated for legitimate purposes that could also be misused for harm.
[33] See: www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/default.htm.
[34] Susan B. Epstein and Sarah A. Lister, Congressional Research Service, *Zika Response Funding: Request and Congressional Action*, September 30, 2016.
[35] Lindsay, B.R., "FEMA's Disaster Relief Fund: Overview and Selected Issues," CRS Report R43537, Congressional Research Service, May 7, 2014.
[36] See: www.fema.gov/media-library/assets/documents/31789.
[37] There is a Public Health Emergency Fund that was authorized in 1983 and placed at the disposal of HHS, but it has not been replenished since 1993, despite repeated national level infectious disease emergencies. In addition to being moribund, it is specific to HHS and therefore more narrow than what we propose here. There is also a Public Health and Social Services Emergency Fund. This fund is used by the Assistant Secretary for Preparedness and Response to fund some preparedness activities, but it has not been used as a contingency or reserve fund.
[38] For example, NIH has the authority to spend research funds on an emergency basis via special solicitations for emergency research, or plusing up existing solicitations with emergency funds, or directing funds to its intramural laboratories, or by rapidly signing contracts (for vaccine trials, development, etc.).