THE APOLLO PROGRAM FOR BIODEFENSE

WINNING THE RACE AGAINST BIOLOGICAL THREATS

A RECOMMENDATION BY THE
BIPARTISAN COMMISSION ON BIODEFENSE

January 2021

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EXECUTIVE SUMMARY

The COVID-19 pandemic is a stark wake-up call for the United States to take biological threats seriously. The virus has taken the lives of more than 400,000 Americans and cost our economy trillions of dollars in just a year. The risks of future pandemics are increasing as technological progress eases barriers to modifying pathogens, raising the specter of novel biological agents causing diseases much worse than humanity has ever faced. Meanwhile, U.S. vulnerabilities to biological attacks have never been clearer to our adversaries.

However, there is a path forward. *The Apollo Program for Biodefense* would provide the United States the opportunity to mobilize the nation and lead the world to meet these challenges: a world where we detect and continually trace any new pathogen from the source; where we can distribute rapid point-of-person tests to every household in the country within days of that detection; where effective treatments are already in-hand; where vaccine development and rollout occur in weeks rather than years; and where pandemics will never again threaten the lives and livelihoods of Americans and people around the world.

With clarity of purpose, this world is possible within the next decade. While ambitious, consider that in 1960, it was hard to imagine landing a person on the moon. Yet in 1961, President John F. Kennedy committed the United States to achieve that goal "before the decade is out." Nine years later, with 161 days to spare, the United States accomplished the Apollo 11 mission and made human history. The United States can, and must, similarly put an end to pandemics before this decade is out.

The existential threat that the United States faces today from pandemics is one of the most pressing challenges of our time; and ending pandemics is more achievable today than landing on the moon was in 1961. Advances in the life sciences, accelerated by the pandemic, have brought technology to an inflection point where ending pandemics is within our grasp, but only if we commit ourselves.

Even the most ambitious program (about $10 billion annually) would be a small fraction of the current cost of the COVID-19 pandemic and an investment in our health, economy, and national security. Along with the needed structural, policy, and leadership changes detailed in the Commission's 2015 *National Blueprint for Biodefense, The Apollo Program for Biodefense* would effectively end the era of pandemic threats by 2030.

RECOMMENDATIONS

To achieve *The Apollo Program for Biodefense*:

- **Implement the National Blueprint for Biodefense –** The Administration and Congress should fully implement the recommendations in the Commission's 2015 report, *A National Blueprint for Biodefense: Leadership and Major Reform Needed to Optimize Efforts*, to enable the Nation to defend against intentionally introduced, accidentally released, and naturally occurring biological events.
- **Produce a National Biodefense Science and Technology Strategy –** The Administration should produce and implement a National Biodefense Science and Technology annex to the National Biodefense Strategy to achieve *The Apollo Program for Biodefense* before the decade is out.
- **Produce a Cross-Cutting Budget –** The Administration should include funds for *The Apollo Program for Biodefense* as part of a unified biodefense budget and in the President's Budget Request.
- **Appropriate Multi-Year Funding –** Congress should appropriate long-term multi-year funding to implement *The Apollo Program for Biodefense*.

The Apollo Program for Biodefense is an ambitious goal-directed program to develop and deploy the technologies needed to defend against all biological threats, empower public health, and prevent pandemics, no matter what the source.

TECHNOLOGY PRIORITIES

With input from over 125 experts, the Bipartisan Commission on Biodefense has identified the following core technology priorities for The Apollo Program for Biodefense:

- Vaccine Candidates for Prototype Pathogens
- Multi-Pathogen Therapeutic Drugs in Advance of Outbreaks
- Flexible and Scalable Manufacturing of Pharmaceuticals
- Needle-Free Methods of Drug and Vaccine Administration
- Ubiquitous Sequencing
- Minimally- and Non-Invasive Infection Detection
- Massively Multiplexed Detection Capabilities
- Point-of-Person Diagnostics
- Digital Pathogen Surveillance
- A National Public Health Data System
- An Integrated National Pathogen Surveillance and Forecasting Center
- Next-Generation Personal Protective Equipment
- Pathogen Transmission Suppression in the Built Environment
- Comprehensive Laboratory Biosafety
- Technologies to Deter and Prevent Bad Actors

INTRODUCTION

COVID-19: YET ANOTHER WAKE-UP CALL

The COVID-19 pandemic has killed over two million people around the world to date,[1] ravaged health systems,[2] and destroyed economies.[3] It has also exposed destabilizing divisions within[4] and among countries[5] and revealed domestic and global weaknesses in biodefense. For these reasons and more, we must do everything in our power to ensure that the devastation caused by a pandemic never happens again.

Catastrophic infectious disease outbreaks have occurred regularly throughout history[6] and experts agree that they will occur with even greater frequency in the future.[7] The COVID-19 pandemic has resulted in more American deaths than World War I, the Korean War, the Vietnam War, the Gulf War, the War in Afghanistan, and the Iraq War altogether.[8] COVID-19 will likely cost the United States over $16 trillion.[9] We spend billions preparing for other threats to American lives, which may or may not occur. Spending on biological risk reduction would be far less than the significant cost of continuing to let future pandemics devastate the United States again.

The Commission's baseline 2015 report, *A National Blueprint for Biodefense: Leadership and Major Reform Needed to Optimize Efforts*, warned that the United States was inadequately prepared for biological threats.[10] Five years later, the U.S. experience with COVID-19 continues to validate our original findings. In addition to revealing U.S. vulnerability to naturally occurring diseases, the effects of the pandemic exposed national vulnerabilities and weaknesses in the Nation's ability to respond to biological events.

We acknowledge that technology is only one part of an ambitious program to end pandemics. We described other crucial elements in the *Blueprint for Biodefense*,[9] including strengthened public health systems; integrated and cooperative federal, state, local, tribal, and territorial relationships; effective public-private partnerships; multi-year funding; agency responsibilities clarified in advance of crises; and reduced regulatory bottlenecks.

Yet technology holds great promise. Within weeks of recognizing the existence of a novel coronavirus, scientists mapped its entire genome and developed and produced vaccines

faster than ever before. We accomplished these previously unimaginable feats because of forward-looking programs, ranging from the Human Genome Project to the advanced research programs that led to many of the vaccines currently in clinical trials.

We must stop fighting the last war. We need new strategies and defenses. Through *The Apollo Program for Biodefense*, we can make invisible biological enemies visible and take pandemic threats off the table by the end of the decade.

THE FUTURE LANDSCAPE OF BIOLOGICAL THREATS

COVID-19 will not be the last biological threat we face. The world can no longer consider a devastating biological event like the COVID-19 pandemic to be a rare, once-in-a-century, occurrence. Future naturally occurring biological threats will likely be more deadly and transmissible than SARS-CoV-2. Interconnected air travel networks, food production methods, climate and land-use changes, and increasing urbanization and human-wildlife interfaces contribute to the increasing risk and frequency of naturally occurring infectious diseases with pandemic potential.[11,12] Animal diseases that spill over to humans are increasing in frequency and represent approximately 75% of the world's emerging infectious diseases.[13]

The world can no longer consider a devastating biological event like the COVID-19 pandemic to be a rare, once-in-a-century, occurrence.

The 1918 influenza pandemic may have killed over 50 million people.[14] The next biological threat could be far more devastating. Other diseases like smallpox are more contagious than COVID-19[15] and 30–100 times more lethal.[16] Advances in biotechnology have also made it easier to obtain or modify these pathogens,[17] creating the possibility of pandemics emerging from deliberate attacks or laboratory accidents. COVID-19 will also not be the worst biological threat we will face.

Biological threats jeopardize national security. COVID-19 put a U.S. aircraft carrier out of commission for two months,[18] sent the Joint Chiefs of Staff into quarantine,[19] breached the White House, and hospitalized the Commander-in-Chief.[20] The pandemic brightly illuminates how our national security vulnerabilities increase and our deterrence capabilities falter during biological events. Rogue states wishing to challenge American primacy could take advantage of the Nation's disease-stricken state to test our country's ability and willingness to maintain global order.

The visibility of our vulnerabilities increases the likelihood of biological attacks in the future,[21] as do the continued breakthroughs in biotechnology that lower the technical barriers to producing biological weapons. The likelihood of an accidental release of pathogens from laboratories may also increase as nations build more high containment laboratories and conduct more biomedical research.[22,23]

We must bolster our defenses against these threats. The cost, while considerable, is manageable.

THE PATH FORWARD: THE APOLLO PROGRAM FOR BIODEFENSE

The path forward must include solutions rooted in public policy, science, technology, and innovation. Operation Warp Speed (a public-private partnership created to facilitate and accelerate the development, manufacturing, and distribution of COVID-19 vaccines, therapeutics, and diagnostics)[24] demonstrates that we can achieve ambitious technological goals with unprecedented speed during a pandemic. However, the Nation needs a broader, preemptive, and sustained effort to better protect against future biological threats. To succeed, we need to think big, on the scale of the lunar Apollo Program that brought humanity to the moon.[25]

The Nation has a history of taking on grand technological challenges in times of need, such as the Manhattan Project (to split the atom), the Interstate Highway System (to create a network of highways to connect the entire nation),[26] and the Global Positioning System (to enable geolocation anywhere on or near the earth).[27] Those efforts share similarities in scale, ambition, necessity, and difficulty of execution, and demonstrate our ability to engage in systematic, large-scale execution and funding of a goal-oriented and coordinated effort to achieve the technological capabilities the Nation needs.

These projects also resulted in critical ancillary products. The lunar Apollo Program, for example, produced a variety of revolutionary spinoff technologies, including solar panels and pacemakers.[28] *The Apollo Program for Biodefense* could produce breakthroughs in areas as varied as precision medicine, sustainable food production, manufacturing at scale, and even space travel (just as space travel led to innovations in health and medicine). These advances could also accelerate the growth, and improve the strength, of the U.S. bioeconomy,[29] which is already larger than the U.S. semiconductor industry.[30] Such a significant propellant to the bioeconomy could create additional jobs and economic growth for the United States while simultaneously helping to stave off foreign economic competitors. It is no coincidence that Russia called its new COVID-19 vaccine Sputnik V after the Soviet era satellite that triggered the space race in 1957.[31]

Only sustained bipartisan support and U.S. leadership will enable the Nation to develop the new technologies needed to prevent biological events. Only the public sector can provide the strategic direction, coordination, and funding needed to make the Apollo

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Program happen. But only the private sector can produce the tools and innovations at the scale needed. Thus, the public and private sectors must work together, with the private sector providing research, insight, manufacturing, and efficiency, and the government allowing accelerated approvals and liability protection when appropriate.

International engagement in grand challenges can be an effective diplomatic tool. The United States has found this to be the case with grand challenges, such as the Human Genome Project.[32] Other countries, notably China and Russia, have used technological innovation during the COVID-19 pandemic to increase their international influence.[33,34,35] Involving other countries in a U.S.-led *Apollo Program for Biodefense*, with the goal of making the world safe from pandemics, will also strengthen our international relationships.

CALL TO ACTION

The expanding biological threat landscape includes the potential for catastrophe. We are at a turning point. If we harness the American know-how and can-do attitude, we can achieve resilience to biological threats. Alternatively, if we fail to move forward, we could remain permanently vulnerable to biological threats.

Previous national grand challenges focused on singular goals, such as landing on the moon or harnessing the power of the atom. *The Apollo Program for Biodefense* would not be limited to a singular goal (e.g., a moonshot), but would achieve multiple groundbreaking technological advances with a single, overarching goal—to gain technological superiority over biological threats. We envision a time when people will look back and wonder how we ever let infectious diseases wreak havoc on society and how we tolerated seasonal influenza, let alone COVID-19 and biological weapons.

Now is the time to advance technological solutions to the problems COVID-19 has revealed with horrific clarity. Operation Warp Speed took some first steps, making the most of new technologies, converging fields of study, and introducing multiple promising innovations on the cusp of realization. When the original Apollo Project began, the know-how needed to get to the moon did not exist. **Today we possess the scientific capabilities to achieve the mission of *The Apollo Program for Biodefense*.** Now we must bring them together to make this promise real.

RECOMMENDATIONS

The need to control COVID-19 created momentum to produce many technologies that we previously lacked the will and resources to pursue before the pandemic began. We need to build on that progress and push for technological advances to protect us from the next biological threat. These can come to fruition by the end of this decade, but only with leadership, resources, and interest that go beyond technical constraints and the usual crisis-neglect cycle timelines.

As with the effort to eradicate smallpox, we have the opportunity to do what once may have seemed impossible. We should not accept biological threats as inevitable when *The Apollo Program for Biodefense* can prevent outbreaks from spreading worldwide or occurring in the first place. While outbreaks may be inevitable, pandemics are not. The following ambitious recommendations have the potential to reshape our world if adopted and implemented fully.

The Administration and Congress should fully implement the recommendations in the Commission's 2015 *National Blueprint for Biodefense*. Recommendations 27–33 from the Blueprint are of relevance to *The Apollo Program for Biodefense*. These recommendations address the need to prioritize innovation over incrementalism (Rec. 27), incentivize the medical countermeasures enterprise (Rec. 28), incentivize the development of rapid point-of-care diagnostics (Rec. 30), and develop a modern environmental detection system (Rec. 31). The implementation of the *Blueprint*, in concert with *The Apollo Program for Biodefense*, would enable the Nation to defend against intentionally introduced, accidentally released, and naturally occurring biological threats.

The Administration should develop and implement a National Biodefense Science and Technology Strategy. The Administration should commence with *The Apollo Program for Biodefense* immediately to create the capabilities needed to defend against all biological threats and prevent pandemics before the decade is

out. Developing a National Biodefense Science and Technology Strategy is a crucial first step. White House leadership of this strategy will be necessary to coordinate interagency efforts across the federal government and harmonize contributions from academia and the private sector. To achieve this whole-of-America approach, the Administration should produce a National Biodefense Science and Technology Strategy with a focus on the technology priorities of *The Apollo Program for Biodefense* (see Appendix A). The Administration should provide this strategy in an annex to the National Biodefense Strategy.

A dedicated Deputy Assistant to the President within the National Security Council should lead the implementation of *The Apollo Program for Biodefense*, and the Director of the Office of Science and Technology Policy should have an integral role in the prioritization and development of the required technology capabilities.

In accordance with Recommendation 4 of *A National Blueprint for Biodefense* to unify biodefense budgeting, **Congress should require the Office of Management and Budget to provide a cross-cutting budget for The Apollo Program for Biodefense as a component of a unified biodefense budget.** A unified approach to budgeting is a vital part of any strategic interagency effort and would ensure that activities across the government are coordinated, complementary, and effective.

Congress should require the Office of Management and Budget to provide a cross-cutting budget for The Apollo Program for Biodefense as a component of a unified biodefense budget.

Congress should provide multi-year appropriations to implement *The Apollo Program for Biodefense*. This funding should be commensurate with the goals of the program and aligned with the magnitude of the threat, as opposed to historical appropriations. Funding should also include multi-year budget authority to allow agencies to procure systems and medical countermeasures that take years to develop and produce. Multi-year funding breaks the cycle of panic and neglect by providing a predictable and more stable time horizon for planning and investment in research, development, and production. This helps the government attract the best talent and private sector capital.

CONCLUSION

The Apollo Program for Biodefense **is relatively expensive, but the cost of inaction is remarkably higher. COVID-19 demonstrates all too painfully the cost of a pandemic to our economy, our standing in the world, and most importantly, the lives and livelihoods of our citizens. A realistic, achievable effort to ensure that such a biological crisis never happens again is clearly worth the investment.**

APPENDIX A: TECHNOLOGY PRIORITIES

The following technologies and capabilities should be top priorities for *The Apollo Program for Biodefense*. This list does not include all technologies that could have a substantial impact but contains those deemed especially promising.

- Vaccine Candidates for Prototype Pathogens
- Multi-Pathogen Therapeutic Drugs in Advance of Outbreaks
- Flexible and Scalable Manufacturing of Pharmaceuticals
- Needle-Free Methods of Drug and Vaccine Administration
- Ubiquitous Sequencing
- Minimally- and Non-Invasive Infection Detection
- Massively Multiplexed Detection Capabilities
- Point-of-Person Diagnostics
- Digital Pathogen Surveillance
- A National Public Health Data System
- An Integrated National Pathogen Surveillance and Forecasting Center
- Next-Generation Personal Protective Equipment
- Pathogen Transmission Suppression in the Built Environment
- Comprehensive Laboratory Biosafety
- Technologies to Deter and Prevent Bad Actors

These priorities vary widely. In many cases, the technology already exists, or experienced incredible innovation and momentum from the ongoing pandemic, and the challenge remains in effectively integrating it with existing systems or scaling it to more ambitious levels. In other cases, exciting capabilities exist only as promising demonstrations or prototypes, and investments would need to target bringing technology to full maturity and wide deployment.

The priorities listed here also only address state-of-the-art technologies. Long-term success will require a continual assessment of changing capabilities over time. Trends in telehealth, automation, and robotics, to name a few, will continue and provide additional resilience to biological threats. In all instances, Congress and the Administration must fund, support, and coordinate the efforts needed to bring these capabilities to fruition.

Success will also require a whole-of-government approach. Relevant agencies and departments span the federal government, and all must be stakeholders in the success of *The Apollo Program for Biodefense*. The removal of institutional and bureaucratic barriers and the advancement of innovative incentive mechanisms will be necessary to bring some of the technologies to fruition. Such changes could include prize competitions, advanced market commitments, and regulatory awards. NSC, OSTP, and the National Science and Technology Council should provide leadership through established or joint committees. They should bring together the relevant departments, agencies, and Executive Office of the President components to ensure engagement and coordination of science and technology efforts.[36]

VACCINE CANDIDATES FOR PROTOTYPE PATHOGENS

Vaccine development is a time-consuming endeavor that has traditionally taken several decades per pathogen. Advances in many fields have enabled new approaches to vaccine development with much shorter timelines.[37] However, even with these innovations, vaccine development is a multi-step process that takes precious time.

Fortunately, vaccine development for one pathogen is often translatable to other pathogens in the same viral family.[38] Thus, the extent to which we have previously invested in vaccine development against the same or related pathogens determines our capacity to rapidly develop a vaccine against a new pathogen.[39]

Although scientists frequently discover new viral species that infect humans, the number of viral families that these species belong to has plateaued. Therefore, by investing in vaccines for at least one prototype pathogen in each of the 25 viral families known to infect humans, we could reduce the global burden of infectious disease while simultaneously preparing for the next unknown biological threat. These efforts would also help develop a strong and diverse research community, better prepare us to address new threats rapidly as they emerge, and prevent the need for difficult and blunt interventions.

By investing in research and development at home and providing resources to international public-private partnerships, the United States could provide leadership and coordination globally, while also enabling the Nation's talent to lead scientifically.

Operation Warp Speed has generated significant momentum for vaccine development capability that should continue beyond the COVID-19 pandemic to prevent the next.

We should continue research to validate generalizability. When we need to use the same vaccine approach in the future, rapid entry into Phase 1 clinical trials will be possible by leveraging data from previous clinical trials. For pathogens that are currently endemic and that frequently cause outbreaks, clinical trials should progress through Phase 2 and 3, to serve affected populations and provide a stronger basis for efficacy for a given vaccine design.

MULTI-PATHOGEN THERAPEUTIC DRUGS IN ADVANCE OF OUTBREAKS

At the very beginning of an outbreak of a novel pathogen, our best pharmaceutical line of defense will be those drugs that have either already been approved by the FDA, or those that have advanced far into clinical trials and can be rapidly deployed. For example, Remdesivir—a drug with a validated safety profile in Phase 1 clinical trials against Ebola, and that had preclinical data showing activity against multiple viruses—including coronaviruses—was able to rapidly proceed into Phase 3 clinical trials and was the first drug to receive an EUA from the FDA. While Remdesivir was not panacea for patients admitted to the hospital, previous trials made the rapid pace at which Phase 3 trials started possible. Unfortunately, drugs like Remdesivir are rare due to systematic underinvestment by the pharmaceutical industry in the development of treatments for acute viral diseases.

To ensure that we have a multitude of drugs ready at the beginning of the next pandemic, we need to make investments in the development of multi-pathogen therapeutics—those that can be effective against multiple phylogenies of viruses.[40,41,42] Previous efforts to develop multi-pathogen therapeutics have largely targeted direct-acting small molecule antivirals. However, new modalities are emerging that may result in increased breadth and potency and which warrant extra investment, including host-directed antivirals and monoclonal antibodies targeting regions conserved across multiple viral species.[43,44] Funding the development of a diverse repertoire of multi-pathogen therapeutics through Phase 1 clinical trials—and, for endemic pathogens that currently affect populations throughout the world, Phase 2 and 3 clinical trials—would ensure that we could treat patients as early as possible in an outbreak, no matter the pathogen. Also, we can gain valuable information about the process of drug development that would inform efforts to develop even more effective therapeutics after an outbreak has occurred and the specific viral pathogen identified.

FLEXIBLE AND SCALABLE MANUFACTURING OF PHARMACEUTICALS

Following the successful development of therapeutics and vaccines against a novel pathogen, they must be rapidly manufactured at scale, both initially for clinical trials and later for distribution to the public. Currently, many of the drug and vaccine modalities that we rely on are not readily amenable to both flexible and scalable manufacturing. Small molecule drugs often require multiple steps to synthesize, and each requires its own set of reaction conditions that may vary by temperature, pressure, and reagents, as well as different isolation and purification steps. As a result, manufacturing processes for small molecules are often specific to each drug, making it difficult to repurpose existing facilities to scale manufacturing of a new drug.

Recombinant proteins form the basis of the plurality of vaccine and therapeutic candidates developed specifically against COVID-19. While existing manufacturing infrastructure supports large-scale recombinant protein production, the need to use cell culture for their production increases the time required to produce each batch of vaccine. Also, each protein may require its own expression, isolation, purification, and formulation conditions, making it difficult to repurpose existing facilities for the development and manufacturing of a new recombinant protein. Recombinant protein-based vaccines were, therefore, months behind leading vaccine candidates in entering COVID-19 clinical trials.

These leading vaccine candidates largely rely on platform technologies (i.e., technologies that use the same processes for manufacturing, formulation, and delivery of a drug or vaccine against multiple different pathogens). Such platform technologies typically involve genetically encoding the therapeutic or vaccine candidate in mRNA, DNA, or a viral vector, enabling the production of different therapeutic or vaccine candidates simply by changing a genetic sequence.[45] As a result, a facility designed to manufacture a therapeutic or vaccine candidate using a platform technology against one pathogen could be quickly repurposed against a new pathogen without much need to make changes to physical infrastructure or established production processes.[46]

The U.S. government should broadly invest in the advancement of platform technologies to ensure that therapeutic and vaccine candidates against the next pandemic pathogen can be rapidly manufactured at scale. Certain technical challenges that stand in the way of platform technologies becoming more broadly utilized could be overcome with further research. For example, unstable viral vectored and mRNA vaccines require constant refrigeration, complicating the logistics of their distribution to the public. Research into formulations that would reduce the dependence on a cold chain for distribution could significantly increase the utility of these vaccines. Also, mRNA and DNA vaccines have thus far lacked significant validation in human clinical trials. Further clinical experience with these nucleic acid-based vaccines would allow us to iteratively improve their

safety and efficacy profiles. Finally, while much research effort has gone towards the development of vaccine candidates that leverage platform technologies, the same cannot be said for therapeutic candidates that leverage the same technologies. Monoclonal antibodies are drugs that are currently produced as recombinant proteins, making them expensive and time-consuming to manufacture. If we develop and produce them using platform technologies instead, they might be significantly more scalable in a pandemic. We need further preclinical and clinical research to validate the applicability of platform technologies to the delivery of therapeutics.

With enough investment in their maturation, platform technologies might eventually become well-established as a means of producing pharmaceutical products during and between pandemics, ensuring that we would always have a large, manufacturing base that could be rapidly redirected to produce medical countermeasures at the beginning of a pandemic. Also, if we can build up a strong track record of safety and efficacy for a given platform in the clinic, we can benefit from more flexible regulatory standards for products developed using that platform subsequently. Streamlining manufacturing and regulatory approval processes that platform technologies might enable could allow us to develop, manufacture, test, and distribute medical countermeasures in months, not years, ultimately saving countless lives and livelihoods in the next pandemic.

NEEDLE-FREE METHODS OF DRUG AND VACCINE ADMINISTRATION

Once discovered, developed, and manufactured, we still need to distribute drugs and vaccines to the public. Today, most drugs and vaccines that would be useful during a pandemic require intravenous or intramuscular delivery—and thus, a healthcare provider to administer them. During a global pandemic, there may not be enough healthcare workers available to help treat or vaccinate the world's population, especially in countries with less-developed healthcare systems. Also, the widespread fear of needles may reduce the population uptake of a new vaccine. Thus, we need new methods of drug and vaccine delivery that would enable self-administration so that these medical countermeasures reach the most individuals possible.

Several different technologies exist that could facilitate the self-administration of drugs and vaccines. Microneedle patches—which are bandage-like patches that enable the simple delivery of a drug or vaccine through the skin—have been extensively investigated for influenza vaccine delivery, and have the advantage of reduced reliance on a cold chain for storage and transportation, and pain-free administration.[47] Intranasal or inhalable drugs or vaccines may also enable self-administration and would deliver the medical countermeasure to the respiratory tract, which would be of particular medical benefit against a respiratory pathogen.[48] Finally, while oral delivery is common for small molecule drugs, it has seen limited use with biologic drugs and vaccines. If technical barriers in

oral delivery could be overcome, this method of administration could be the most readily adopted by patients. We could deliver self-administrable drugs and vaccines through the mail or patients could pick them up at their local pharmacy, greatly reducing the logistical challenges of delivering these pharmaceuticals to potentially billions of people.

The U.S. government should invest in the advancement of the aforementioned technologies which enable transdermal (microarray patches), intranasal, inhalable, and oral delivery of drugs and vaccines. We can deliver pharmaceuticals that use these methods by developing them for infectious diseases for which needle-based delivery is currently predominant (e.g., influenza, measles), which can serve as proving grounds for these technologies. We should advance these pharmaceuticals through at least Phase 1 clinical trials to enable timely evaluation of initial pharmacokinetics (for drugs) or immunogenicity (for vaccines). However, we should take care to ensure that any devices required for delivery are easy to use and manufactured on a large scale. With further advancement of self-administered vaccines, we could dramatically streamline the process by which we get life-saving treatments and vaccines to the public.

UBIQUITOUS SEQUENCING

Nucleic acid sequencing (i.e., the reading of genetic material) is now widespread and has seen orders of magnitude decreases in cost, while simultaneously achieving increases in throughput. Sequencing provided the critical information to identify SARS-CoV-2 as a novel threat and enabled that information to travel around the world *faster* than the virus, enabling the design and manufacture of medical countermeasures. While impressive, it has substantially more to offer.

Metagenomic sequencing, the reading of all genetic material from a sample, offers advantages that many other capabilities struggle to rival.[49] All pathogens have genetic material and produce tell-tale signs in an infected individual, known as host-responses. Sequencing allows us to read these signals, and is crucial for early detection, characterization of pathogens, epidemiological tracking, attribution, and development of other biotechnologies generally. Crucially, sequencing offers the ability to detect pathogens without looking for a specific threat, which is essential to identifying novel pathogens, whether natural or engineered.

Despite continued advances, often outpacing Moore's law, sequencing technology has critical bottlenecks to achieving the ubiquity, simplicity, and affordability needed.[50] If realized, sequencing could become routine in the clinical setting, as well as in high-risk low-resource areas of the world, expanding access to the most capable diagnostic tool. Sequencing could serve as the diagnostic for diseases generally and permit novel pathogen detection early and beyond our borders. All this, while also being robust against genetic changes in pathogens and offering the details needed to track, and ultimately reduce pathogen transmission.

To advance sequencing, we must increase investments in novel sequencing modalities, prioritizing methods enabling miniaturization and decreases in reagents or even reagent-free sequencing. Coupled with research and development focused on microfluidics and on-chip sample preparation, we can realize the vision of truly hand-held, affordable, easily operated sequencers. Decreasing the cost and applying advances in bioinformatics to the output would enable sequencing to become ubiquitous and permit the incorporation of sequencers into several products and settings that are currently prohibitive.[51] Sequencing broadly and frequently would provide a baseline understanding of the genetic material around us, permitting the early detection of new threats, while providing the critical diagnostic capacity needed to reduce the global infectious disease burden.

MINIMALLY- AND NON-INVASIVE INFECTION DETECTION

The detection of an infection is most commonly pathogen-specific and initiated after the onset of symptoms or suspected exposure. Detection at this point is often too late and can miss both asymptomatic and pre-symptomatic infections where unsuspecting individuals may spread the disease further. In response to an outbreak, it should be possible to deploy simple point-of-person tests to detect infections and guide resources for interventions, but these types of tests will not be available immediately. Even once they are available, tests will not be continuously conducted and must be done at some interval. New sensing capabilities, though, such as non-invasive volatolomics (the detection of volatile compounds emitted by an individual) and wearables could permit constant passive monitoring of markers of infection without interfering with or inconveniencing our daily lives. Furthermore, non-invasive and minimally-invasive detection techniques could provide avenues to monitor high-risk, high-concern, and sentinel populations for infections, without disrupting daily life.

We are on the verge of the ability to detect whether the body is currently infected with any pathogen, known or unknown, through the interrogation of host biomarkers. Increasingly, we can also detect infection indicators non-invasively through advances in wearables[52] and volatolomics.[53] These techniques can accurately measure digital biomarkers (e.g., physiological, biometric, biophysical, biochemical, mobility, and circadian rhythm changes) constantly and longitudinally, and detect subtle changes from an established baseline indicative of the onset of infection. This allows the device to prompt the user to change behavior or seek a clinical diagnosis.

Minimally invasive technologies (i.e., those that permit sample acquisition without pain, discomfort, inconvenience, or risk) would also facilitate molecular diagnostics for the identification of pathogens. This capability would allow for the detection of pre-symptomatic exposure, and asymptomatic infection and spread without the need for individuals to present in a clinical setting, allowing for early detection and substantially improved monitoring of novel biological threats.

Sensors are already shrinking in size, becoming more affordable, and increasingly capable. Yet, there is a need for more work on the integration and analytic systems that would permit drawing rapid inferences from them. We should make investments in the development of sensing and sampling capabilities, as well as testing of technologies to fully understand their potential and challenges. Additionally, particular attention should be given to the privacy of users of any device undertaking constant monitoring to prevent exploitation by malicious actors. If achieved, we could build the ability to detect novel and seasonal infections into our environment, while also facilitating advances in telemedicine and pushing capabilities into more austere areas.

MASSIVELY MULTIPLEXED DETECTION CAPABILITIES

Historically, diagnostic capabilities were specific to the pathogen, slow, and expensive. Single-pathogen diagnostics require clinical suspicion and are not readily available, or available at all, for some pathogens. If we suspect multiple pathogens, then we would need to run several assays, thereby increasing the cost and time to a diagnosis. Multiplexed detection capabilities address these challenges and bring new benefits by simultaneously testing for multiple pathogens, resistance genes, biomarkers, and analytes in a single simple assay.[54] Massively multiplexed detection capabilities in the form of pan-viral and pan-microbial assays have also been demonstrated, ushering in a new paradigm for diagnostics.[55]

Syndromic panels via multiplexed PCR assays (e.g., those used to test for approximately 25 of the pathogens most associated with respiratory infections) are currently available in many parts of the world, but do not include most known pathogens. While adequate for most presentations of infectious disease, crucially, these panels do not cover less common and novel pathogens. Massively multiplexed panels can address these limitations by including virtually all known human pathogens and even detect novel pathogens based on conserved sequence homology[56] (i.e., the ability to detect similar regions in a pathogen's genetic tree). While the ability to detect almost any known pathogen is a tremendous advantage, for wide deployment, these arrays will need to become cheaper, more robust, simpler to operate, and faster. They must also achieve high sensitivity and specificity and ultimately be interpretable to clinicians.

To bring about these capabilities, the United States should make massively multiplexed assays a priority and provide funding for their research, development, and prototyping. New CRISPR-based massively multiplexed panels are particularly promising.[57] Other methods beyond these techniques have also been demonstrated previously, and new methods may also be possible. We should prioritize techniques enabling the tests to move out of centralized laboratories, and especially those that can operate in resource-constrained settings. The detection of viral pathogens for any host, including agricultural plants and animals, rapidly and with confidence would provide a capability to complement metagenomic sequencing and pathogen-specific point-of-person diagnostics.

RAPID POINT-OF-PERSON DIAGNOSTICS

Rapid point-of-person diagnostics, also known as point-of-need diagnostics, are tests that can rapidly identify an infection wherever the individual is located. Point-of-person diagnostics stand in contrast to clinically administered diagnostics, which often require transportation to centralized laboratories, and days or weeks before rendering results.

In accordance with Recommendation 30 of the *National Blueprint for Biodefense*[58] and the recommendations made in *Diagnostics for Biodefense: Flying Blind with No Plan to Land*,[59] the Commission urges the U.S. federal government to pursue rapid point-of-need diagnostics and the FDA to develop pathways for diagnostics to be approved for their public health potential to reduce community transmission.[60] Rapid testing can enable detection. Tests that take more than three days to produce a result are essentially useless in the context of outbreak control since beyond that point contract tracing becomes increasingly difficult.

Point-of-person diagnostics should be considered public health instruments, as opposed to simply clinical tools. Rapid tests should be readily available, minimally-invasive, portable, and user-friendly (i.e., easy to conduct and interpret). The end goal is to integrate point-of-person diagnostics with public health data systems. These tests can also extend testing to communities and populations that cannot readily access care.[61] Smartphone apps and other digital tools can aid in both the use and interpretation of results, as well as make results available to public health authorities. Rapid low-cost tests also allow for repeated use, which can be essential for novel pathogens with unknown incubation time, and for essential and frontline workers with multiple potential exposures. In the absence of such diagnostics, testing through a centralized laboratory will only increase the risk of spread by requiring individuals to present themselves publicly (especially in the case of extremely contagious pathogens). Additionally, a longer wait time places too much faith in a person's ability to quarantine for the appropriate duration.

DIGITAL PATHOGEN SURVEILLANCE

Digital pathogen surveillance systems, which use internet-based and other electronically available data (e.g., medical bulletins, search queries, social media), have shown some improvement in recent years, including the provision of early warning signs for COVID-19. These systems, which have the potential for near real-time warning ability, international detection, and automated operation, could complement more traditional public health surveillance systems. With access to international airline routes, known disease networks, and anonymized mobility data, to name a few, we can predict the spread of infection and focus on resources and interventions in advance of outbreaks.

Limited access to information, poor integration of public and private data, and failure to bring the best talent and latest innovations to solve the problem of real-time digital surveillance have limited the capability of extant systems to detect biological events early enough to respond effectively and contain the threat. By leveraging advances in machine learning, and in particular natural language processing,[62] we can continuously track vast amounts of data and filter the noise to provide relevant information to public health experts. This information is useful to prompt further investigation, allocate resources, and inform clinicians and public health authorities about potential pathogens to consider in their routine work.

The federal government should implement a system that monitors biological threats within and outside of U.S. borders. We should leverage data sources (e.g., medical bulletins, livestock reports, satellite data, social media, online forums), in concert with the National Pathogen Surveillance and Forecasting Center ensuring data interoperability. The government should clear obstacles to access necessary data, incentivize innovation in the field through inducement prizes, and fund long-term efforts to continuously update the system with new data and capabilities as they become available.

A NATIONAL PUBLIC HEALTH DATA SYSTEM

As past outbreaks and the current pandemic have demonstrated, reliable, accurate, and comprehensive data is necessary for effective decision making during a crisis. Without timely and relevant information, it is not possible to prioritize resources and interventions, coordinate efforts, and respond in a manner the American people deserve. Although it is an enormous undertaking, a National Public Health Data System would provide the capabilities needed to effectively address the spectrum of biological threats.[63] To be successful, the system must be able to efficiently integrate, curate, and analyze data in a timely manner from federal, state, local, tribal, and territorial public health agencies.[64]

The Coronavirus Aid, Relief, and Economic Security (CARES) Act provided the CDC with $500 million for public health data modernization and to support system-to-system interoperability and cloud-based centralized repositories. These efforts, while ongoing, will hopefully provide a strong foundation for future efforts to further ensure that data are simple to gather and deposit (while preserving privacy), available in real-time, and secured against cyberattacks. We should design continuous and timely integration of emerging technologies and data streams into the system from the start, with aims of reducing the burden of reporting and keeping outputs from the system simple to interpret and act on.

Our priority should be to establish and sustain a national and integrated public health data capability. With this foundation, we could integrate additional capabilities as they become available or advanced (e.g., digital pathogen surveillance, new streams of clinical and laboratory data, access to electronic health records, anonymized human movement,

new visualization capabilities, improved analytics). The government should continue to prioritize public health data and sustain investments in both the maintenance and advancement of the system.

A NATIONAL PATHOGEN SURVEILLANCE AND FORECASTING CENTER

An integrated real-time national pathogen surveillance and forecasting center with advanced capabilities to detect and model naturally occurring, accidentally released, and intentionally introduced biological threats does not currently exist. The abilities to identify and forecast threats rapidly is critical at the beginning of an outbreak and the understanding of infectious disease prevalence, including seasonal pathogens, are essential components of public health planning and response.[65] Aggregating diverse data sources in real-time and forecasting infectious disease outbreaks are necessary to prevent or rein in the spread of biological threats. Improved forecasting through modeling also allows for better projection of the pandemic potential that a threat poses and aids in the prioritization of resources, mobilization of a response, and initiation of countermeasure development and deployment.[66]

Current infectious disease forecasting capabilities rely on data that are sometimes unavailable for weeks. An assortment of academic groups usually coordinates to create a forecast, but they must be able to gather and analyze data quickly for it to be accurate and useful. The United States should be ahead of the curve, take these threats more seriously, and establish a permanent National Pathogen Surveillance Forecasting Center. This center would maintain forecasting capacity, improve science, and invest resources in the building and maintenance of the best models, pipeline, and community of researchers. Furthermore, the Center should integrate the National Public Health Data System and aggregate information from clinical molecular diagnostics, distributed sentinel surveillance, digital pathogen surveillance, laboratory biosafety monitoring, and animal and environmental pathogen surveillance. This would allow for improved detection of novel biological threats and a better understanding of rapidly evolving outbreaks and attacks.

Effective modeling also requires reliable data and a thorough understanding of pathogen transmission and available public health interventions. Additionally, it is also necessary to have data on historical trends of transmission, population mobility, and individual decisions in response to public health threats.[67] Forecasting success will also depend on the ability to communicate and relay relevant information in an effective manner (e.g., through visualizations or other dashboards) to decision makers. As some have noted, weather forecasting through the National Weather Service successfully takes advantage of, and integrates data from automated weather stations, radar sites, and satellites; maintains archival data; and progressively improves forecasts.

The ability to forecast the trajectory of a pathogen rapidly and reliably is crucial for the United States to address seasonal infectious diseases, and to prepare for and respond to emerging and engineered threats. By establishing a National Pathogen Surveillance and Forecasting Center as a permanent federal institution, the United States could advance these capabilities and ensure future preparedness.

NEXT-GENERATION PERSONAL PROTECTIVE EQUIPMENT

Personal protective equipment (PPE) can be used to protect against a broad-spectrum of biological threats. However, the current state of PPE burdens its users, requires experience in proper usage, is seldomly reusable, is not widely available to all populations, and does not properly fit everyone (e.g., children).[68] Additionally, since the primary goal of PPE is to prevent the wearer from becoming infected, not enough emphasis has been placed on preventing the wearer from infecting others. Shortages of PPE leave frontline and essential workers at risk, threatening their health and reducing their capacity to respond.

The COVID-19 pandemic has highlighted limitations in our knowledge of PPE and exposed an inadequate ability to rapidly scale up production. However, the pandemic has also catalyzed efforts to make PPE reusable, spurred new ideas about respirator designs, seen the advent of personalized PPE, and eventually brought new production capacity to fruition. While these efforts mark advancements, focused research efforts and innovative approaches could achieve much more.

To develop the next generation of PPE, we should make innovations in the following areas: 1) reusable, sterilizable, and self-disinfecting equipment; 2) modular designs responsive to a wide range of threats, including those which go beyond biological threats; 3) personalization to ensure adequate protection, comfort, and attractiveness; 4) rapid production from widely available materials without supply vulnerabilities; 5) the ability to neutralize pathogens; 6) sensing capabilities to detect potential exposures; and 7) protection beyond traditional masks, respirators, gloves, gowns, etc., that safeguard the wearer without burden. The government should invest in and incentivize the development of these PPE innovations through inducement prize challenges, intramural and extramural research and development efforts, advance purchase commitments and consistent acquisition, and use-inspired basic research programs, such as the DARPA Personalized Protective Biosystem effort. Establishing distributed capacity will ensure PPE is available in advance, and maintaining capability will ensure increased production and surge in response to a threat. Additionally, the government should develop standards and metrics for the evaluation of all forms of PPE to quantify capabilities, standardize comparisons, and assess progress.

PATHOGEN TRANSMISSION SUPPRESSION IN THE BUILT ENVIRONMENT

Transmission of most known pathogens occurs in human-built environments (e.g., offices, healthcare facilities, schools, public transportation, planes) via air, droplets, and fomites.[69] While we have exerted significant effort to engineer and make the built environment robust against fires, earthquakes, and other threats, we have put little effort into engineering and making our world robust against pathogens. Suppressing pathogen transmission, especially in high-risk and high-traffic spaces, would reduce the spread of infectious diseases, extinguish some outbreaks, and buy critical time to combat more aggressive pathogens. With permanent incorporation into the environment, we could continuously defend against threats, even prior to detection, and without the dramatic changes in human behavior needed to reduce pathogen transmission.[70]

To reduce the effective transmissibility of most airborne, droplet, vector-borne, and fomite-transmitted pathogens, we should make investments in:

- affordable air filtration and sterilization systems
- deliberate design of airflows
- self-sterilizing surfaces
- easily sterilized materials, robust against harsh sterilization
- robotic and autonomous integrated sterilization
- fomite neutralizing technologies
- integrated real-time pathogen sensing capabilities

Conducting pilot studies in select high-risk environments would help to achieve a deeper understanding of how to re-engineer the built environment to reduce pathogen transmission before eventually expanding implementation throughout all population dense environments in the Nation. We should fund research and development efforts to foster a field of study and discover innovative technologies to further advance capabilities. As part of a modernization effort, the federal government should invest in technologies to retrofit current infrastructure, such as HVAC systems and public transport, and incentivize the incorporation of suppression technologies into new production through tax credits and grants, before ultimately incorporating proven aspects into regulation.

COMPREHENSIVE LABORATORY BIOSAFETY

While high-containment laboratories already have an impressive number of safeguards in place, they could benefit from continuously updated research given the high risks involved. Recent biosafety lapses have included smallpox, anthrax, and contagious strains of influenza.[71,72] Indeed, some believe the 1977 H1N1 pandemic arose from a lab accident or botched vaccination experiment.[73]

Our risk tolerance in laboratories worldwide[74] working with biological threats should be comparable to that of air travel, where safety is engineered into the airlines and airports, and monitoring occurs constantly to detect and prevent human-generated and technology-based accidents. A constant focus on and prioritization of safety ensures that the complex and previously risky nature of flight can be undertaken safely.

We continuously innovate automobile safety technologies (e.g., lane departure warnings, blind spot monitoring, pedestrian detection). We should apply a similar approach to laboratory biosafety. This includes the refinement of current capabilities, analogous to advances in airbags for automobiles, to the introduction and rigorous testing of new technologies. Ultimately, we may realize the benefits of high-containment laboratory work while minimizing the risks to the greatest extent possible by developing pathogen monitoring capabilities, improved engineering controls, and risk assessment and analysis tools.[75] While training personnel is essential and the core of biosafety,[76] insider threats should also be more seriously considered, and safeguards put in place to deter and prevent any malicious behavior.

Additional funding is necessary for the study of laboratory accidents and the development and testing of new capabilities and tools to achieve comprehensive laboratory biosafety systems. These should be tested in safe environments, continuously incorporated into current high-containment labs, and ultimately integrated into all biosafety labs.

TECHNOLOGIES TO DETER AND PREVENT BAD ACTORS

The ability to investigate, analyze evidence, and attribute deliberate biological events is essential for both deterrence and response to a deliberate or accidental threat.[77] As tools are developed and the barriers to engineering pathogens continue to decrease, the number of possible actors may increase. Technologies are required to ensure safety is built in and capabilities developed in advance to prevent and deter action.

Unfortunately, biological attribution, genetic engineering detection, and microbial forensic techniques have only made small strides since the anthrax attacks of 2001. In the two decades since, there have been advancements in machine learning and physical characterization techniques, and artificial intelligence evolved from an “AI winter” to “AI summer.” However, we have yet to see these technologies extensively applied,

despite recent academic studies and government programs hinting at their impressive capabilities.[78,79] In particular, it should be possible to harness advances in machine learning techniques from several disciplines and apply them to distinguish natural and engineered DNA and to inform attribution. Training these machine learning tools will require access to relevant datasets which we must establish in advance.

Once developed, these capabilities could be broadly deployed and integrated into routine laboratory, clinical, and environmental settings as sentinels monitoring for engineered pathogens, in addition to being available for forensics applications. To advance these techniques, the federal government should make use of its investment capability and inducement prizes, as this would encourage the application of their capabilities developed for other applications to these problems. With additional dedicated funding to research, develop, acquire, and operate such technologies, as well as maintain the relevant repositories, we could establish a robust and known capability to detect, analyze, and attribute biological threats.

APPENDIX B: METHODOLOGY

The Bipartisan Commission on Biodefense was established in 2014 to inform U.S. biodefense and provide recommendations for change. The Commission, supported by academia, foundations, and industry, determines where the United States falls short in addressing bioterrorism, biological warfare, and emerging and reemerging infectious diseases.

RESEARCH QUESTIONS

To examine an Apollo Program for Biodefense, we developed the following research questions:

- What should be the top priorities for an Apollo Program for Biodefense?
- Are investments in the development of technologies commensurate with the challenge of biodefense?
- Is new funding required?
- What should we be doing that we are not already doing to address biological threats more adequately with technology?
- How will the biological threat landscape evolve over the next decade and what technologies are needed to ensure preparedness?
- How can the public and private sectors contribute to an Apollo Program for Biodefense?
- How can we be sure that new technologies for biodefense have limited dual-use potential?
- How will technological convergence shape the biological threat landscape moving forward? What should be taken into consideration?
- What sorts of policy initiatives could drive technological innovation for biodefense on the scale of an Apollo program?

PRELIMINARY RESEARCH

The Commission reviewed previous research efforts; scientific studies; previous U.S. government research and development programs; and federal strategies, plans, funding, and research and development programs related to defense against naturally occurring, accidentally released, and intentionally introduced biological threats and catastrophic biological risks. This review: (1) allowed for an assessment of the comprehensiveness and effectiveness of research and development efforts for biodefense; and (2) determined direction for an Apollo Program for Biodefense. This review also informed the structure and topics of a formal meeting of the Commission, and interviews and roundtables with subject matter and government experts.

INTERVIEWS OF EXPERTS

The Commission conducted interviews with 66 academic, industry, non-governmental, and governmental experts to inform the recommendations contained in this report. Experts were invited to participate based on their prior knowledge of and experience with public health security, technological development, biosecurity, and biodefense. Staff protected the privacy of each expert to speak openly and candidly, and did not attribute opinions to the institutions, organizations, agencies, departments, or employers with which they were affiliated. Opinions were considered on aggregate. This report contains the views of the Commission and not necessarily those of individual experts.

ROUNDTABLES

The Commission hosted four roundtables at which experts discussed challenges and solutions that an Apollo Program for Biodefense should address in the following areas:

- Ambitious pathogen biosurveillance innovations;
- Improving PPE and built environments;
- Advancing medical countermeasures to combat biological threats; and
- Ambitious improvements to microbial forensics and attribution.

The Commission held these roundtables using virtual platforms in September 2020. Participants came from a diverse range of backgrounds, including academia, industry, non-governmental organizations, and government. To encourage frank and open discussion, the Commission held these roundtables under Chatham House Rule. Staff provided questions to participants in advance to help facilitate discussion. During these roundtables, participants discussed ambitious proposals, and solutions for a wide range of biological threats.

ANALYSIS

Commission staff used qualitative methods to analyze information and data obtained during the literature review, interviews, and roundtables conducted. Staff synthesized and evaluated ideas, feedback and suggestions given, alongside the individual expert interviews and literature review, to help inform the development of this report. Staff further evaluated findings and recommendations considering the Commissioners' own experiences. Staff did not use statistical and other quantitative methods for this analysis.

LIMITATIONS

Several biodefense programs and policies; intelligence, raw data, and documents; appropriations and budget documents; and other sensitive information are classified or otherwise unavailable. The Commission did not review these materials. The Commission produced this report in keeping with time constraints associated with funding for this activity.

APPENDIX C: INTERVIEWED EXPERTS

The Bipartisan Commission on Biodefense thanks the following individuals for their contributions. The final version of this report reflects the aggregated view of all evidence gathered by the Commission and does not necessarily represent the view of any individual expert. All experts' opinions were their own and not those of the organizations with which they are affiliated.

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