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TECHNOLOGIES TO ADDRESS
Global Catastrophic Biological Risks

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Technologies to Address

Global Catastrophic Biological Risks

Infectious disease emergencies can arise with little notice and have serious detrimental and lasting effects on health and society. In the past century, we have seen global emergencies like the 1918 influenza pandemic, which killed 50-100 million people; the emergence of the deadly SARS and MERS coronaviruses; and the 2013-2016 Ebola epidemic in West Africa, which resulted in more than 28,000 cases and 11,000 deaths and had devastating impacts on that region, as just a few examples.

As a subset of infectious disease emergencies, global catastrophic biological risk (GCBR) is a special category of risk involving biological agents—whether naturally emerging or reemerging, deliberately created and released, or laboratory-engineered and escaped—that could lead to sudden, extraordinary, widespread disaster beyond the collective capability of national and international organizations and the private sector to control.

While rare, the risks of severe pandemics and GCB events are increasing because of factors like climate change, population growth and urbanization, and rapid affordable global travel. In addition, advances in biotechnology that enable easier and more targeted manipulation of biology increase the chances that microbes may be misused or will become the accidental cause of a pandemic.

Yet, while biotechnology does pose some societal risk, investment in the technologies described here, and others, is also an important component in helping to safeguard the world from a devastating biological event. When applied thoughtfully, technology can improve our ability to recognize and address emerging biological problems.

Executive SUMMARY

Goals of the Report

1. Pinpoint areas of need for technological solutions to address severe pandemics and GCB events;
2. Identify technologies that have significant potential to reduce GCBs; and
3. Provide context for those technologies, demonstrating their promise, limitations, and conditions under which they might be developed and employed successfully.

Framing Technology Requirements

Should a severe pandemic emerge, response will need to be global. But many countries will not have the capacity to respond effectively, which will make the whole world vulnerable.

Properties of the technologies needed to prevent or respond to these events are likely to be qualitatively and quantitatively different from those used in routine public health and medical practice. Through this research, we focused on properties that transformative technologies in GCBR reduction might possess. These include:

- Better sensitivity to facilitate prevention
- Improved capacity to make response decisions earlier
- Distributed approaches to improve scale and access
- Rugged or easy to use in a variety of settings
- Reduced time lags in development, availability, and fielding

Methodology

In order to identify potentially relevant technology solutions for severe pandemics and GCB events, the research team conducted a horizon scan to

PURPOSE OF THE PROJECT

This study highlights some promising classes of technologies, including an assessment of their potential relevance to reducing pandemic and global catastrophic biological risks.

understand the technology space and highlight areas of technology development and upcoming changes that could benefit GCBR reduction. As part of the horizon scan, the research team conducted a literature review and interviewed a number of experts in the field to inform judgments regarding

the current and future state of the science.

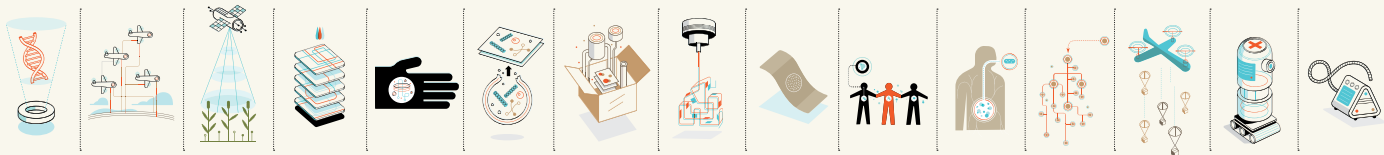
Once technologies were identified, a common set of evaluation questions, based on the Heilmeyer catechism, were applied to each technology, as were high-level judgments on technology readiness, potential impact, and amount of investment needed to make implementation successful.

Evaluation questions:

- What is the technology?
- What problem does it solve?
- How do we do it now?
- What does success look like?

Technologies

Five broad categories of technologies were investigated for this report, each including a set of potentially significant technologies or classes of technologies for prevention and response to severe infectious disease emergencies.



DISEASE DETECTION, SURVEILLANCE, AND SITUATIONAL AWARENESS

Ubiquitous Genomic Sequencing and Sensing: As a surveillance tool, ubiquitous sequencing would allow for the near-real-time characterization of pathogen biology, including determinations of virulence, transmissibility, and sensitivity or resistance to medicines or vaccines.

Drone Networks for Environmental Detection: Networks of land-, sea-, and air-based drones autonomously conducting environmental surveillance would be one way to help fill gaps in monitoring of the environment for biological disruption to important ecosystems and bioterrorism events. Drones can traverse different ecosystems to collect data using a variety of sensors and tools, ranging from optical cameras to complex biotechnology.

Remote Sensing for Agricultural Pathogens: Advanced satellite imaging and image processing technologies can be used for ongoing, widespread, systematic agricultural surveillance to monitor the health of important crops and other vegetation in order to detect potential threats before they become widespread.

INFECTIOUS DISEASE DIAGNOSTICS

Microfluidic Devices: Microfluidic devices are “lab on a chip” diagnostic devices that have the potential to augment or replace traditional laboratory testing equipment in some contexts, thus making diagnostics more accessible, usable, and useful at the bedside and in resource constrained environments.

Handheld Mass Spectrometry: The future of mass spectrometry is a handheld, truly portable unit that can provide advanced diagnostic capabilities in the field and at the point of care. Some mass spectrometry technologies may even provide pathogen-agnostic or pan-domain diagnostic capability, eliminating the need to even differentiate among bacteria, viruses, fungi, or protozoa before conducting diagnostic tests.

Cell-Free Diagnostics: Cell-free diagnostics do away with the cell membrane to use the machinery within bacterial cells in combination with engineered genetic circuits to make proteins for diagnostic purposes. These cell-free diagnostics can generate rapid colorimetric outputs visible to the

naked eye for easy interpretation. The cell extracts can also be freeze-dried onto paper for use in austere environments.

DISTRIBUTED MEDICAL COUNTERMEASURE MANUFACTURING

3D Printing of Chemicals and Biologics: 3D pharmaceutical printing could be used for distributed manufacturing of MCMs as well as personalized drug dosing and formulations. 3D printers now have the capacity to synthesize key chemicals and pharmaceuticals almost anywhere a printer can go, and work is also under way to explore use of this technology to print vaccines.

Synthetic Biology for Manufacturing MCMs: Synthetic biology provides the opportunity for novel approaches to both finding and producing therapeutics, as well as the capability of producing these therapeutics in a distributed and tailored way. This could mean that drugs and vaccines are discovered more quickly and produced much faster and in much larger quantities than is possible with traditional manufacturing techniques. ➡

**MEDICAL
COUNTERMEASURE
DISTRIBUTION,
DISPENSING, AND
ADMINISTRATION**

Microarray Patches for Vaccine Administration: The microarray patch (MAP) is an emerging vaccine administration technology that has the potential to modernize the conduct of mass vaccination campaigns. The widespread adoption of MAP technology would significantly decrease a population's time to complete immunization operations by enabling self-administration during emergencies.

Self-Spreading Vaccines: Self-spreading vaccines are genetically engineered to move through populations like communicable diseases, but rather than causing disease, they confer protection. The vision is that a small number of individuals in a target population could be vaccinated, and the vaccine strain would then circulate in the population much like a pathogenic virus, resulting in rapid, widespread immunity.

Ingestible Bacteria for Vaccination: Bacteria can be genetically engineered to produce antigens in a human host, acting as a vaccine, which triggers immunity to pathogens of concern. These bacteria can be placed inside capsules that are temperature stable, and they can be self-administered in the event of a pandemic.

Self-Amplifying mRNA Vaccines: SAM vaccines use the genome of a modified virus with positive sense RNA, which is recognizable to our human translational machinery. Once delivered inside a human cell, the SAM is translated and creates 2 proteins: an antigen of interest to stimulate an immune response, and a viral replicase for intracellular amplification of the vaccine. The ability of SAM to self-replicate results in a stronger, broader, and more effective humoral and cellular immune response than some other vaccines.

Drone Delivery to Remote Locations: Drone transportation networks can enable the rapid delivery of clinical materiel and

pharmaceutical supplies to areas that are difficult to access, either due to physical or topographical barriers or the risk of infection for human responders.

**MEDICAL CARE AND
SURGE CAPACITY**

Robotics and Telehealth: Robotics and telehealth are 2 broad categories of healthcare technologies that may be relevant during the medical response to a GCB event. Successful use of these technologies during such an event would facilitate medical care in nontraditional environments like the home.

Portable, Easy-to-Use Ventilator: In a severe outbreak of respiratory disease, ventilators will be needed for the sickest patients to support breathing during the worst of their illness and while they recover. The availability of an inexpensive, portable mechanical ventilator with an intuitive and largely automated user interface could allow for the care and survival of many more patients than would be possible if a pandemic emerged today.

CONCLUSIONS

This report highlights 15 technologies or categories of technologies that, with further scientific attention and investment, as well as attention to accompanying legal, regulatory, ethical, policy, and operational issues, could help make the world better prepared and equipped to prevent future infectious disease outbreaks from becoming catastrophic events.

To realize the promise of these technologies will require significant dedicated effort and investment. While this is occurring for vaccine development, and to some extent for surveillance, other needs for pandemic and GCB event prevention and response must be addressed if we are to confront these threats in a serious way. One possible approach to closing these gaps would be through the formation of a consortium of technology developers, public health practitioners, and policymakers aimed at understanding pressing problems surrounding pandemic and GCB risks, and jointly developing technology solutions.


Major infectious disease emergencies can arise with little notice and can have serious detrimental and lasting effects on health and society. In the past century, we have seen more than a few global emergencies: the 1918 influenza pandemic, which killed 50-100 million people; the emergence of the deadly SARS and MERS coronaviruses; and the 2013-2016 Ebola epidemic in West Africa, which resulted in more than 28,000 cases and 11,000 deaths and had devastating

Introduction

STATEMENT OF THE PROBLEM

impacts on that region, as just a few examples. History, too, teaches us about the ravages of new and unknown diseases, from the plague that swept Europe to smallpox and other infectious diseases that devastated the New World. Pathogens continue to emerge and adapt rapidly around the world, and experts expect that there will be a severe, potentially catastrophic pandemic in the future, even if it is difficult to know the specific etiology and timing. And modern scientific advances—particularly in synthetic biology—wielded by skilled individuals with destructive intentions could result in biological threats that far surpass anything the natural world might produce.

Global catastrophic biological risk (GCBR) is a special category of risk involving biological agents—whether naturally emerging or reemerging, deliberately created and released, or laboratory-engineered and escaped—that could lead to sudden, extraordinary, widespread disaster beyond the collective capability of national and international organizations and the private sector to control. If unchecked, GCBRs could lead to events that result in immense suffering, loss of life, and sustained damage to national governments, international relationships, economies, societal

stability, and/or global security. A combination of conditions would be the most likely circumstances under which a global catastrophic biological event would emerge. These could potentially include a rapidly spreading and/or highly and quickly lethal biological agent; a significant alteration of biological ecosystems that results in environmental and climate changes; a naïve global population; and concurrent environmental, social, and political circumstances that make response and recovery difficult. 

INTRODUCTION

Yet, despite the rising biological risks presented by increased globalization and technological advances, investment in science and technology is also one of our best hopes for safeguarding the world from a devastating biological event. Technology, when applied thoughtfully, can change the equation by improving our ability to recognize and address emerging biological problems and can greatly reduce biological risk. Biotechnology is inherently dual use, in that it can be harnessed both for good and for ill, so use of new technologies must balance risks and benefits. This study was conceptualized as a way to improve understanding of promising technological opportunities, assess their relevance to this problem set, and catalyze their use for good in reducing GCBRs.

Responding to severe epidemics, pandemics, and global catastrophic biological events requires us to detect emerging problems, diagnose infections, conduct surveillance, and provide treatments and clinical care for patients. While systems to respond are in place in many areas of the world, traditional approaches can be too slow or limited in scope to prevent biological events from becoming severe, even in the best of circumstances. For example, influenza is readily transmissible from person to person, and the world has not yet been able to prevent an influenza epidemic from spreading globally. As another example, the spread of Ebola in West Africa had catastrophic effects for residents in affected countries before the global response gained traction and brought the epidemic under control.

Traditional outbreak response has historically relied on simple, low-tech tools. These tools, including paper and pencil, must be rugged, adaptable, and user-friendly because of field conditions, resource constraints, and the chaotic nature of crises. This type of response remains critically important for today's emergencies, but it can and should be augmented by novel methods and technologies to improve the speed, accuracy, and reach of the response.

Broadly, there are 2 communities that develop and/or use technological innovation in the course of responding to public health crises: the public health and global health community and the applied life sciences community.

In global health, a new level of awareness of and focus on technological innovation for epidemic response arose during and following the 2013-2016 Ebola epidemic in West Africa. Organizations like the World Economic Forum published commentaries on technology needs in response to epidemics, and the US Agency for International Development (USAID)—in partnership with the White House Office of Science and Technology Policy (OSTP), the US Centers for Disease Control and Prevention (CDC), and the Department of Defense (DoD)—issued a grand challenge on fighting Ebola.¹ This program sought innovative technology solutions to address 6 categories of innovation, ranging from more effective and usable personal protective equipment (PPE) to technologies that support behavior change in communities. Following on the Ebola model, USAID also

issued a grand challenge for development to combat Zika and future threats,² which has garnered hundreds of responses. And like efforts around Ebola and Zika, some global health organizations have focused on developing technologies to improve access to and quality of healthcare and public health provision in under-resourced locations around the world.

The life sciences community, including academic and government laboratories and biotechnology and pharmaceutical companies, are often called on in the midst of public health crises to research and develop therapeutics, vaccines, and medical devices (commonly referred to as medical countermeasures, or MCMs) to help in addressing an outbreak. For example, the VSV vaccine currently being tested in the Democratic Republic of the Congo against Ebola underwent rapid research and development by government-funded laboratories during the last Ebola crisis. The product was then acquired by a large pharmaceutical company, Merck, to enable clinical testing and scale-up. Outside of public health crises, the life sciences community is working to develop innovative approaches to MCM development and diagnostics that can be useful for both routine and emergent threats to global health.

Beyond these 2 communities, the innovation landscape for health emergencies is ad hoc and not well institutionalized. The application of other types of technologies, such as IT, wearables, and drones, which are having transformative effects on other parts of the global economy, have largely not been used to help address outbreaks.

Programs and Organizations Working on Technologies for Infectious Disease Prevention and Response

Because the concept of global catastrophic biological risk is relatively new, this is the first

analysis to focus on assessing technologies for the purpose of reducing GCBR. However, there are other important, ongoing efforts to assess and develop technologies that address infectious disease threats, including pandemics; emerging infectious diseases in humans, plants,

and animals; intentional biological threats; and global health. While these efforts (see below) are not targeted directly at responding to potentially catastrophic biological risk, some will be directly or indirectly relevant to GCBR reduction.

The Coalition for Epidemic Preparedness Innovations (CEPI) was established in 2017 to support and manage the development of new vaccines for infectious diseases. This initiative limits its research and development (R&D) efforts to the period between new drug discovery research and vaccine delivery to the public, and it encompasses advanced R&D and clinical trials to ensure safety and efficacy.

The Defense Advanced Research Projects Agency (DARPA) Biological Technologies Office (BTO) has a unique focus on addressing potentially serious biological threats—both intentionally caused and naturally occurring. There are a number of programs at DARPA, including the **Pandemic Prevention Platform (P3)** and **Safe Genes** projects, among others, that will be important for mitigating GCBRs. DARPA-BTO's focus is specifically military threats and applications, but it also aims to protect domestic and global civilian populations from serious biological threats.

The **Global Health Technologies Coalition** has a specific focus on R&D for technologies that improve global health generally. Their initiatives include technologies that may be useful in a pandemic or GCB event, but they are mainly geared toward improving day-to-day public health and health care around the world in non-emergencies.

The **In-Q-Tel Lab BNext** is focused on demonstrating the power of technologies to identify and mitigate infectious disease outbreaks. In particular, BNext focuses on integrating novel data technologies into public health response to epidemics with the goal of improving the speed and efficacy of response operations in order to save lives and minimize economic, political, social, and military impacts.

The Intelligence Advanced Research Projects Activity (IARPA) has a number of programs on detection and response to epidemics, primarily focused on intentional or accidental events and intelligence collection problems. Programs like **FunGCAT** and **FELIX** specifically aim to reduce risk from novel threats arising from advances in genetic engineering, and programs like **OSI**, **SILMARILS**, and **MOSAIC** are focused on surveillance for health events using a variety of sources. These programs will be beneficial to national security and biotechnology as a whole.

Microsoft and IARPA's **Project Premonition** aims to “detect pathogens before they cause outbreaks,” specifically through analysis of DNA obtained from the blood meals of captured mosquitoes. Their work is focused on developing drones that find mosquitoes, traps that collect mosquitoes, and genomics and machine learning approaches to identifying and understanding pathogens that might be present in mosquito samples.

FIND is an international organization that focuses on developing and delivering diagnostic technologies for infectious diseases with outbreak potential, particularly to low-resource settings around the world.

Purpose of the Project

The purpose of this project is to raise awareness of powerful technological solutions that may get us closer to our collective objective of improved preparedness and response to pandemics and global catastrophic biological events. This project was designed to explore extant and emerging technologies with the potential to radically alter the trajectory of severe infectious disease events with catastrophic potential for humanity.

We recognize that reducing GCBRs is a multifaceted, complex undertaking and that novel technologies alone will not be a panacea; people, policies, consistent funding, infrastructure, and aligned incentives will also be extremely important. Additionally, we recognize that other critical work is already ongoing in both the public and private sectors in adjacent areas such as vaccine and drug development, biosurveillance, epidemiology, ecology and conservation, and plant and animal health to address these risks. This project does not aim to duplicate existing efforts.

It is broadly true, however, that the adoption and use of novel technologies for the purpose of epidemic control and public health often lag well behind the innovation curve because they do not have a lucrative market driving their development. This leaves unrealized opportunities for improved practice.

Goals of the Report

To enable and enhance the positive use of technologies for response to serious infectious disease threats, this report identifies technologies that, with strategic investment over the next 5 to 10 years, might significantly reduce GCBRs. This is not an exhaustive list or an endorsement of specific companies, but it provides examples of technologies that we identified as potentially transformative. We generated this list through a review of the field and interviews with a wide array of experts.

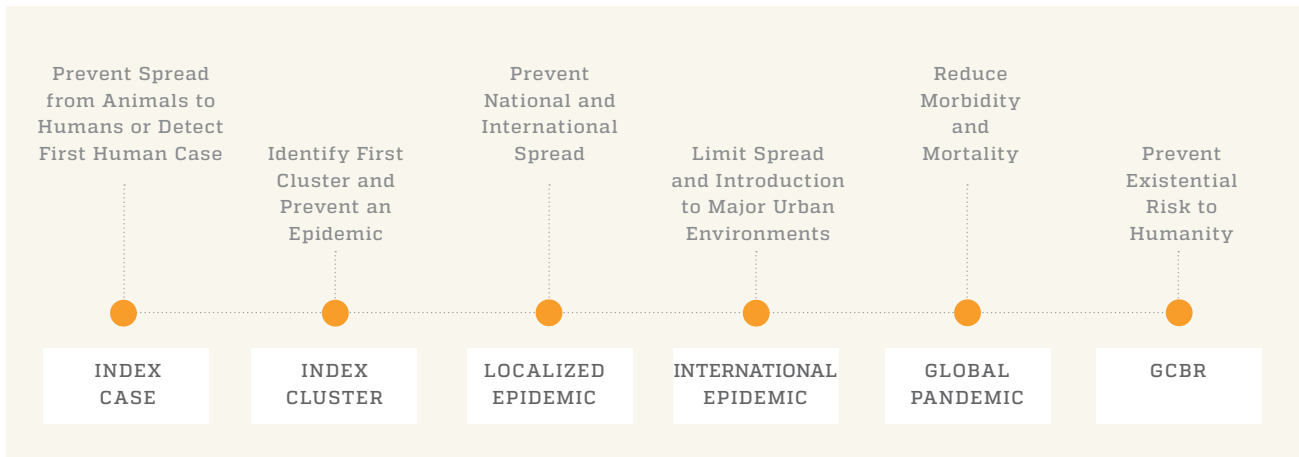
The primary goals of this report are to:

- Pinpoint areas of need for technological solutions to address severe pandemics and global catastrophic biological events;
- Identify technologies that have significant potential to reduce GCBRs; and
- Provide context for those technologies, demonstrating their promise, limitations, and conditions under which they might be developed and employed successfully.

This report should be used to guide further detailed analyses of the viability, use cases, and resource needs to realize the benefits of these and similar technologies.

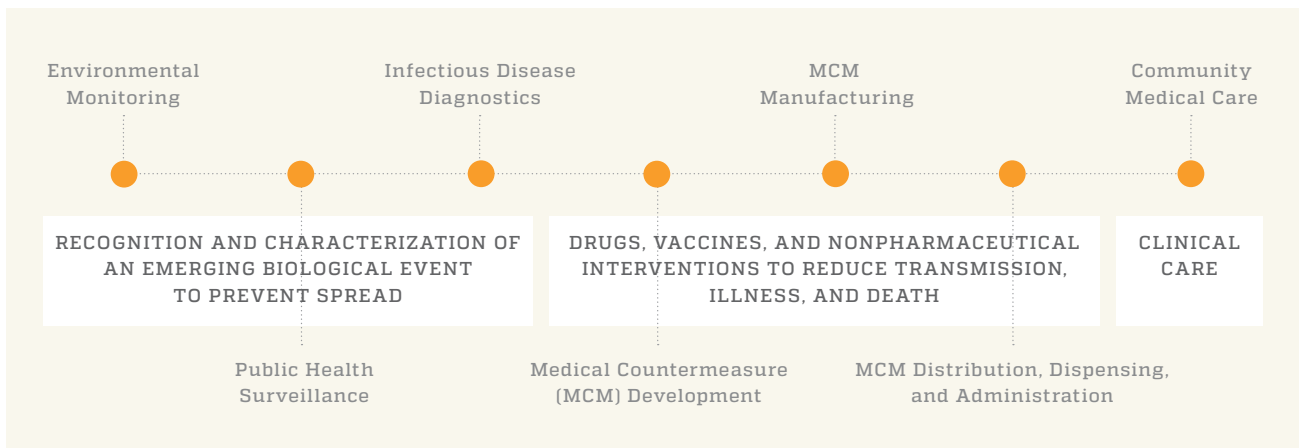
Framing Technology Requirements for This Report

In broad terms, in order to alter the course of a potential global catastrophic biological event, technologies must either help prevent the emergence and geographic spread of a biological pathogen or reduce disease severity and societal consequences, or both. Several inflection points exist during an unfolding biological event at which effective interventions can be implemented with maximal impact to interrupt event progression. Here are examples of those potential points of intervention:



Technologies can be applied at each of these inflection points in a number of ways to reduce biological risk, including through:

- Better detection, surveillance, and characterization of a GCB event such that action can be taken to quickly prevent or quell a biological event; or
- Increased speed and global extent of the response, in both high- and low-resource settings, to mitigate the impacts of an unfolding event.



Severe pandemics and catastrophic biological events are qualitatively and quantitatively different from the epidemics and health threats we face regularly. Because these events are so severe, a focus on prevention and early detection should be a priority in order to avert a catastrophe. Should a severe pandemic emerge, response will need to be global. Many countries will not have the capacity to respond effectively, which will make

the whole world vulnerable. So, to facilitate response, diagnostics, medical countermeasures, and medical care will need to be available and accessible in a timely way to all affected countries.

Properties of the technologies needed to help reduce these risks are also likely to be qualitatively and quantitatively different from those used in routine public health and medical practice. Throughout this research, we focused on a number of properties that transformative

technologies in GCBR reduction might possess. These include:

- Better sensitivity to facilitate prevention;
- Improved capacity to make response decisions earlier;
- Distributed approaches to improve scale and access;
- Rugged or easy to use in a variety of settings; and
- Reduced time lags in development, availability, and fielding.

Methodology

TECHNOLOGY IDENTIFICATION PROCESS

Because global catastrophic biological risks are a relatively new topic of interest and inquiry, one would not expect to find a well-established body of literature surrounding this problem. However, to identify potentially relevant technology solutions for GCBRs, we conducted a horizon scan to understand the technology space and highlight areas of technology development and upcoming changes that could benefit GCBR reduction.³ As part of the horizon scan, we conducted a literature review and interviewed experts in the field to inform judgments regarding the current and future state of the science.

LITERATURE REVIEW

In order to identify potential transformative technologies and prospective experts for interviews, we conducted an initial literature review of emerging technologies. We reviewed non-peer-reviewed grey literature, including company press releases and technology reviews, and peer-reviewed scientific literature for recent developments in the biological sciences and biotechnology. Searches were conducted through PubMed, Google, Google Scholar, and Web of Science databases, looking back 5 years. This was not a comprehensive review of existing

technologies, as such a review would have had to cover a vast technology space; however, it did result in the identification of emerging themes and industries, technology areas for further investigation, and individuals to interview.

Specific technologies that were identified as candidates for inclusion in this report garnered additional, more targeted literature reviews to gain a deeper understanding of the state of the technology as well as to inform judgments of how technologies might be applied to GCBR reduction.

SEMI-STRUCTURED INTERVIEWS WITH EXPERTS

The research team iteratively identified potential interviewees through the literature review and through snowball sampling from recommendations of other experts. We sought input from experts with a broad view of emerging technologies as well as those with deeper subject matter knowledge on specific technologies. Areas of expertise represented in the interviews included bioinformatics, computer science, drones, robotics, microbiology, synthetic biology, agricultural science, epidemiology, chemistry, bioengineering, and vaccine and diagnostic development, among others. We did not attempt to achieve a statistically representative sample of technology experts, but we did aim to gather input from individuals with a range of perspectives and from a variety of technology areas. In total, we spoke with 53 experts (Appendix I) between June and December 2017.

The research team conducted semi-structured interviews based on an initial set of questions specifically developed to provide interviewees with the opportunity to describe potential technologies of interest (Appendix II).

Researchers conducting the interviews then probed further on various topics that emerged over the course of the interviews. For example, when interviewees suggested technologies that they believed could make a significant

impact on GCBRs, we invited them to envision how these technologies could be used operationally, to explore the potential speed with which these interventions could be brought to bear on an emerging GCBE, and to describe how these technologies could fill current gaps in response. All interviews were conducted by at least 2 team members, but often the full research team was in attendance. After each interview, we discussed salient themes and determined if additional literature review was required.

TECHNOLOGY EVALUATION PROCESS

The evaluation and assessment of technologies occurs frequently in both the public and private sectors, and multiple approaches have been developed to aid funders and technologists. One institution that has become synonymous with innovation is DARPA. From 1975 to 1977, George Heilmeier was the director of DARPA. In order to routinize the technology evaluation process and guide funding decisions, he developed the following series of questions, which became known as the Heilmeier Catechism:^{4,5}

- What are you trying to do?
Articulate your objectives using absolutely no jargon.
- How is it done today, and what are the limits of current practice?
- What is new in your approach, and why do you think it will be successful?

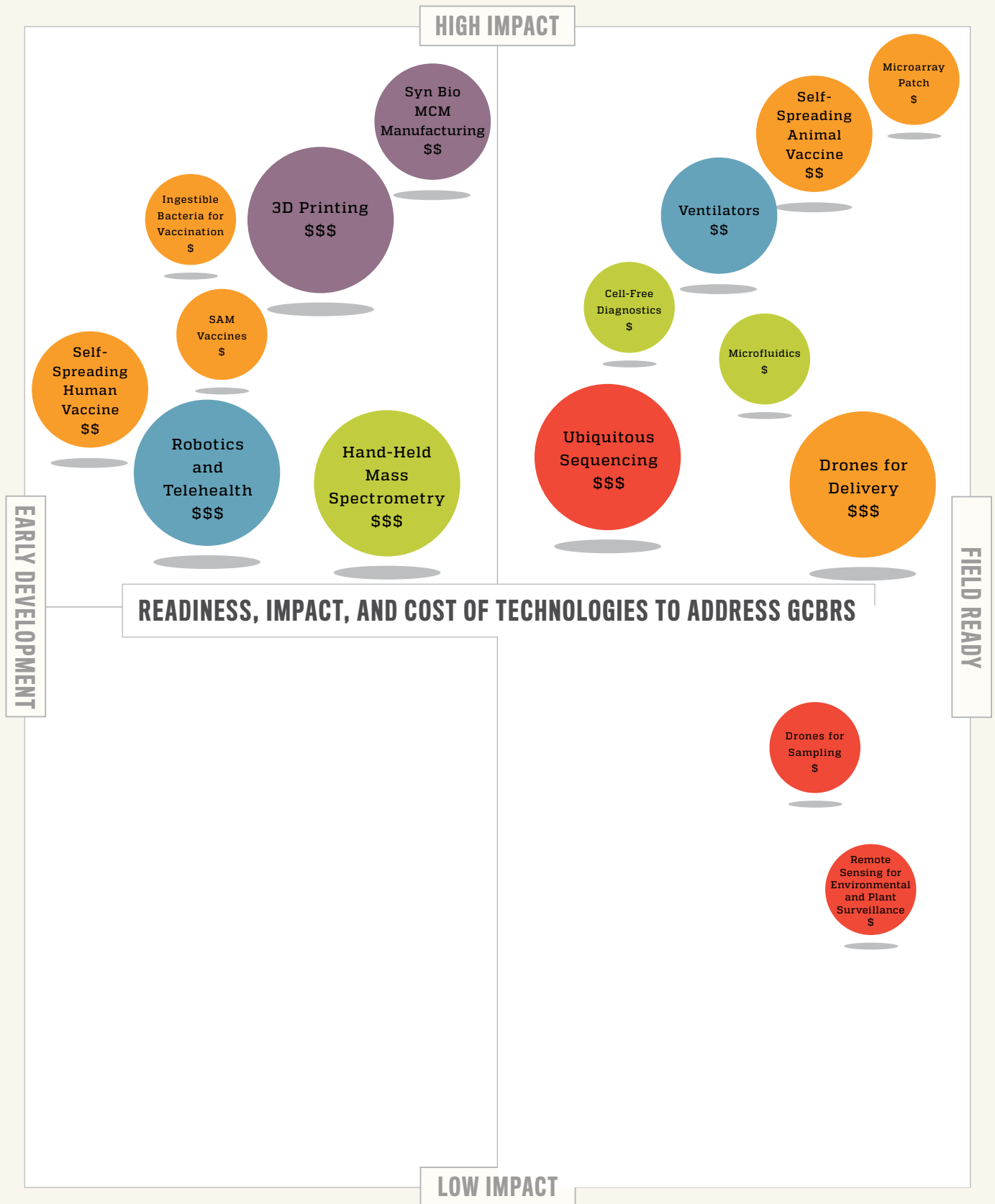
- Who cares? If you are successful, what difference will it make?
- What are the risks?
- How much will it cost?
- How long will it take?
- What are the mid-term and final “exams” to check for success?

The research team perceived value in this approach and tailored Heilmeier’s questions to this project’s specific aims, resulting in the following questions:

- What is the technology?
- What problem does it solve?
- How do we do it now?
- What does success look like?

These questions provided a common framework with which to describe and evaluate the potential impact of the identified technologies and technology classes that may be used to detect or counter a GCB event. Based on the literature review and the interviews with experts, the research team evaluated each candidate technology using the Heilmeier-inspired questions above, prepared a summary of findings (including key readings), and provided a high-level judgment regarding:

- The readiness of each technology (from early development to being field-ready);
- The potential impact of the technology on GCBR reduction (from low to high); and
- The amount of investment that would be needed to meaningfully deploy the technology (from low \$ to high \$\$\$).



Review and Revision Process

Following the technology selection process and the initial drafting of this report, we asked a subset of selected interviewees (Appendix III) and other subject matter experts to review the draft document. Reviewers were asked to provide comments on the report as a whole and on individual sections or technology descriptions to ensure that the assessment accurately represented the state of the technology. Comments and suggestions from reviewers were incorporated into the final report.

Much of this report focuses on specific technologies or technology applications that could be directly beneficial in preventing, detecting, or responding to GCB events. However, those technologies cannot be implemented in isolation;

Overarching Themes in Technologies

they all rely on systems, people, and policies to function. This section discusses overarching approaches or interstitial technologies that enable data collection, analysis, and sharing, and without which many of the technology benefits highlighted in this report could not be realized.


DNA Sequencing

It has been just over 40 years since DNA sequencing was first conducted and just under 20 years since the start of the human genome project, which aimed to sequence the 3 billion nucleotide bases that comprise the human genetic code. It took approximately 13 years to sequence the first human genome, at a cost of more than US\$3 billion. Today, those 3 billion bases can be sequenced in a matter of days and for about \$1,000. Sequencing technologies have advanced so rapidly that their capabilities far exceed expectations based on Moore's Law, which predicts that computing speed should double every 2 years.⁶

As DNA sequencing technologies continue to progress, applications of sequencing will likely become much more useful for addressing a variety of infectious disease threats. Sequencing is already a necessary component in detecting an emerging pathogen, identifying pathogen mutations and susceptibility to

various treatments, and developing vaccines and therapeutics. In the future, it is likely that sequencing will become more democratized and decentralized, which, in turn, could enable more rapid and effective prevention of and response to potentially serious emerging epidemics and other biological emergencies around the globe.

Enabling Approaches for Data Collection, Analysis, and Sharing

Big data, whether collected through epidemiological and environmental surveillance or genetic sequencing, is an important challenge in addressing GCB events. While generating these data is necessary and important, there must also be an accompanying capability to share, interpret, and extract useful information in order to apply findings to reducing biological risk and advancing pandemic preparedness and response. 

OVERARCHING THEMES IN TECHNOLOGY

OMICS

Fields such as functional genomics, transcriptomics, and proteomics aim to harness new information and tools to characterize the structure, function, and dynamics of biological units such as genes, RNA transcripts, and proteins. This can help in understanding how biological pathogens and human immune systems function and can make discovery of vaccine and drug targets faster and more efficient. For example, innovations in proteomics now allow high-throughput characterization of the structures and functions of large numbers of proteins, thus enabling drug discovery platforms, identification of vaccine candidates, understanding of pathogenicity mechanisms, and detection of diagnostic markers. To date, researchers have developed several public and commercial proteomic databases to help facilitate research and analysis, including: **The Human Protein Atlas**, **Global Proteome Machine Database (GPMDB)**, **DeepPep**, **UniProt**, **neXtProt**, and **Geonomenon**. Additionally, the **ProteomeXchange Consortium** combines world-leading mass spectrometry (MS)-based proteomics repositories, such as the **PRIDE** database (UK), **PeptideAtlas**, **MassIVE** (US), and **jPOST** (Japan) all into one easy-to-use open-access website.

BIG DATA ANALYTICS AND ARTIFICIAL INTELLIGENCE

Recent advancements in artificial intelligence (AI) are now being harnessed to analyze massive genomic and proteomic data sets in order to extract clinically relevant

findings. For example, one leader in this field—**Deep Genomics**—uses its AI platform to map pathological genetic pathways to inform drug development. In addition, Google recently released its own genomic AI platform, called **DeepVariant**, which won the 2016 **PrecisionFDA Truth Challenge**, a contest held by the US Food and Drug Administration to help improve the quality and accuracy of genetic testing. One potential application of big data and AI technologies for GCBR reduction is in interpreting ubiquitous environmental pathogen sequencing data to accurately analyze and interpret the vast amount of information gathered in order to provide early detection or advance warning of potentially serious biological events.

DATA SHARING

Many of the technologies in this report rely on internet connectivity, but it is important to remember that many parts of the world are without reliable internet connection.

Current estimates suggest that 53% of the world's population is still not connected to the internet—meaning more than 4 billion individuals still do not have access.⁷ Current models of internet distribution rely on towers that transmit and receive radio waves, which requires the acquisition of land rights as well as the equipment, connectivity, and electricity needed to operate the tower. Establishing this infrastructure in low-resource or rural areas may be challenging or prohibitively expensive.

Google's Project Loon is aimed at tackling this problem, with the ultimate goal of expanding internet connectivity to rural and remote areas around the world. Project Loon uses precise decision-making algorithms to move large balloons attached to transceivers into place, and project radio waves that provide wireless internet service over long distances. The program will place its technology in the stratosphere (20 km above ground), which will allow it to avoid aberrant weather conditions and commercial aircraft.

KEY READINGS

Alipanahi B, Delong A, Weirauch MT, Frey BJ. Predicting the sequence specificities of DNA- and RNA-binding proteins by deep learning. *Nat Biotechnol* 2015;33(8):831-838. <https://www.nature.com/articles/nbt.3300>. Accessed February 28, 2018.

Martens L, Vizcaino JA. A golden age for working with public proteomics data. *Trends Biochem Sci* 2017;42(5):333-341. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5414595/>. Accessed February 28, 2018.

Patel K, Singh M, Gowda H. Bioinformatics methods to deduce biological interpretation from proteomics data. *Methods Mol Biol* 2017;1549:147-161. https://link.springer.com/protocol/10.1007%2F978-1-4939-6740-7_12. Accessed February 28, 2018.



Disease Detection, Surveillance, and Situational Awareness

A number of emerging technologies and methodologies focus on improving infectious disease surveillance, and situational awareness generally, with specific attention to early detection. Often referred to as digital disease detection or digital epidemiology, these methods rely on novel sources of surveillance data, including genomic sequencing and sensing, social media and internet search logs, satellite imagery, or over-the-counter drugstore transaction data.

Traditional surveillance strategies rely on either passive reporting from the healthcare delivery system (eg, electronic medical records or laboratory results) or active reporting from healthcare providers. Although these methods provide reliable, high-quality data, they depend heavily on individuals seeking care. Data on those who either do not need care or are not able to seek it are not captured. Furthermore, traditional surveillance strategies can be delayed, both because of the gap between symptom onset and care-seeking and the delays inherent in reporting mechanisms.

Nontraditional surveillance strategies purport to overcome these shortfalls by monitoring changes in patterns in the community or the environment. Indicators may be nonspecific, like an increase in the number of people searching for flu symptoms online, or they may be pathogen-related, like detection of a novel virus in the environment. In either case, nontraditional surveillance sources function best as supplements to, not replacements for, traditional surveillance systems.



Proponents of nontraditional surveillance strategies believe that they enable faster detection of emerging outbreaks. They argue that earlier detection—either in the environment or in the first case patients infected—can enable a faster public health response, potentially preventing outbreaks from growing out of control through early intervention. Earlier detection could also shorten the time to initiation of MCM research and production, which sometimes is delayed for weeks or months. After an outbreak is established, nontraditional surveillance could give a more comprehensive understanding of what is happening in the community. For example, if the number of people needing care exceeds the capacity of the healthcare system, traditional surveillance systems will underreport the number of people infected. Nontraditional surveillance systems can supplement situational awareness by drawing on other data streams.

The project team believes that nontraditional surveillance strategies, when combined with actionable interventions, have the potential to prevent a GCB event. Surveillance technologies should provide sufficiently compelling evidence to convince epidemiologists, public health practitioners, and political leaders to launch a timely and robust response. Existing syndromic surveillance systems have been plagued with challenges in interpreting signals,^{8,9}

incorporating additional nontraditional data sources would only compound this challenge. In order to be successful, nontraditional surveillance strategies used for detection need to provide strong and compelling evidence that an outbreak has the potential to be a GCBR—well before that possibility is recognized through traditional means. It would need to have a documented track record as a sensitive and specific indicator, and it would need to convey the scope and speed of the outbreak's spread. For situational awareness, syndromic surveillance systems must have a documented track

record of accurately reflecting disease burden in the community, and they should do so in a timely way, with enough geographic resolution to support outbreak response operations.

Surveillance is primarily useful in directing targeted containment efforts enabled through contact tracing, for assessing risk, and for guiding deployment of assets. After a certain threshold (which will certainly be crossed in a GCB event), there is diminishing utility in that strategy. Population-level containment efforts, like universal social distancing, will be more efficient and effective.

KEY READINGS

Brownstein J, Freifeld C, Madoff L. Digital disease detection—harnessing the web for public health surveillance. *N Engl J Med* 2009;360(21):2153-2155, 2157.

German RR, Lee LM, Horan JM, Milstein RL, Pertowski CA, Waller MN; Guidelines Working Group, Centers for Disease Control and Prevention. Updated guidelines for evaluating public health surveillance systems: recommendations from the Guidelines Working Group. *MMWR Recomm Rep* 2001;50(RR-13):1-35.

Reingold AL. If syndromic surveillance is the answer, what is the question? *Biosecur Bioterror* 2003;1(2):77-81. <https://doi.org/10.1089/153871303766275745>. Accessed June 6, 2018.

Steiner-Sichel L, Greenko J, Heffernan R, Layton M, Weiss D. Field investigations of emergency department syndromic surveillance signals—New York City. *MMWR Suppl* 2004;53:184-189.

Terry W, Ostrowsky B, Huang A. Should we be worried? Investigation of signals generated by an electronic syndromic surveillance system—Westchester County, New York. *MMWR Suppl* 2004;53:190-195.

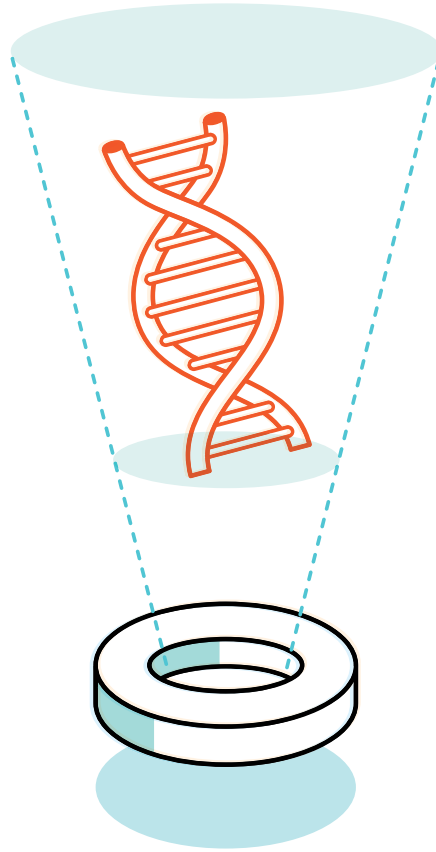


Ubiquitous Genomic Sequencing and Sensing

WHAT IS THE TECHNOLOGY?

The ability to rapidly, accurately, and affordably determine the nucleotide sequence of genes or gene fragments in a given sample is one of the most important advances in the history of the biological sciences. It has substantially improved our ability to detect and describe microbial life. Increasingly, sequence data can provide insights into biological functions, including pathogenicity, transmissibility, and resistance profiles.

Recent technological advances and reduced costs have raised the possibility that sequencing technologies can be significantly expanded in the near future—called “ubiquitous sequencing.” As computational and analytic tools are developed and refined, this flood of sequence data will be translated into an advanced genomic sensing capability that would provide unprecedented awareness and knowledge of the microbiome. One application of these new sensing tools would be the monitoring of a variety of substrates and settings for the presence of known or novel



pathogens, strains, or phenotypes. Genomic sensing systems could be established that would continually monitor the air, water, soil, transportation hubs, mass gatherings, farms, and other microenvironments relevant to pathogen transmission.

To achieve this vision, mobile and easy-to-use sequencing technologies will be needed, and strategic planning regarding what, where, and when to sequence will be essential. Current bottlenecks related to the storage, interpretation, and analysis of large amounts

of genetic information will have to be overcome. But in a testament to the importance of the concept of ubiquitous sequencing, most technologists who participated in this project raised the concept in some way.

One advancement that may enable ubiquitous sequencing, and eventually sensing, is the introduction of nanopore sequencers. Nanopore sequencing is a process by which strands of DNA are transported across a membrane through an electrified carbon nanopore. The physical passage of nucleotides (ie, the constituent molecules of DNA: adenine, thymine, guanine, and

cytosine) through the nanopore generates a change in electrical resistance based on the nucleotide’s distinct shape, which then provides the specimen’s genetic sequence. These devices, as exemplified by Oxford Nanopore Technology’s **MinION**, are extremely portable—they are roughly the size of a candy bar—and are capable of being deployed in nontraditional settings. For example, nanopore sequencers have been used to generate genomic information in outbreak settings including **West African Ebola** and **Zika’s** expansion in the Americas.

WHAT PROBLEM DOES THIS SOLVE?

From an epidemiologic perspective, the rapid availability and analysis of sequence data has become a hallmark of the modern infectious disease outbreak response. From SARS onward, it has become routine and expected that a group of microbiologists with access to samples of the causative pathogen will sequence it and make those data available in a publicly maintained repository like GenBank, where it can inform the practice of epidemiology and medical countermeasures research and development.

One significant benefit of using sequencing technologies as surveillance and diagnostic tools is that they are unbiased. Other molecular diagnostics, such as polymerase chain reaction (PCR), are used to test for the presence of a known pathogen or, in the case of multiplexed assays, multiple pathogens. But if properly implemented, sequencing can be used to identify any pathogen for which samples are available. This is true for both nanopore sequencing and other next-generation sequencing modalities.

The response to infectious disease emergencies would look very different in a world in which genomic sequencing and sensing is ubiquitous. Because these technologies could be widely distributed and networked, the identification, characterization, and analysis of emerging, engineered, or novel pathogens would be expedited. In addition, sequence data can yield significantly more information than current molecular diagnostics. Subsequent interventions such as surveillance, outbreak investigation, and medical countermeasure research would benefit from having more granular information more quickly about the pathogen of interest.

HOW DO WE DO IT NOW?

Before the introduction of nanopore sequencing technology, sequencing was more centralized and laboratory-based. Sequencing technologies were used primarily as tools for research. However, this technology has recently been deployed in outbreak settings—first during the West African Ebola epidemic and then again to characterize the recently emerged Zika virus in South and Central America, where it provided valuable information that helped to guide the responses. Increasingly, powerful sequencing technologies of various kinds are being applied to more practical problems in clinical and public health settings. Despite these successes, however, truly ubiquitous sequencing and sensing has not yet come to fruition.

Although they show promise, all sequencing platforms are plagued by a common set of issues: Sample preparation, analytics, bioinformatics, interpretability, and the overall usability of these tools need to improve if they are to be used more broadly, including by nonexperts.

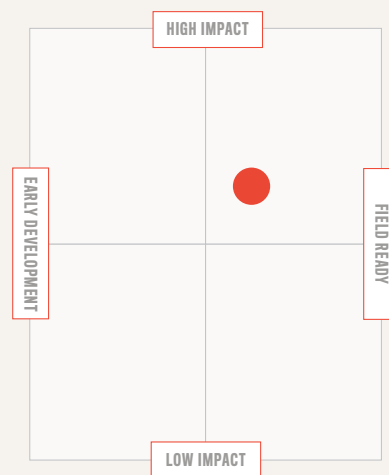
WHAT DOES SUCCESS LOOK LIKE?

Ubiquitous sequencing and sensing appear to hold significant promise for applications relevant to preparedness for and response to GCB events. Three fields in particular—public health surveillance, clinical diagnostics, and medical countermeasure research and development—can benefit significantly from the continued improvement and use of sequencing technologies. As a surveillance tool, ubiquitous sequencing would allow for the near-real-time characterization of pathogen biology, including determining virulence, transmissibility, and sensitivity or resistance to medicines or vaccines. In the future, these tools may also be able to provide evidence of genetic enhancement or modification.

Further refinement of nanopore sequencing technologies will result in their being taken up by a much broader range of users across multiple fields of study. In particular, the further development of large genomic databases and tools that allow for rapid cross-referencing of sample sequences will be valuable.

As a result of this transition from research tool to real-time

sensor, sequencing technologies can enable the collection of data from nontraditional sources. For example, recent proposals have included sequencing the contents of airline lavatories, hospital laundries, municipal sewage systems, and air-handling systems to detect the presence of high-consequence pathogens, possibly providing advance warning of an impending biological event.



KEY READINGS

Erlich Y. A vision for ubiquitous sequencing. *Genome Res* 2015; 25(10):1411-1416. <https://www.ncbi.nlm.nih.gov/pmc/articles/MC4579324/>. Accessed June 6, 2018.

Nordahl Petersen T, Rasmussen S, Hasman H, et al. Meta-genomic analysis of toilet waste from long distance flights; a step towards global surveillance of infectious diseases and antimicrobial resistance. *Sci Rep* 2015;5:11444.

Quick J, Loman NJ, Duraffour S, et al. Real-time, portable genome sequencing for Ebola surveillance. *Nature* 2016;530(7589):228-232. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4817224/>. Accessed June 6, 2018.

Timp W, Mirsaidov UM, Wang D, Comer J, Aksimentiev A, Timp G. Nanopore sequencing: electrical measurements of the code of life. *IEEE Trans Nanotechnol* 2010;9(3):281-294. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3092306/pdf/nihms285056.pdf>. Accessed June 6, 2018.



Drone Networks for Environmental Detection

WHAT IS THE TECHNOLOGY?

Drones are unmanned vehicles—typically associated with aircraft (eg, unmanned aerial vehicles, or UAVs), but terrestrial, aquatic, and subaquatic vehicles exist as well—that can be directly controlled by a remote operator or operated autonomously using preprogrammed instructions. They are perhaps best known for their military applications, including aerial reconnaissance or weapons systems, but drone technology also extends to civilian recreational and commercial applications. These vehicles

can carry a range of payloads and perform a wide variety of functions, depending on the specifications and purpose of the particular unit. System capabilities are primarily a function of 3 factors: (1) fuel capacity (eg, battery), (2) drone and payload mass, and (3) mission parameters (eg, required range, duration, and purpose).

Although drone technology is not new, it has gained popularity with the recent introduction of commercially available off-the-shelf units that are equipped with GPS and cameras. These advances have also enabled public health

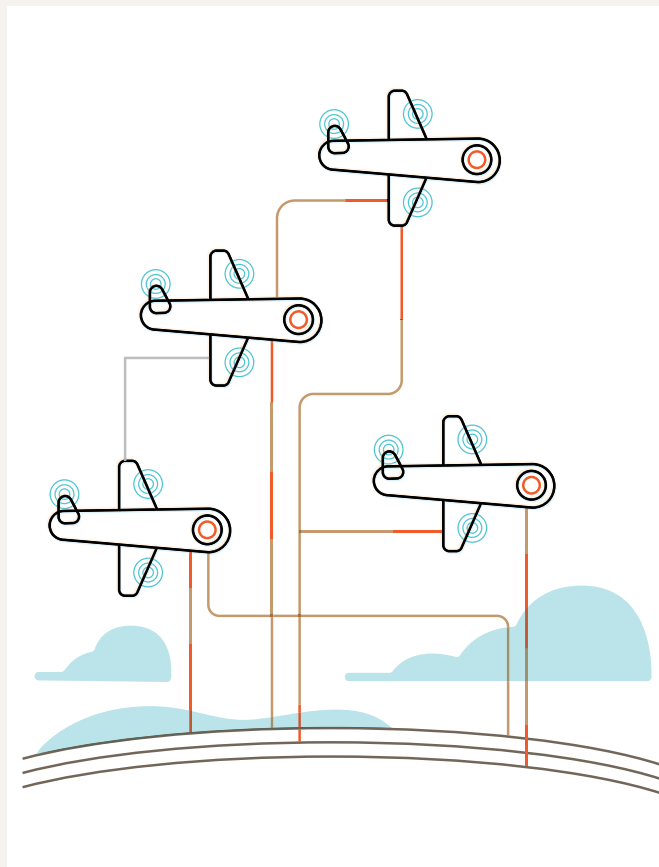
applications of drones. For example, they can be used to collect air and water samples to monitor the environment to detect emerging events, such as an aerosol biological attack or a potentially catastrophic change to environmental ecosystems. Drones are already used to monitor air and water quality and can be fitted with autonomous sample collection and analysis technologies like real-time PCR and sequencing platforms. This capability enables onboard analysis rather than requiring a laboratory to process samples. When multiple drones are used and networked together, they can conduct ongoing environmental surveillance.

WHAT PROBLEM DOES IT SOLVE?

Drones can enable collection of information in areas where humans cannot feasibly operate—for example, areas that are difficult to access or that are contaminated.

Currently, there is no comprehensive strategy in the United States or globally for conducting environmental surveillance. A deliberate aerosol release of a biological agent or a disruption to critical ecosystems could potentially go unnoticed until the effects were very harmful or even irreversible. The

current lack of surveillance is due, in part, to the enormous challenge of surveilling, testing, and analyzing diverse and remote ecosystems. With drone technology, this process could be largely automated to a degree that has not been possible. But even extensive drone networks would leave large swaths of land, air, and sea either unsurveilled or surveilled only intermittently. This technology will be most useful in improving general situational awareness rather than in implementing universal surveillance.



HOW DO WE DO IT NOW?

Environmental surveillance to identify potential GCB events is not routinely or systematically conducted. There are no serious efforts aimed at detecting major ecosystem disruptions, and current programs looking for intentional biological attacks are relatively limited in scope.

The US Department of Homeland Security operates the **BioWatch program**,¹⁰ which conducts airborne environmental sampling at fixed locations to identify bioterrorist attacks involving a limited number of biological threat agents. The BioWatch program also deploys mobile sensors to high-profile events, such as the **Super Bowl**,¹¹ to provide targeted surveillance. While BioWatch air sampling is automated, the system still requires manual retrieval of samples each day for testing at local laboratories, which can potentially **delay event detection** by 24 hours or more.¹² Other environmental surveillance programs, such as **sampling sewage systems to detect poliovirus circulation**,¹³ are almost entirely manual efforts, with similar inherent limitations in sampling and analysis processes and human resources required to implement them.

There are some scientists who observe ecosystems as part of their research portfolios and who may be in a position to identify threats, but there is no comprehensive system in place or framework to guide this type of wide-ranging ecosystem monitoring.

The current ad hoc, piecemeal approach to environmental surveillance is unlikely to provide the coverage or the quality of surveillance needed to detect a serious biological event. Considering the potential consequences of a major environmental change or a deliberate biological attack, this lack of systematic environmental monitoring is potentially a large gap.

WHAT DOES SUCCESS LOOK LIKE?

One way to help fill the environmental surveillance gap would be to have networks of land-, sea-, and air-based drones autonomously conducting environmental surveillance. Drones can traverse different ecosystems to collect data using a variety of sensors and tools, ranging from optical cameras to complex biotechnology.

In some cases, scientists have incorporated miniaturized versions of PCR and sequencing platforms into drones, for real-time sample testing onboard without the need to return to a laboratory.¹⁴ These advances could provide closer-to-

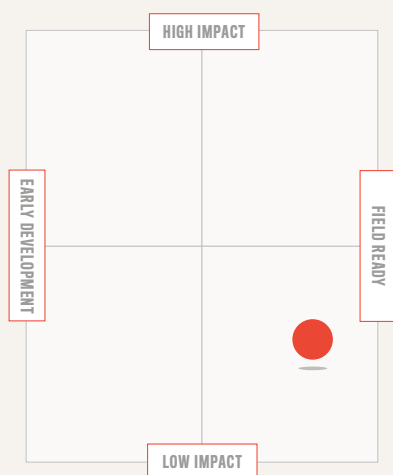
real-time identification of deliberate biological attacks. Drones also could be used to perform contamination assessments for known chemical, biological, or radiological events, testing the safety of affected environments without exposing humans.

Networked drones could help to conduct surveillance of important ecosystems by looking for significant changes in chemical or biological composition of the same substrates. They could also monitor specific biological organisms with important ecological roles, like phytoplankton and other marine plants, which are responsible for producing much of the oxygen needed for life on earth. Beyond complex biological, chemical, and radiological analyses, drones can conduct surveillance using photography and video equipment, which, when combined with measurement and imaging software, can be used to do things like track population activity and movement, assess vegetation and animal health, and detect acute events like explosions or chemical spills.

Despite the promise of drones to enable improved environmental surveillance, there are key obstacles to making this successful. Drones are the platform for data and sample collection, but they must be paired with accurate sensors to be useful for surveillance. These

technologies will need further maturation to make real-time detection reliable and scalable. In addition, a strategic framework for setting priorities and operational bounds for environmental surveillance is needed, as are resources dedicated to ongoing collection and analysis.

In addition, to implement this idea on a broad scale would require adapting legal and regulatory rules for autonomous vehicles. In the United States, there is a complex landscape of state and federal laws and regulations that make it difficult for a standardized approach to emerge. Finally, there are ethical and security implications of widespread environmental surveillance that should be considered to ensure that the negative impacts don't outweigh the positive capabilities that drone networks might provide.



KEY READINGS



Capolupo A, Pindozi S, Okello C, Boccia L. Indirect field technology for detecting areas object of illegal spills harmful to human health: application of drones, photogrammetry and hydrological models. *Geospat Health* 2014;8(3):S699-707. <http://www.geospatialhealth.net/index.php/gh/article/view/298>. Accessed March 2, 2018.

Capolupo A, Pindozi S, Okello C, Fiorentino N, Boccia L. Photogrammetry for environmental monitoring: the use of drones and hydrological models for detection of soil contaminated by copper. *Sci Total Environ* 2015;514:298-306. <https://www.sciencedirect.com/science/article/pii/S004896971500131X>. Accessed March 2, 2018.

Cruz H, Eckert M, Meneses J, Martínez J. Efficient forest fire detection index for application in unmanned aerial systems (UASs). *Sensors (Basel)* 2016;16(6):e893. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4934319/>. Accessed March 2, 2018.

Fornace KM, Drakeley CJ, William T, Espino F, Cox J. Mapping infectious disease landscapes: unmanned aerial vehicles and epidemiology. *Trends Parasitol* 2014;30(11):514-519. <https://www.sciencedirect.com/science/article/pii/S1471492214001469?via%3Dihub>. Accessed March 2, 2018.

Hernandez Bennetts V, Lilienthal AJ, Neumann PP, Trincavelli M. Mobile robots for localizing gas emission sources on landfill sites: is bio-inspiration the way to go? *Front Neuroeng* 2012;4:20. <https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/22319493/>. Accessed March 2, 2018.

Lega M, Kosmatka J, Ferrara C, Russo F, Napoli RMA, Persechino G. Using advanced aerial platforms and infrared thermography to track environmental contamination. *Environ Forensics* 2012;13(4):332-338. <https://www.tandfonline.com/doi/abs/10.1080/15275922.2012.729002>. Accessed March 2, 2018.

Marris E. Drones in science: fly, and bring me data. *Nature* 2013;498(7453):156-158. <https://www.nature.com/news/drones-in-science-fly-and-bring-me-data-1.13161>. Accessed May 22, 2018.

Martin J, Edwards HH, Burgess MA, et al. Estimating distribution of hidden objects with drones: from tennis balls to manatees. *PLoS One* 2102;7(6):e38882. <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0038882>. Accessed March 2, 2018.

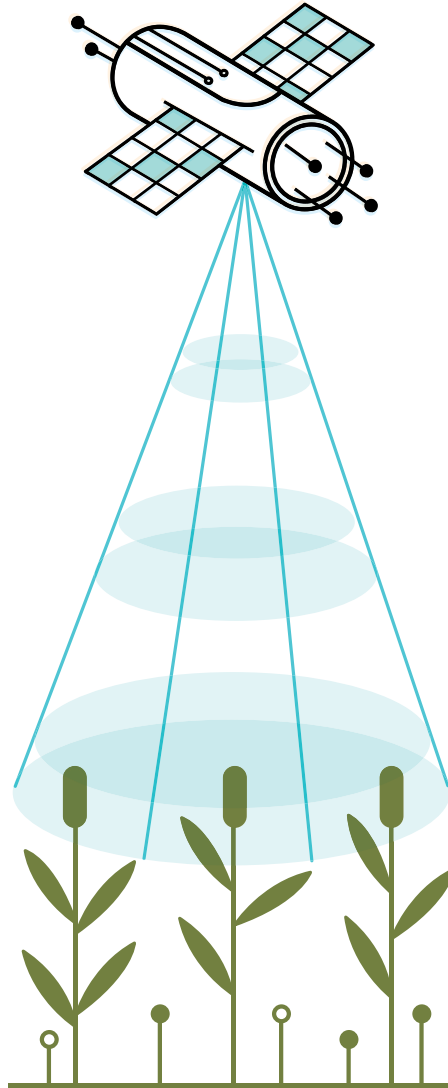
Wolinski H. Biology goes in the air: unmanned aerial vehicles offer biologists an efficient tool for observation and sampling from a safe distance. *EMBO Rep* 2017;18(8):1284-1289. <https://onlinelibrary.wiley.com/doi/pdf/10.15252/embr.201744740>. Accessed May 22, 2018.

Remote Sensing for Agricultural Pathogens

WHAT IS THE TECHNOLOGY?

Civilian satellite imaging has been used since the 1970s for exploration and natural resource management. The first such satellite, **LandSat I**, was capable of 80-meter ground resolution in 4 bands of the infrared spectrum. Over the subsequent decades, satellite technology has improved to facilitate resolutions of 1 meter or less for the entire planet. The range of imaging modalities has also broadened, so that multispectral, hyperspectral, 3-dimensional, and thermal data are also available. Modern consumers can purchase high-resolution remote sensing products—essentially off-the-shelf units—from commercial suppliers like **DigitalGlobe** or from government programs.

Multi-spectral and hyperspectral imaging, for example, can be used to detect and measure the intensity of different color bands of reflected light. This information can be used to assess remotely the health of plant leaves. The optical properties of healthy leaves appear different on imaging from diseased leaves, allowing identification of plant clusters that may be infected with pests or pathogens. These data



can even be used to characterize the disease symptoms of the affected plants, ranging from chlorophyll degradation to dryness.

Meanwhile, advances in digital image processing have enabled automated or semi-automated processing of satellite data. This allows for agricultural surveillance

to be done at scale, with thousands of images processed per day. These complementary technologies together enable ongoing, systematic remote sensing of crop health.

WHAT PROBLEM DOES IT SOLVE?

Extensive disruption to the complex and interdependent global food system would cause food shortages and price increases. Beyond the immediate effects, mass shortages could cause instability in social, economic, and political systems that could reshape the global landscape. This outcome is made somewhat more likely by the predominance of monocultures, which means that a single crop pathogen could severely reduce the yield of crops like corn, rice, or wheat.

Satellite surveillance for agricultural pathogens could mitigate that risk by enabling earlier detection and surveillance of diseased crops. If disease is detected early enough, farmers can contain affected plant clusters to prevent the disease from spreading. Failing that, plant scientists could develop chemical countermeasures or breed resistant strains that could be used to combat the outbreak before it grows large enough to threaten food security.

HOW DO WE DO IT NOW?

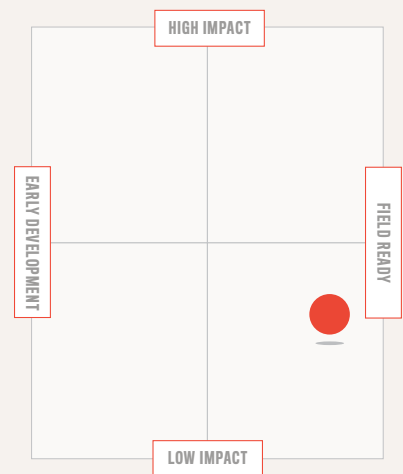
The current system for monitoring crop health is based on stakeholder engagement. Individual farmers monitor their land and report pest and pathogen problems to the National Plant Diagnostic Network (NPDN) or the US Department of Agriculture (USDA). Universities and cooperative extension offices may also identify and report problems. A 2007 Institute of Medicine report on global surveillance noted that for certain plant pathogens or plant systems, effective surveillance systems have been implemented, but these systems are not flexible enough to reliably detect or accommodate new or unusual biological events.¹⁵ Because they target known pathogens, these systems may overlook emerging threats. Imagery-based surveillance allows for more flexibility in detecting emerging threats.

WHAT DOES SUCCESS LOOK LIKE?

The technology to implement ongoing, widespread, systematic conduct of agricultural surveillance already exists in the form of high-resolution satellites and digital image processing methods. These technologies, if applied broadly and systematically, could be used to monitor the health of important crops and other vegetation in order to detect potential threats before they become widespread.

Yet, while the technologies needed to conduct satellite surveillance of plant pathogens already exist, what is missing in current capabilities, according to an Institute of Medicine report, is a central organization charged with monitoring and protecting agricultural security, like the CDC's charge for human health. Although the USDA and NPDN both have responsibilities in this area, their missions are more closely aligned with the short-term business interests of the agriculture industry than with long-term safety and security. A new entity, proposed as a National Center for Plant Biosecurity, could partner with farmers to integrate surveillance through remote sensing of crop

health with response operations to contain the outbreak. The realization of this vision would significantly reduce the risk of a devastating disruption to agricultural and food security.



KEY READINGS

Barbedo JGA. Digital image processing techniques for detecting, quantifying and classifying plant diseases. *SpringerPlus* 2013;2(1):660-671. <https://doi.org/10.1186/2193-1801-2-660>. Accessed June 6, 2018.

Institute of Medicine. Forum on Microbial Threats. Board on Global Health. *Global Infectious Disease Surveillance and Detection: Assessing the Challenges—Finding Solutions. Workshop Summary*. Washington, DC: National Academies Press; 2007.

Marques da Silva JR, Damásio CV, Sousa AMO, Bugalho L, Pessanha L, Quaresma P. Agriculture pest and disease risk maps considering MSG satellite data and land surface temperature. *Int J Appl Earth Obs Geoinf* 2015;38:40-50.

West JS, Bravo C, Oberti R, Lemaire D, Moshou D, McCartney HA. The potential of optical canopy measurement for targeted control of field crop diseases. *Annu Rev Phytopathol* 2003;41(1):593-614. <https://doi.org/10.1146/annurev.phyto.41.121702.103726>. Accessed June 6, 2018.

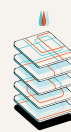


Infectious Disease Diagnostics

In addition to surveillance and detection of potential global catastrophic biological events, rapid and accurate diagnostic capabilities are critical to identifying cases of infectious disease and ensuring that appropriate interventions, both medical and nonmedical, are implemented. One of the biggest challenges in outbreak response, particularly for emerging infectious diseases, is the availability of reliable diagnostic assays that can quickly and accurately determine infection status. This capability is especially important early in an outbreak, as responders attempt to characterize the pathogen and disease and contain the outbreak while it is still a manageable size. For example, WHO identified poor diagnostic availability early in the outbreak as a principal barrier to containing the 2013-2016 West Africa Ebola epidemic.¹⁶ Similarly, during the 2016 Zika epidemic in the Americas, even pregnant women—a high-risk population—in well-resourced areas in the United States waited as long as a month to receive their Zika diagnostic test results, potentially delaying appropriate protective actions.¹⁷

Since the days of Louis Pasteur, in vitro culture (eg, bacterial, viral, fungal) has largely served as the gold standard for diagnosing infections. But culturing pathogens takes time, and some pathogens are extremely difficult to grow in vitro.

Additionally, culturing specimens is often complicated by the presence of other pathogens in the specimen that are not associated with the disease in question, which can lead to false-positive or confusing results.



Aside from culture, other diagnostics have typically been customized products developed for specific diseases. However, the future promises to be more pathogen-agnostic. Technologies such as handheld mass spectrometry or genetic sequencing aim to classify pathogens, regardless of their etiology. These technologies could be used to differentiate between strains of a pathogen, epidemiologically link confirmed cases of a disease, or even screen specimens for novel pathogens for which diagnostics do not yet exist—all with lower likelihood of false-positive or -negative results.

Most existing advanced diagnostic capabilities (eg, genetic sequencing)—while smaller, faster, and more capable than previous generations—still require significant investments in equipment, supplies, maintenance, training, and infrastructure to remain functional.

Another trend in diagnostics, a shift toward paper-based microfluidics, aims to mitigate these limitations by providing a robust capability for rapid and accurate diagnosis without the need for advanced training, expensive equipment, or access to electricity. These diagnostics can be used by clinicians and epidemiologists (or potentially even nonexpert responders) in the field or in austere environments with limited infrastructure. Additionally, this technology can keep the cost of

production extremely low (per unit) and results in products that require essentially no maintenance or upkeep. Because of their low cost, these products could even provide basic screening capability for a range of infections, which can better inform initial response operations.

Similarly, cell-free diagnostics aim to provide shelf-stable, robust capabilities in rugged environments. These systems harness the relevant functional machinery of cells for new purposes. The cells themselves are no longer viable, but the machinery can be freeze-dried for use in the field, requiring only the addition of water to reactivate the cell-free system for its intended use.

These technologies show high promise to rapidly develop and deploy diagnostic capabilities to any environment for a wide range of pathogens—and in the case of genetic sequencing technology, all known and unknown pathogens.

Diagnosis is a critical step in understanding the scope of an outbreak and implementing effective public health and medical interventions. Rapid, accurate, and robust diagnostic capabilities are particularly critical early in an outbreak response, especially in areas without well-established public health services and utility infrastructure.

Unfortunately, diagnostic development often suffers from the familiar “valley of death” experienced with many infectious disease medical countermeasures—that is, diagnostic development often stalls after the discovery phase because of a lack of available financing and a viable market for final products. So, in addition to funding and resources for diagnostics research and development, progress in this area will need significant attention to economic incentives and creative financing approaches will be essential.

KEY READINGS

Chua AC, Cunningham J, Moussy F, Perkins MD, Formenty P. The case for improved diagnostic tools to control Ebola virus disease in West Africa and how to get there. *PLoS Negl Trop Dis* 2015;9(6):e0003734.

<https://doi.org/10.1371/journal.pntd.0003734>. Accessed February 14, 2018.

Shorten RJ, Brown CS, Jacobs M, Rattenbury S, Simpson AJ, Mepham S. Diagnostics in Ebola virus disease in resource-rich and resource-limited settings. *PLoS Negl Trop Dis* 2016;10(10):e0004948. <https://doi.org/10.1371/journal.pntd.0004948>. Accessed February 14, 2018.

Peeling RW, Boeras DI, Nkengasong J. Re-imagining the future of diagnosis of neglected tropical diseases. *Comput Struct Biotechnol J* 2017;15:271-274. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5358522/>. Accessed February 16, 2018.



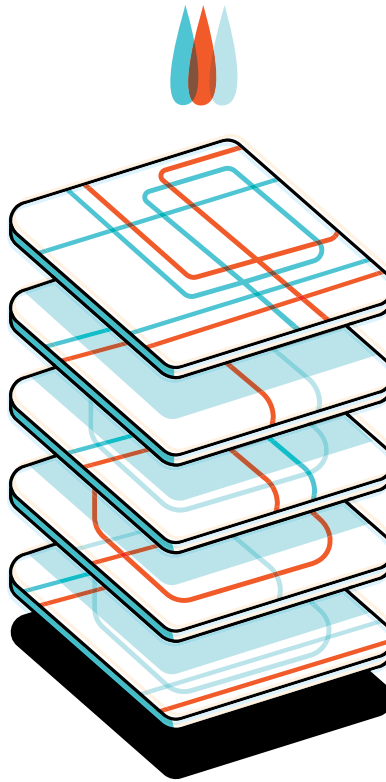
Microfluidic Devices

WHAT IS THE TECHNOLOGY?

Microfluidic devices are “lab on a chip” devices that have the potential to augment or replace traditional laboratory testing equipment, making diagnostics more accessible, usable, and useful at the bedside and in resource-constrained environments. These devices are available in plastic or paper versions that provide similar functionality but with their own unique capabilities.

The plastic version of a microfluidic device is a small—often credit card-sized or smaller—object with embedded channels throughout. The channels are lined with cells, reagents, antibodies, or other diagnostic components, and the diagnostic samples, taken from a sick individual, are forced through the channels, usually propelled by a pump. The fluids interact with the reagents in the channels to yield the test result. Several processing steps can be combined on a single chip, which increases efficiency and decreases the amount of training a user requires.

The paper versions work like a pregnancy test, with samples drawn through the paper fibers via capillary action. The device contains 1 or more reagents, and when the sample encounters the reagent, it changes color to indicate



the test result. Paper microfluidic devices are disposable, easy to administer and interpret, and could potentially cost just a few cents each, but they are often limited to less complex reactions than the plastic versions.

WHAT PROBLEM DOES IT SOLVE?

Microfluidic devices, particularly those that are paper-based, could be revolutionary for diagnosing infectious diseases in the field. Rather than relying on access to centralized care providers and laboratories, healthcare workers could potentially distribute microfluidic devices to clinics or

even to households. Decentralizing laboratory functions would increase testing capacity and decrease delays in diagnosis and treatment. This alternative testing strategy could also be combined with telemedicine to extend clinical care to remote or poorly resourced settings. Paper-based microfluidic diagnostics could also be distributed by mail or drone, thus helping to reduce the number of people seeking tests from hospitals, laboratories, and public health clinics.

HOW DO WE DO IT NOW?

Current diagnostic processes often require confirmation by

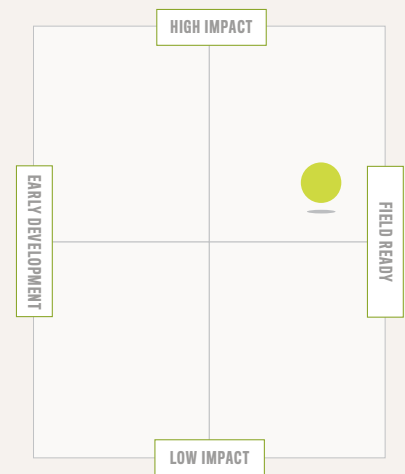
centralized laboratories. This pipeline faces several limitations: It requires (1) patient access to health care, (2) transport of the sample to a centralized laboratory, (3) laboratory testing capacity, and (4) necessary sample processing time, which can be several hours or even days. Each of these steps is a potential point of failure, and each extends the time to diagnosis, which, in turn, slows the isolation of infectious cases. Cheap, widely distributed microfluidic devices could improve diagnostic capacity and reduce delays in each of those 4 potential chokepoints.

WHAT DOES SUCCESS LOOK LIKE?

Microfluidic devices would be most successful if they were mass produced and distributed at very low cost. Rapid, point-of-care confirmatory testing would increase diagnostic capacity and decrease the time to diagnosis and isolation. The very low cost of paper-based tests would make repeat testing feasible, so that individuals could test themselves daily at home, if necessary. If infections were caught early enough through regular testing, affected individuals could self-isolate and potentially reduce their contact with susceptible people. Those who test negative on a given day could continue to participate in the community, which would reduce societal disruption and fear.

One major challenge facing microfluidic devices, particularly paper-based devices, is a lack of market potential. Paper-based microfluidic devices could cost just a few cents each, providing a very slim profit margin to incentivize

the R&D needed to prepare these devices for clinical use. Furthermore, use of these devices would have the most impact in under-resourced areas or settings, further limiting their profitability for prospective manufacturers. Microfluidic devices may also have a lower sensitivity and specificity than traditional, laboratory-based diagnostics, which may require the 2 methods to be used in combination.



KEY READINGS

Hu J, Wang S, Wang L, et al. Advances in paper-based point-of-care diagnostics. *Biosens Bioelectron* 2014;54:585-597. <https://doi.org/10.1016/j.bios.2013.10.075>. Accessed June 6, 2018.

Martinez AW, Phillips ST, Whitesides GM, Carrilho E. Diagnostics for the developing world: microfluidic paper-based analytical devices. *Anal Chem* 2010;82(1):3-10. <https://doi.org/10.1021/ac9013989>. Accessed June 6, 2018.

Martinez AW, Phillips ST, Carrilho E, Thomas SW 3d, Sindi H, Whitesides GM. Simple telemedicine for developing regions: camera phones and paper-based microfluidic devices for real-time, off-site diagnosis. *Anal Chem* 2008;80(10):3699-3707.

Walker NF, Brown CS, Youkee D, et al. Evaluation of a point-of-care blood test for identification of Ebola virus disease at Ebola holding units, western area, Sierra Leone, January to February 2015. *Euro Surveill* 2015;20(12). <https://doi.org/10.2807/1560-7917.ES2015.20.12.21073>. Accessed June 6, 2018.

Yager P, Edwards T, Fu E, et al. Microfluidic diagnostic technologies for global public health. *Nature* 2006;442(7101):412-418. <https://doi.org/10.1038/nature05064>. Accessed June 6, 2018.

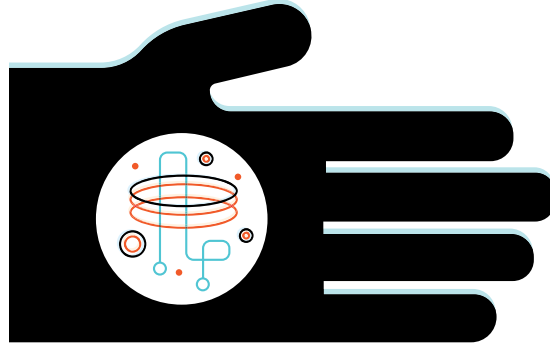


Hand-Held Mass Spectrometry

WHAT IS THE TECHNOLOGY?

A mass spectrometer precisely determines the mass of chemical and biological material in a specimen in order to reveal the composition of the sample. Mass spectrometry has been used for decades in chemical analysis, but it has advanced rapidly in recent years to include analysis of biological specimens. In fact, the US Food and Drug Administration (FDA) approved the first mass spectrometer diagnostic test in 2013 for bacterial and fungal infections.¹⁸ Advances in mass spectrometry have enabled devices to detect proteins and peptides that serve as biomarkers for specific pathogens, without requiring a specimen to be cultured.

Traditional mass spectrometers ionize and vaporize sample particles and then accelerate a beam of these particles through a magnetic field. The spectrometer determines the mass of the particles based on the time required for them to reach the detector or on their deflection from the center of the beam. A newer approach to mass spectrometry uses **carbon nanpores** in an electrically resistant membrane, rather than ion beams. The nanpores are temporarily blocked (fully or partially) by particles in solution (eg, proteins), resulting in disruptions to the electrical current, which can be analyzed to determine the presence of target proteins in the specimen.



Most mass spectrometers currently in use are large and expensive to operate; however, like many technologies, “mass spec” models are now shrinking in size while maintaining (or even gaining) functionality. Newer mass spectrometry units are now about the size of a desktop printer, but novel mass spec approaches, such as the use of carbon nanpores, could potentially enable the development of much smaller units. The future of mass spectrometry is a handheld, truly portable unit that can provide advanced diagnostic capabilities in the field and at the point of care.

WHAT PROBLEM DOES THIS SOLVE?

Some mass spectrometry technologies—in particular, PCR electrospray ionization mass spectrometry (PCR-ESI/MS)—may provide pathogen-agnostic or **pan-domain diagnostic capability**,¹⁹ eliminating the need to even differentiate among bacteria, viruses, fungi, or protozoa before conducting diagnostic tests. And if the pathogen is truly novel, the

detection of relevant proteins or peptides via mass spectrometry could potentially help classify it among known pathogens or, at the very least, identify it as a true unknown. Another advantage of mass spectrometry is the time required to conduct diagnostic tests. Mass spectrometry can determine the composition of specimens, including biological material, in a matter of minutes or even seconds.²⁰

HOW DO WE DO IT NOW?

With the exceptions of culturing and sequencing, the vast majority of current approaches to diagnosis require a priori knowledge or presumption of the pathogen (or type of pathogen) in question to determine the appropriate test. This limitation poses significant challenges for truly novel or engineered pathogens (which would not be part of any differential diagnosis or have an existing test available), extremely rare pathogens (which may be very low on a differential diagnosis and not warrant priority testing), or infections presenting with either nondescript symptoms common to many diseases (eg, fever) or atypical symptoms.

Other challenges with diagnosis include accuracy, speed, and portability. There are few diagnostic technologies that are highly sensitive and specific, work rapidly, and are portable and rugged enough to be useful in the field or at the bedside.

WHAT DOES SUCCESS LOOK LIKE?

Handheld versions of mass spectrometry, particularly PCR-ESI/MS, could provide pan-domain diagnostic capability at the point of care, easily deployable for remote field operations. Technology to rapidly conduct on-site diagnosis for any pathogen—or at least to identify the presence of a previously uncharacterized pathogen—could be a critical tool for rapidly characterizing and initiating response activities for an outbreak, particularly those involving emerging, rare, or novel pathogens or in areas without ready access to advanced laboratory facilities.

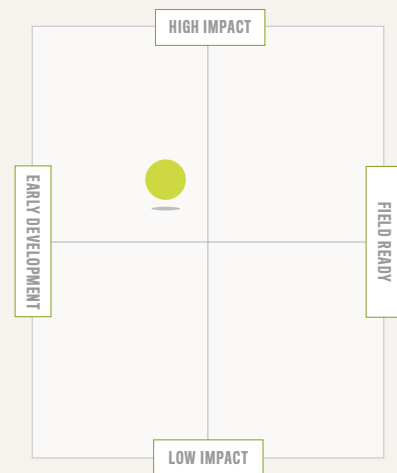
The speed at which mass spectrometry can provide diagnostic results—on the order of seconds to minutes—makes it an attractive tool for conducting screening operations. Such a tool could enable local health authorities to rapidly and accurately identify an affected population and implement appropriate pharmaceutical or nonpharmaceutical interventions to control an outbreak.

Some of the current limitations of mass spectrometry for clinical use are the size and weight of the equipment and the cost required to purchase and maintain it. A recent **crowd-funded effort** to produce a handheld mass spectrometer—not marketed as a diagnostic tool—was **met with mixed reviews** based on the development time and limited capabilities.²¹ But at a cost below \$300, it could potentially demonstrate the future feasibility

of similar products that could incorporate improved accuracy and analytic algorithms for rapid, portable, on-site pathogen detection and characterization.

Finally, to realize the potential benefits of this diagnostic technology, more work will be needed to test mass spec for use operationally in an outbreak context—particularly in identifying unknown pathogens. Testing for unknowns is a difficult problem. Use of this technology for that purpose will need to be validated in some systematic way and accompanied by operational and

technical guidance before these tests are fielded more broadly.



KEY READINGS

Li T, Fan L, Wang Y, et al. Molecularly imprinted membrane electro-spray ionization for direct sample analyses. *Anal Chem* 2017;89(3):1453-1458. <http://pubs.acs.org/doi/full/10.1021/acs.analchem.6b02571>. Accessed February 14, 2018.

Fleurbaaji F, van Leeuwen HC, Klychnikov OI, Kuijper EJ, Hensbergen PJ. Mass spectrometry in clinical microbiology and infectious diseases. *Chromatographia* 2015;78(5-6):379-389. <https://link.springer.com/article/10.1007/s10337-014-2839-x>. Accessed February 14, 2018.

Robertson JWE, Rodrigues CG, Stanford VM, Rubinson KA, Krasilnikov OV, Kasianowicz JJ. Single-molecule mass spectrometry in solution using a solitary nanopore. *Proc Natl Acad Sci U S A* 2007;104(20):8207-8211. <http://www.pnas.org/content/104/20/8207.full>. Accessed February 14, 2018.

Vetor R, Murray CK, Mende K, et al. The use of PCR/Electrospray Ionization-Time-of-Flight-Mass Spectrometry (PCR/ESI-TOF-MS) to detect bacterial and fungal colonization in healthy military service members. *BMC Infect Dis* 2016;16:338. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4957419/>. Accessed February 14, 2018.

Wolk DM, Kaleta EJ, Wysocki VH. PCR-electrospray ionization mass spectrometry: the potential to change infectious disease diagnostics in clinical and public health laboratories. *J Mol Diagn* 2012;14(4):295-304. <http://www.sciencedirect.com/science/article/pii/S1525157812000967?via%3Dihub>. Accessed February 14, 2018.

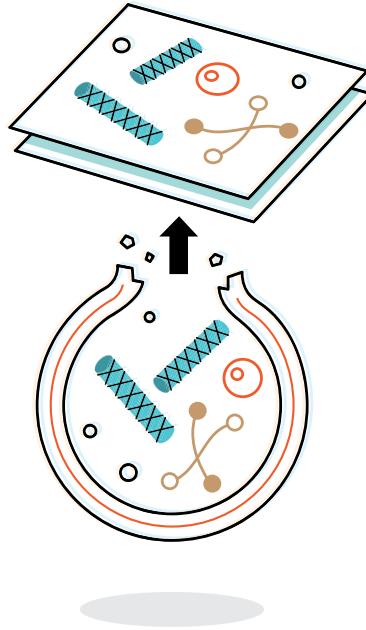


Cell-Free Diagnostics

WHAT IS THE TECHNOLOGY?

Cell-free diagnostics harness the power of engineered genetic circuits and bring them out of the lab and into the field using freeze-dried cell-free extracts.²² Synthetic biology methods traditionally have been carried out in living cells. However, the heterogeneity of living cells and the natural barrier of the cellular membrane can make engineering specific biological functions challenging. To address these challenges, some new diagnostics have done away with the cell membrane and simply use the machinery within a cell. By lysing bacterial cells and collecting the transcription/translation machinery, researchers can now create cell-free extracts capable of making proteins. These extracts, combined with genetic circuits—which consist of the necessary genetic regulatory network that controls expression of specific genes—allow for the production of a measurable, precise product.

For diagnostics, a new approach to genetic control of translation using highly programmable **ribo regulators** known as Toehold switches²³ allows for tight translational control of a gene. A riboregulator consists of a partially complementary pair of RNA sequences: a sensor strand that normally forms a hairpin loop whose structure prevents the ribosome from initiating translation of a protein product,



and a trigger RNA that relieves the translational repression. The sensor strand has an “exposed single-stranded region called the toehold sequence that is designed to be complementary to the trigger RNA.”^{23(p333)} The trigger RNA—in terms of diagnostics this would be the viral or bacterial RNA one is trying to detect—would then bind to the toehold sequence, which will linearize the hairpin structure. This can be used to initiate the production of enzymes that generate a colorimetric output visible to the naked eye for rapid detection of the presence of a pathogen.

In a proof of concept study, Pardee et al showed that these cell-free extracts containing complex synthetic gene networks can be freeze-dried onto paper or other porous material and, when reconstituted in water, showed

comparable activity to fresh from frozen reactions.²⁴ In the same paper, scientists created sensors able to distinguish between different strains of Ebola.²⁴ A later study further refined this concept by incorporating CRISPR/Cas9-based modules, and researchers were able to discriminate between Zika viral strains with single-nucleotide base resolution.²⁵

WHAT PROBLEM DOES THIS SOLVE?

Molecular diagnostics for field use during pandemic situations must be developed quickly; they should be highly sensitive and specific, inexpensive, and rapidly deployable; and they should provide timely diagnostic capabilities in low-resource areas. Additionally, they need to be easy to use and interpret without technical expertise, and production should be highly scalable for implementation on a global scale. Cell-free-based diagnostic platforms address many of these important practical limitations.

Currently, it is estimated that it would take about 1 week from sequence acquisition to manufacturing of **cell-free paper-based diagnostic sensors**, with a cost as low as 2¢ to 4¢ per sensor.²⁵ Detection time has been recorded in as little as 25 minutes when a high concentration of RNA is present, and 40 minutes when very little RNA is present. Importantly, these freeze-dried cell-free paper-based reactions maintain their activity for over 1 year when stored at room temperature, making them usable in a field setting.

HOW DO WE DO IT NOW?

The gold standard for diagnosis is still culture. Other approaches include polymerase chain reaction (PCR) and antibody-based detection. But there are drawbacks to these approaches. Culture can take a long time—in some cases weeks—and some organisms cannot be cultured at all. Commercial antibody production typically takes from 2 to 6 months, and cross-reactivity can limit the diagnostic value of standard antibody-based detection methods. Finally, nucleic acid amplification techniques such as PCR require expensive laboratory equipment and advanced technical expertise to run and analyze test results. The reagent cost alone for PCR ranges from \$1.50 to \$4 per reaction, and PCR reactions take at least an hour, and often several hours, before quantification. These are the kinds of functional barriers that prevent the use of diagnostic technologies in remote and low-resource locations, where containment of infectious disease spread is critical.

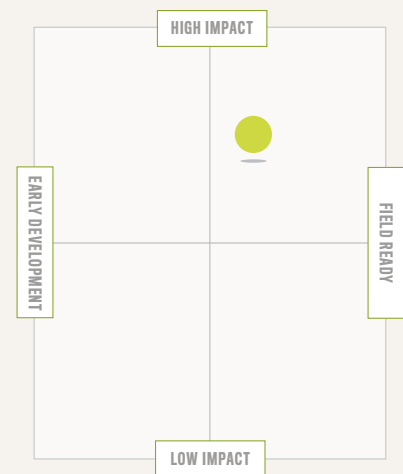
WHAT DOES SUCCESS LOOK LIKE?

Cell-free diagnostic tests have the potential to substantially reduce response time in a pandemic situation. One major condition for this technology to be successful is further improvement in sample preparation techniques. Although the creation of these cell-free-based diagnostics would be done at a centralized lab and distributed widely, users would still need to

prepare samples by extracting and amplifying RNA. With the proper equipment, sample preparation can take about 2 hours. However, low-resource settings might lack the required equipment and expertise. Nucleic acid sequence-based amplification (NASBA) is currently the best method of sample preparation. Although NASBA would normally be too costly to use in low-resource settings, since the cell-free diagnostic test would require only a fraction of a microliter, the cost would be reduced significantly (\$0.51/μL). However, NASBA is prone to contamination and, as a result, could lead to false-positives. Further studies are required to ensure that the rate of false-positives is at an appropriate level and that the reads are diagnostically significant. Work is currently ongoing to address this issue by creating a third-generation diagnostic reader with onboard capabilities for sample preparation and incubation.

Additionally, although sensor development would take only about

a week, and the cell-free-based sensors do not rely on cold-chain for transport, strategic logistical distribution plans still need to be developed to ensure rapid wide distribution of the cell-free diagnostics. Lastly, a supportive regulatory environment is crucial to the development and use of these in vitro paper-based diagnostics. Because of the ill-defined compositional nature of cell-free systems, the FDA may need to approach cell-free diagnostics differently than they would other technologies.



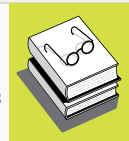
KEY READINGS

Ausländer S, Fussenegger M. Synthetic biology: toehold gene switches make big footprints. *Nature* 2014;516(7531):333-334.

Lu Y. Cell-free synthetic biology: engineering in an open world. *Synth Syst Biotechnol* 2017;2(1):23-27.

Pardee K, Green AA, Ferrante T, et al. Paper-based synthetic gene networks. *Cell* 2014;159(4):940-954.

Pardee K, Green AA, Takahashi MK, et al. Rapid, low-cost detection of Zika virus using programmable biomolecular components. *Cell* 2016;165(5):1255-1266.



Distributed Medical Countermeasure Manufacturing

For the world to effectively combat a global catastrophic biological event, medical countermeasures (MCMs)—that is, vaccines and drugs—will need to be manufactured rapidly and in mass quantities across the globe. Regardless of the speed at which MCMs are discovered and developed in the midst of a public health emergency, the capability to scale up production and to provide global MCM availability (irrespective of the country of origin or socioeconomic status) will be essential.

MCM manufacturing as it currently exists represents a potentially rate-limiting step in delivering lifesaving countermeasures to those who need them. Market forces have reduced manufacturing capacity for many types of vaccines and drugs in the United States and internationally over the past several decades, and current manufacturing practices are often slow and single-purpose. Although important

efforts are under way to plan for manufacturing scale up or to quickly retrofit manufacturing plants to produce MCMs during a crisis, these efforts have thus far not produced the needed capacity in the United States or elsewhere in the world. As a result, and especially in the case of a GCB event, a new approach to MCM manufacturing may be needed.



Technologies highlighted in this section of the report have the potential to enable the production of MCMs in a range of locations and in a shorter time frame than traditional manufacturing approaches. This concept of distributed manufacturing may be transformational for democratizing MCM access during a pandemic response. They could potentially facilitate the rapid creation of drugs and vaccines to combat novel pathogens with little history of countermeasure development, facilitating necessary improvements in the timing of outbreak response efforts.

Distributed MCM manufacturing will need to overcome several economic, regulatory, legal, and ethical challenges to be successful. By and large, current MCM manufacturing systems are not distributed, so economic incentives and business models will need to be adjusted, potentially significantly, to accommodate such a change. Likewise, laws, regulations, and regulatory bodies would need to adapt to realize the benefits and anticipate and reduce the risks that would come with distributed approaches.

KEY READINGS

Ravi S, Adalja AA. Strengthening the US medical countermeasure enterprise for biological threats. *Health Secur* 2017;15(1):12-14.

U.S. Department of Health and Human Services. *2016 Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Strategy and Implementation Plan*. 2016. https://www.medicalcountermeasures.gov/media/36937/2016_phemce_sip.pdf. Accessed June 6, 2018.

U.S. Government Accountability Office. *Biological Defense: Additional Information That Congress May Find Useful as It Considers DOD's Advanced Development and Manufacturing Capability*. GAO-17-701. July 2017. <https://www.gao.gov/products/GAO-17-701>. Accessed June 6, 2018.

U.S. Government Accountability Office. *National Preparedness: HHS Has Funded Flexible Manufacturing Activities for Medical Countermeasures, but It Is Too Soon to Assess Their Effect*. GAO-14-329. March 2014. <https://www.gao.gov/products/GAO-14-329>. Accessed June 6, 2018.



Synthetic Biology for Manufacturing Medical Countermeasures

WHAT IS THE TECHNOLOGY?

Genetically engineered strains of bacterial organisms, such as yeast and salmonella, can increasingly be programmed to manufacture many kinds of useful products, including **drugs and vaccines**.²⁶ Synthetic biology takes advantage of the fact that bacterial biosynthetic pathways have natural built-in modularity, meaning they can be edited and re-ordered to customize the products being produced by bacterial cells. These pathways, which are used naturally by bacteria to make chemical compounds and biological products such as proteins, can be reprogrammed to make different products and in large amounts. Bacteria like yeast in their natural forms have been **used by humans** for centuries to make products like alcohol.²⁷ Now, with novel gene editing and other biotechnologies, bacteria can be altered for industrial production of many kinds of molecules and proteins. Synthetic biology products produced to date range from silks, to flavors and scents, to pharmaceutical products.

This approach to MCM development and manufacturing is still relatively new, but research is proceeding at a rapid pace. The capability now exists to produce a range of therapeutic chemical compounds using synthetic biology. One of the first successful test cases for pharmaceutical production using synthetic biology is the drug artemisinin, an antimalarial chemical compound. Semi-synthetic artemisinin can now be produced on a large scale in yeast (*Saccharomyces cerevisiae*), because one of



its precursor chemicals can be synthesized instead of being harvested from sweet wormwood plants. **Production of artemisinin** both proved the viability of synthetic biology for drug production and advanced the science of programming bacteria for this purpose.²⁶

Biological organisms can also be engineered to secrete therapeutic proteins like human growth hormone, antigens to be used in vaccines, and monoclonal antibodies for treatment of infectious diseases. Recent research shows it is possible to combine genetic engineering of bacterial organisms and synthetic biology kits (small bioreactors) to produce therapeutically relevant levels of biologic drugs quickly. Experimental bioreactor platforms are already being tested in field settings. For example, as a proof of concept, they have recently been used to synthesize small amounts of personalized therapeutics in locations like ambulances.²⁸

WHAT PROBLEM DOES THIS SOLVE?

Synthetic biology provides the opportunity for novel approaches to both finding and producing therapeutics, as well as the capability

of producing these therapeutics in a distributed and tailored way. This could mean that drugs and vaccines are discovered more quickly and produced much faster and in much larger quantities than is possible with traditional manufacturing techniques. Additionally, because manufacturing capacity could be made available globally, more of the world could have rapid access to vaccines and drugs in an emergency.

HOW DO WE DO IT NOW?

Most of the world's large molecule drugs are produced by a small number of companies with manufacturing facilities that are highly specific to the products they are producing. There is limited flexibility in manufacturing and relatively little capacity for surge production should the need arise.

For biological products like antigens and antibodies, production is further limited by the availability and yield of culture techniques like cell or egg culture. As an example of current limitations, most of the world's manufacture of annual influenza vaccine depends on the availability of chicken eggs for growth of vaccine virus. There are a number of drawbacks to this process, including that some people have allergies to chickens and, therefore, cannot receive vaccines produced this way. In addition, flu viruses must mutate in order to grow in eggs, making them less like circulating flu strains and less likely to be effective against them. Additionally, if specific **pathogen-free egg** supplies are disrupted, vaccine production could be limited or halted entirely.²⁹

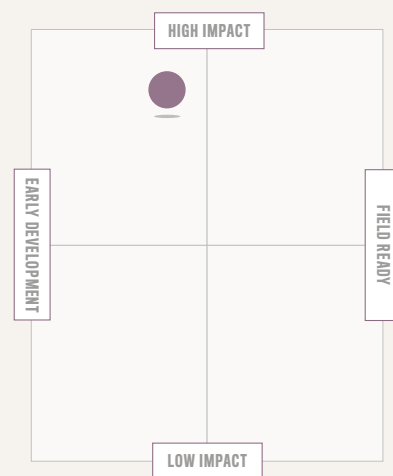
WHAT DOES SUCCESS LOOK LIKE?

With continued advancement in synthetic biology approaches to chemical and biologic product synthesis for MCMs, models of centralized drug production may be significantly disrupted. In the context of a pandemic or GCB event, engineered chassis organisms (eg, yeast) that express MCMs (eg, monoclonal antibodies) could be rapidly disseminated to scientists around the world, who, in turn, could begin to use both small, portable bioreactors and larger reactors to produce the desired product locally.

In a worst-case GCB event scenario, bioreactors used for production of other types of products, like beer, could be repurposed temporarily to produce drugs and vaccines on a massive scale, thus distributing production capacity to many more places and making products available to those who need them in time to make a difference. While there would be serious challenges to implementing this vision, in a truly catastrophic event, it may be one of the few options to slow a pandemic and prevent catastrophic impacts on humanity.

While the use of synthetic biology in distributed manufacturing has significant promise in the long term, it is still a novel concept that requires serious planning and consideration. There are important safety concerns related to ensuring the quality and efficacy of products produced through these methods in

a distributed way. Especially in an emergency context, traditional good manufacturing practices (GMPs) and regulatory frameworks aimed at ensuring quality and safety would need to be reevaluated. And because this is a radical departure from current manufacturing practice, there may be **pushback** from the pharmaceutical and agricultural industries due to the disruptive nature of a distributed manufacturing model.³⁰



KEY READINGS

Breitling R, Takano E. Synthetic biology advances for pharmaceutical production. *Curr Opin Biotechnol* 2015;35:46-51.

<https://www.sciencedirect.com/science/article/pii/S0958166915000233#bib0430>. Accessed June 7, 2018.

May M. Synthetic biology's clinical applications. *Science* September 25, 2015. <http://www.sciencemag.org/custom-publishing/technology-features/synthetic-biology-s-clinical-applications>. Accessed June 7, 2018.

Paddon CJ, Keasling JD. Semi-synthetic artemisinin: a model for the use of synthetic biology in pharmaceutical development. *Nat Rev Microbiol* 2014;12(5):355-367. <https://www.nature.com/articles/nrmicro3240>. Accessed June 7, 2018.

Perez-Pinera P, Han N, Cleto S, et al. Synthetic biology and microbioreactor platforms for programmable production of biologics at the point-of-care. *Nat Commun* 2016;7:12211. <https://www.nature.com/articles/ncomms12211.pdf>. Accessed June 6, 2018.

Poust S, Hagen A, Katz L, Keasling JD. Narrowing the gap between the promise and reality of polyketide synthases as a synthetic biology platform. *Curr Opin Biotechnol* 2014;30:32-39. <https://www.sciencedirect.com/science/article/pii/S0958166914000834>. Accessed June 7, 2018.

Shukla AA, Wolfe LS, Mostafa SS, Norman C. Evolving trends in mAb production processes. *Bioeng Transl Med* 2017;2(1):58-69. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5689530/pdf/BTM2-2-058.pdf>. Accessed June 7, 2018.



3D Printing of Chemicals and Biologics

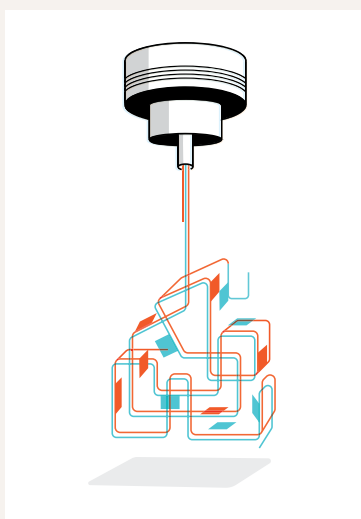
WHAT IS THE TECHNOLOGY?

Three-dimensional (3D) printing is the process of building an object in successive layers by fusing or depositing materials. This technology is increasingly available on a scale and at a price that allows broad distribution of 3D printing capabilities to individual users. Using digital instructions, a 3D printer can produce an object out of existing materials or reagents in almost any shape. This technology could be applied to devices and parts, biological components, and pharmaceuticals, among other uses.

The use of 3D printing to reduce the impact of a GCB event would likely hinge on whether 3D printing capabilities could be established locally, in businesses and homes. Continued gains in accessibility and affordability have already enabled a **consumer market** for basic 3D printers.

The range of uses and potential for 3D printing is expanding as the field explores new applications and develops associated processes. 3D printing encompasses many different applications, requiring different types of manufacturing components, including different hardware, software, and materials.

Much of the current excitement around this technology focuses on its ability to facilitate personalized medicine through printing of active pharmaceutical ingredients. If applied to health emergencies, 3D pharmaceutical printing could be used for distributed manufacturing of MCMs as well as personalized drug dosing and formulations. 3D printers now have the capacity to synthesize key chemicals and pharmaceuticals almost anywhere a printer can go,³¹ and work



is also under way to explore use of this technology to print vaccines.³²

WHAT PROBLEM DOES THIS SOLVE?

3D printing has many possible applications in the GCB context. Most promising is its potential to address distribution and access problems in current MCM manufacturing. Centralized manufacturing could lead to significant time lags and logistical burdens in distribution as well as inequities in access. In addition, 3D printing may facilitate the creation of drug delivery systems that overcome barriers related to drug stability or intermittent dosing.

As 3D printing technology has advanced and become more widely available, the costs of owning and operating a 3D printer have declined significantly. 3D printing technology is increasingly accessible to nonexperts, allowing for distributed use in places not traditionally considered suitable for manufacturing. The manufacture of MCMs at many sites worldwide would reduce the need to transport them across long distances and could make

MCMs available to populations in difficult-to-reach areas. In a situation in which a potential GCB event was identified early and an MCM was rapidly identified, local 3D printing of MCMs could help stop a GCB event before it expanded globally.

3D printing may also solve formulation problems for MCMs. In particular, because of its ability to create more flexibility in dosing, 3D printing could improve drug access for pediatric populations and others who may not be able to take standard MCM formulations. It may also facilitate the use of MCMs that are difficult to transport in active form. This technology could facilitate the use of other emerging technologies that have been highlighted in this report, from on-site **printing of drone parts**³³ to the distributed **manufacture of synthetic biology tools**. And 3D printing may help accelerate the process of MCM discovery and testing through the use of **3D-printed tissues**³⁴ that can be printed in the field and used as **drug evaluation platforms**.³⁵

HOW DO WE DO IT NOW?

Currently, MCM manufacturing occurs at centralized manufacturing sites, most often on dedicated manufacturing platforms. But countermeasure production needs to be distributed, often across or between continents, to sites where users can access the products. Some MCMs require cold chains and have other transport considerations, further complicating distribution. In addition, large-scale production of a new countermeasure may take a significant amount of time to

establish at traditional manufacturing sites. Pharmaceutical companies must anticipate the production needs of MCMs in order to ensure product availability and reliable profit margins, so it may be difficult to maintain a continuous supply of low-demand products. In the event that out-of-production products are needed, it could take time to reestablish the necessary production capacity to meet higher-than-anticipated demand.

WHAT DOES SUCCESS LOOK LIKE?

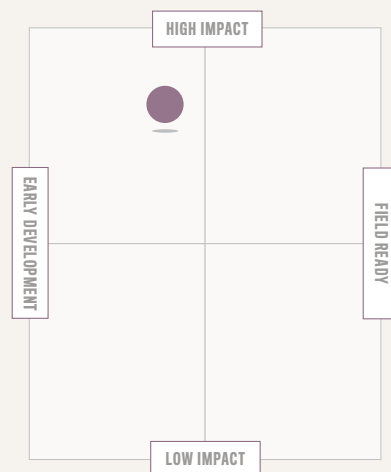
Although advances in efficiency would be required to match the volume of centralized production, 3D printing could allow for greater and earlier access to MCMs developed in response to or identified in a GCB event. Some envision **3D manufacturing of pharmaceuticals in every home**.³¹ This may be possible in the distant future, but a more likely scenario is widely distributed 3D printing technology available in a number of local facilities, such as labs, pharmacies, hospitals, and public health departments.

In a world with enabled and distributed 3D printers, certified printing algorithms could be disseminated at the speed of the internet, and MCMs could be manufactured simultaneously at hundreds or thousands of sites across the globe, from large cities to rugged field sites. MCMs could then be distributed at the local level immediately following manufacture. In the more distant future, 3D printers may be useful in every

phase of MCM development: printing the necessary chemical starting materials for drugs and all equipment needed for the process.

Some barriers exist to the widespread use of this technology during a GCB event. Regulatory changes will be required to enable distributed use of 3D printers, including for the manufacturing tools and processes themselves and for the countermeasures produced using 3D printers. However, notably, the FDA has **approved 3D printed drugs** in the past.³⁶ Chemical and biological precursors to 3D printing will need to have reliable supply chains to enable distributed manufacturing, and precursors need to be distributed equitably to both resource-rich and resource-poor areas of the world. If MCMs require precursors that are not commonly available or easily produced on site (eg, through synthetic biology), prepositioning

of necessary precursors may present an additional barrier to the use of this technology. 3D printing technology has become more widely available over the past decade, but specific technologies to print pharmaceuticals or biological components, as well as access to the necessary precursor ingredients and tools, are not always at hand. Increased access and lower costs are needed to improve capacity.



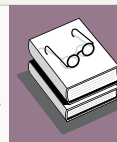
KEY READINGS

Hernandez D. Craig Venter imagines a world with printable life forms. *Wired* October 16, 2012. <https://www.wired.com/2012/10/printable-life-forms/>. Accessed January 9, 2018.

Kitson PJ, Marie G, Francoia JP, et al. Digitization of multistep organic synthesis in reactionware for on-demand pharmaceuticals. *Science* 2018;359(6373):314-319.

Murphy SV, Atala A. 3D bioprinting of tissues and organs. *Nat Biotechnol* 2014;32(8):773-785.

Ventola CL. Medical applications for 3D printing: current and projected uses. *PT* 2014;39(10):704-711.



Medical Countermeasure Distribution, Dispensing, and Administration

Once drugs and vaccines make it through discovery, R&D, testing, and manufacturing, they still need to be delivered and administered directly to individuals who can benefit from them. This process, sometimes termed “the last mile,” is difficult to do quickly and effectively. Catastrophic conditions would require rapid mass administration of MCMs in order to reduce morbidity and mortality, which will be a significant challenge. So, even in cases where drugs or vaccines are stockpiled and ready for use, there is no guarantee that they will be distributed (transported to the affected area) and dispensed (provided or administered to individuals) in time to make a difference.

In the United States, doctors’ offices, pharmacies, and points of dispensing (PODs)—pre-identified locations where MCMs are provided to the affected population—are the primary places where MCMs would be dispensed or administered on a

mass scale in a serious emergency like a bioterrorism attack or pandemic. Affected populations would be required to come to central locations to be vaccinated by healthcare professionals or receive therapeutics.



Medical Countermeasure Distribution, Dispensing, and Administration

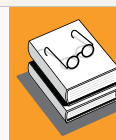
Drawbacks of this approach include the need for a potentially large number of healthcare providers (particularly for vaccine administration), the potential for increased transmission due to people gathering centrally, and a lack of equal access for all segments of an affected population. During past infectious disease emergencies, vulnerable populations—including minorities, rural populations, individuals with disabilities, and individuals of low socioeconomic status—had varying degrees of access to or ability to obtain MCMs. For example, during the 2009 H1N1 influenza pandemic, as the new vaccine became publicly available slowly over time, health departments in the United States and health ministries internationally had difficulty reaching and vaccinating high-priority and vulnerable populations. In the United States, only 34% of people in initial priority groups and 29% of adults at high risk were vaccinated.³⁷ Internationally, the average national vaccine coverage rate was only 13%.³⁸

In a truly severe pandemic or GCB event in which vaccines are available, vaccination coverage would need to be much higher than it was in 2009 in order to make a meaningful difference in controlling or stopping spread of

the disease. In this section, we describe several technologies that could greatly facilitate the “last mile” of MCM distribution, dispensing, and administration—making effective pandemic and GCB event response more feasible.

KEY READINGS

Nicholson A, Wolleck S, Kahn B, Herrmann J; Board on Health Sciences Policy; Health and Medicine Division; National Academies of Sciences, Engineering, and Medicine. *The Nation's Medical Countermeasure Stockpile: Opportunities to Improve the Efficiency, Effectiveness, and Sustainability of the CDC Strategic National Stockpile: Workshop Summary*. Washington, DC: National Academies Press; 2016.



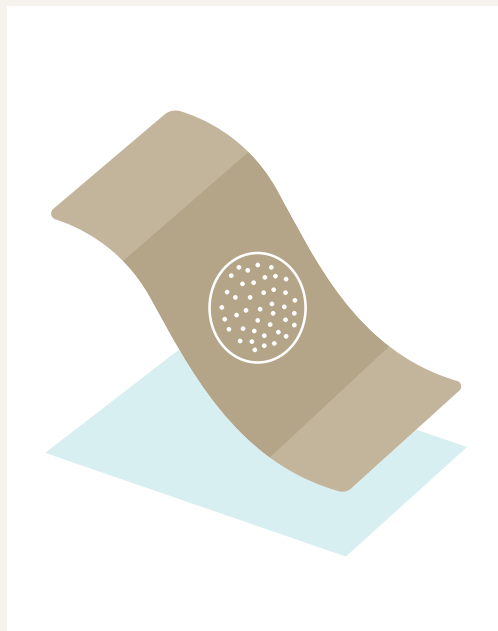
Microarray Patches for Vaccine Administration

WHAT IS THE TECHNOLOGY?

A microarray patch (MAP; also called a microneedle patch) is an emerging technology for administering vaccines that has the potential to modernize mass vaccination campaigns. MAPs have been proposed for use against measles, influenza, and other infectious diseases and could theoretically be developed for most vaccine-preventable diseases. Currently, MAPs are being evaluated by the CDC and PATH for global health applications, but they could be highly useful in emergency response settings as well.

Several different types of MAPs have been developed, the most promising of which is comprised of an array of small, **water soluble, thermostable cones** that are embedded with the antigen of choice and held against the skin by an adhesive bandage. Once applied and pressed into the skin, the cones dissolve within minutes, delivering the antigenic payload into the dermal tissue.

MAPs are a reliable, pain-free method of delivering an intradermal (ie, into the skin) injection that could minimize the amount of vaccine needed to confer immunity. Additionally, in the context of a severe pandemic or GCB event, they could enable



self-administration of vaccines, which would not require advanced medical training or expertise. Immunologically, antigens delivered via intradermal administration are taken up by specialized antigen-presenting cells (APCs) that reside in the skin. These cells take in and process antigen from the vaccine, transmit it to the lymphatic system, and present the antigen to T and B cells. T-cells are able to recognize and kill virus-infected cells, and B-cells can make antibodies against an invading virus, thereby generating a protective immune response.

WHAT PROBLEM DOES THIS SOLVE?

In the setting of a GCB event involving an infectious disease amenable to vaccination, the ability to generate rapid,

population-wide vaccine coverage will likely be a high priority and may be the only viable way to meaningfully protect large numbers of people. Unfortunately, recent experiences with infectious disease emergencies, notably the 2009 H1N1 influenza pandemic, have demonstrated that we lack the ability to rapidly immunize the US population, let alone the global population.

Severe epidemic and pandemic disease events like influenza, Ebola, and Zika have catalyzed **initiatives** to expedite vaccine research, development, and manufacturing.³⁹ However, relatively little attention has been paid to addressing the logistical and technological aspects of administering vaccines in an emergency—particularly for pandemics and GCB events, when vaccination will need to be completed rapidly. A primary bottleneck in this process is the small number of healthcare providers—relative to the susceptible population, which could potentially be the entire planet for a wholly novel pathogen—who would or could be pressed into service to implement a mass vaccination campaign during an emergency. This is especially true in the developing world, where even the routine provision of medical care, including vaccination, is an ongoing and persistent challenge.

Medical Countermeasure Distribution, Dispensing, and Administration

HOW DO WE DO IT NOW?

Today, most vaccines are administered using a needle and syringe. While this is a tried and true delivery method, it has several downsides, including the need for healthcare providers to administer the injection, the risk to healthcare providers of needlestick injuries and exposure to blood-borne pathogens, and pain for the recipient.

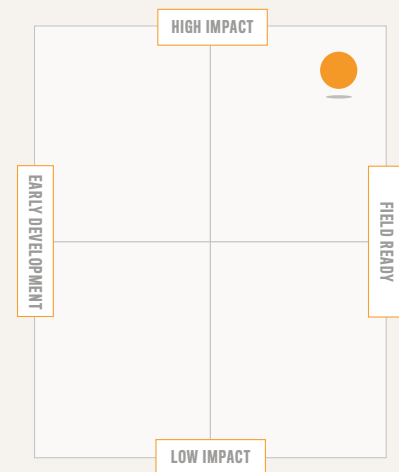
It typically takes weeks or months for a coalition of public health authorities, pharmacists, and healthcare providers to immunize large populations. Using MAPs would fundamentally change the vaccination process from one of administering vaccines to one of distribution and self-administration, resulting in significant savings of time and resources.

In theory, mass vaccination could be performed within days using MAPs for self-administration. During a GCB event, any time saved in vaccination operations—including R&D, production, distribution, and administration and dispensing—could translate into a significant number of illnesses prevented and lives saved.

WHAT DOES SUCCESS LOOK LIKE?

Widespread adoption of MAP technology could significantly decrease the time to complete immunization operations by enabling self-administration during emergencies. Pandemic vaccines could be distributed via more logistically efficient means—such as commercial shipping companies or the postal service—or they could use the current POD models that are already established. Public health and healthcare personnel would still be required to dispense or administer vaccines to some subsections of the population (eg, homeless individuals, those with allergies to the primary vaccine) and conduct necessary surveillance of adverse events, but the resources required to implement these programs would be significantly less than for a traditional mass

vaccination POD. A worthy, but admittedly ambitious, goal would be the eventual elimination of the needle and syringe administration of all vaccines, which could potentially lower barriers to obtaining routine vaccinations like measles, mumps and rubella (MMR); diphtheria, tetanus, and pertussis (DTap); and seasonal influenza.

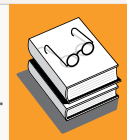


KEY READINGS

Durrheim DN, Goodson JL. Time for an immunisation paradigm shift. *Trans R Soc Trop Med Hyg* 2017;111(2):41-42.

Engelke L, Winter G, Hook S, Engert J. Recent insights into cutaneous immunization: how to vaccinate via the skin. *Vaccine* 2015;33(37):4663-4674.

Prausnitz MR. Engineering microneedle patches for vaccination and drug delivery to skin. *Annu Rev Chem Biomol Eng* 2017;8:177-200.



Self-Spreading Vaccines

WHAT IS THE TECHNOLOGY?

Self-spreading vaccines—also known as transmissible or self-propagating vaccines—are genetically engineered to move through populations in the same way as communicable diseases, but rather than causing disease, they confer protection. The vision is that a small number of individuals in the target population could be vaccinated, and the vaccine strain would then circulate in the population much like a pathogenic virus. These vaccines could dramatically increase vaccine coverage in human or animal populations without requiring each individual to be inoculated. This technology is currently aimed primarily at animal populations. Because most infectious diseases are **zoonotic**,⁴⁰ controlling disease in animal populations would also reduce the risk to humans.

There are 2 main types of self-spreading vaccines: recombinant vector vaccines and live viral vaccines. Recombinant vector vaccines combine the elements of a pathogenic virus that induce immunity (removing the portion that causes disease) with a transmissible viral vector. Cytomegalovirus is one candidate vector for recombinant vaccines, because

it is highly species-specific and moderately transmissible. Live viral vaccines are attenuated, meaning that the vaccine viruses are much less pathogenic than wild-type and would be similar to the oral polio vaccine or the live attenuated influenza vaccine (LAIV) in that those vaccines can sometimes transmit from person to person.

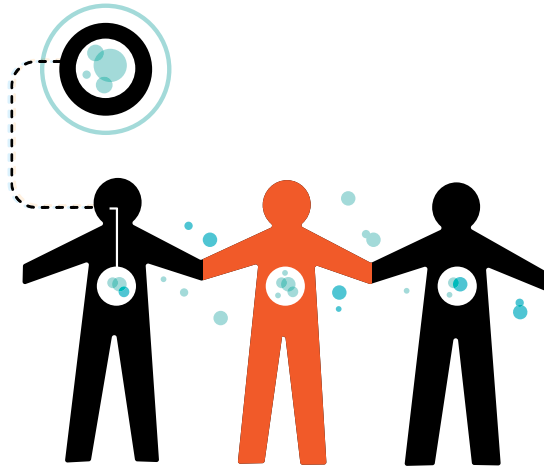
Although there are substantial technical challenges in genetically engineering viruses, synthetic biology tools such as CRISPR/Cas9 are likely to aid researchers in overcoming these hurdles in the coming years. Self-spreading vaccines have already been used to protect wild rabbits from myxomatosis and to control Sin Nombre virus in rodent populations. Additional work is targeting Ebola virus in apes and bats, Lassa virus in rats, and bovine tuberculosis in badgers.

WHAT PROBLEM DOES THIS SOLVE?

The most practical and useful application of self-spreading vaccines would be to control disease spread in wild animal populations (also known as sylvatic spread). A vaccine would be administered to a few selected animals in hotspots among target populations including nonhuman primates, bats, or rodents. The vaccine would then spread within the target

population, eliminating the need to vaccinate each animal. Successful disease control in animal populations could limit the number of infected animals and thereby reduce the opportunity for the disease to spill over into humans, thus stopping outbreaks in humans before they ever emerge. Such a sylvatic strategy would reduce the overall number of outbreak opportunities in humans, but it could not interrupt an outbreak once it becomes established in humans.

In the event of a grave public health threat, self-spreading vaccines could potentially be used to broadly inoculate human populations. Like the approach in animals, only a small number of vaccinated individuals would be required in order to confer protection to a larger susceptible population, thus eliminating the need for mass vaccination operations, including PODs.



HOW DO WE DO IT NOW?

Current mass vaccination strategies require each individual to be inoculated with 1 or more doses of vaccine. For humans, this can be accomplished at PODs or doctors' offices, by healthcare providers, but for wild animal populations there is the added challenge of animals being difficult to track and catch.

One relatively successful approach to vaccinating wild animal populations is through use of oral baits. For example, oral rabies vaccine baits have been dropped aurally into animal habitats to reach vulnerable species like foxes and bats. This approach relies on development of a suitable and stable vaccine and timely bait uptake, and it may not reach all vulnerable animals. Nevertheless, it has contributed significantly to rabies elimination in a number of geographic areas,⁴¹ and it is also being used for other diseases like Lyme disease.⁴²

In human pandemics, each element in the pipeline of vaccine production, distribution, and administration would have significant difficulties in scaling effectively to address the crisis. For example, if vaccine cannot be produced at scale, or if the healthcare system cannot flex to accommodate the administration of millions of doses of vaccine, the effectiveness of the response will be diminished.

**WHAT DOES SUCCESS
LOOK LIKE?**

If used in animals, successful implementation of self-spreading vaccines would prevent spillover of pathogens with pandemic potential into human populations without the need for difficult and costly mass vaccination operations in animal populations. For example, inoculation of relatively few bats and nonhuman primates against Ebola could potentially limit or eliminate human outbreaks. Sufficient coverage could even eradicate animal diseases, permanently eliminating these risks to both animals and humans.

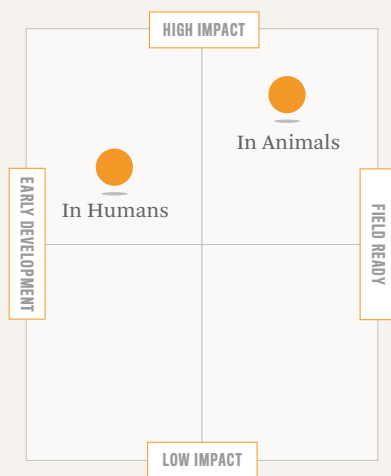
For human use, targeted release of weakly transmissible self-spreading vaccine early in an outbreak could create herd immunity in communities and prevent an outbreak from becoming a pandemic. If introduced later, after an outbreak has become widespread, self-spreading vaccines could still help to protect susceptible individuals and limit the number of new cases and prevent catastrophic outcomes.

While self-spreading vaccines could help reduce illness and death in a severe pandemic, this approach comes with several big challenges. One important component of the current vaccination approach for humans is the informed consent process. In order to receive a vaccine, individuals (or their legal guardians) must be informed about the risks of vaccination by a healthcare provider and provide their consent before being vaccinated. Those who decline are not forced to receive a vaccine. In the case of self-spreading vaccines, the individuals directly vaccinated would have this option, but those

to whom the vaccine subsequently spreads would not. Additionally, self-spreading vaccines would potentially infect individuals with contraindications, such as allergies, that could be life-threatening. The ethical and regulatory challenges surrounding informed consent and prevention and monitoring of adverse events would be critical challenges to implementing this approach even in an extreme event.

Finally, there is a not insignificant risk of the vaccine virus reverting to wild-type virulence, as has sometimes occurred with the oral polio vaccine—which is not intended to be fully virulent or transmissible, but which has reverted to become both neurovirulent and transmissible in rare instances. This is both a medical risk and a public perception risk; the possibility of vaccine-induced

disease would be a major concern to the public. Modeling efforts suggest that making self-spreading vaccines weakly transmissible might reduce the risk of reversion to wild-type virulence by limiting the number of opportunities for the virus to evolve. However, weakly transmissible vaccines would have to be introduced to more people to obtain sufficient immunity in the target population.



KEY READINGS

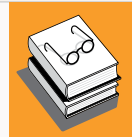
Bull JJ, Smithson MW, Nuismer SL. Transmissible viral vaccines. *Trends Microbiol* 2018;26(1):6-15. <https://doi.org/10.1016/j.tim.2017.09.007>. Accessed June 25, 2018.

Murphy AA, Redwood AJ, Jarvis MA. Self-disseminating vaccines for emerging infectious diseases. *Expert Rev Vaccines* 2016;15(1):31-39. <https://doi.org/10.1586/14760584.2016.1106942>. Accessed June 25, 2018.

Nuismer SL, Althouse BM, May R, Bull JJ, Stromberg SP, Antia R. Eradicating infectious disease using weakly transmissible vaccines. *Proc Biol Sci* 2016;283(1841). <https://doi.org/10.1098/rspb.2016.1903>. Accessed June 25, 2018.

Torres JM, Sánchez C, Ramírez MA, et al. First field trial of a transmissible recombinant vaccine against myxomatosis and rabbit hemorrhagic disease. *Vaccine* 2001;19(31):4536-4543. [https://doi.org/10.1016/S0264-410X\(01\)00184-0](https://doi.org/10.1016/S0264-410X(01)00184-0). Accessed June 25, 2018.

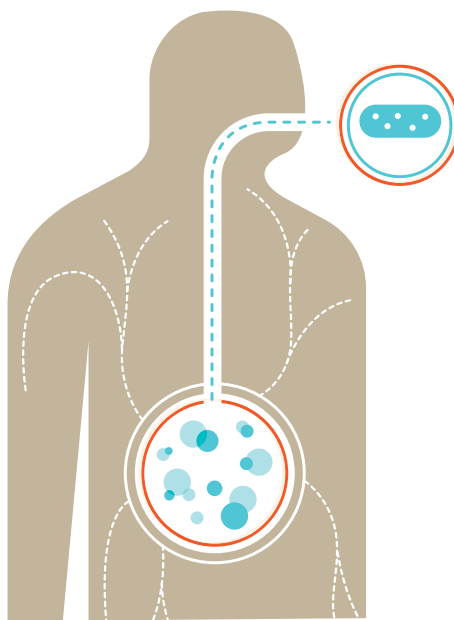
Tsuda Y, Caposio P, Parkins CJ, et al. A replicating cytomegalovirus-based vaccine encoding a single Ebola virus nucleoprotein CTL epitope confers protection against Ebola virus. *PLoS Negl Trop Dis* 2011;5(8):e1275. <https://doi.org/10.1371/journal.pntd.0001275>. Accessed June 25, 2018.



Ingestible Bacteria for Vaccination

WHAT IS THE TECHNOLOGY?

Bacteria can be genetically engineered to produce antigens in a human host, acting as a vaccine, which triggers immunity to pathogens of concern. One such vaccine platform (Vaxonella, created by Prokarium) turns a genetically engineered attenuated strain of the *Salmonella enterica* bacterium into an in vivo bioreactor to create recombinant vaccines. These bacteria are placed inside capsules that, once swallowed, dissolve in the small intestine and release the bacteria. Through natural processes, these bacteria traverse the intestinal mucosa through microfold cells, which carry them to aggregated lymphoid follicles known as Peyer's patches. Within these lymphoid follicles, antigen presenting cells (APC), such as dendritic cells and macrophages, naturally respond and phagocytose an invading bacterium. Once inside these human immune cells, the engineered bacterium begins to express antigens that trigger the APCs to stimulate all arms of the



immune system. The bacterium itself is then quickly destroyed by the body's immune cells.

Typhella, a vaccine for typhoid fever, has already been made using this platform and has been shown thus far to be safe and effective in 5 phase I and 3 phase II clinical trials. The ease with which the *Salmonella enterica* strain can be genetically manipulated lends itself to producing a wide range of vaccine antigens.

WHAT PROBLEM DOES THIS SOLVE?

Simplified and low-cost administration makes oral vaccines an attractive option, but previous oral vaccines have had challenges related to efficacy and safety. Some oral vaccines are inferior to those delivered via injection because they are unable to elicit a sufficient immune response through the gut. Other vaccines, like the oral polio vaccine, may be protective and effective for outbreak response, but they can revert to a disease-causing form and spread from person to person.

Through the use of synthetic biology, the Vaxonella platform overcomes several of the limitations that have prevented widespread use of oral vaccines. Because, in this case, antigen is being made within the body's own cells, there is no need for the costly protein purification techniques used to develop antigen in a laboratory. Additionally, by using the bacteria's natural protein expression system, antigens can be created more easily than they could

be in the lab. And because the bacteria would produce antigen in APCs and not before, it is possible to express antigens that would normally be toxic to the chassis bacteria themselves. This allows the platform to make vaccines with antigens that, due to their toxicity, are not compatible with other vaccine platforms. Finally, using attenuated bacteria with genetic deletions greatly reduces the chance of the bacteria reverting to wild type and causing disease.

There are several logistical and social barriers that this type of oral vaccine would also help overcome. The Vaxonella platform produces thermostable vaccine products that can be stored at 40°C for several weeks, making vaccination more cost-effective and logistically easier because cold chain is not necessary. Oral formulation of this type of vaccine also avoids the need to have healthcare providers administer it. And avoiding the pain and discomfort associated with needle pricks will also increase patient compliance.

HOW DO WE DO IT NOW?

Many vaccines made using current methods rely heavily on cold chain to ensure product quality, which can account for up to 50% of distribution costs.⁴³ This is a major barrier in producing cost-effective vaccines for low-resource settings, where there is already an increased risk of infectious disease outbreaks due to weakened healthcare and sanitation infrastructure and malnutrition.

Subcutaneous and intramuscular injections remain the primary form of vaccine administration, but healthcare providers are needed to administer vaccines, making it logistically challenging to respond to an emergency in a timely and efficient manner.

There are currently only a handful of licensed oral vaccines, because of difficulties in effectively transporting viral antigens across the gut epithelium. Furthermore, complex viral antigens display intricate folding structures that make them very technically difficult, time-consuming, and costly to produce as traditional subunit vaccines for injection.

WHAT DOES SUCCESS LOOK LIKE?

This type of oral vaccine platform could enable the development of a vaccine within a substantially reduced time frame, at a fraction of the current cost. Without the need for cold chain, distribution and dispensing would be greatly facilitated, and ease of administration could ameliorate much of the logistical burden medical responders currently face, allowing more people to be vaccinated.

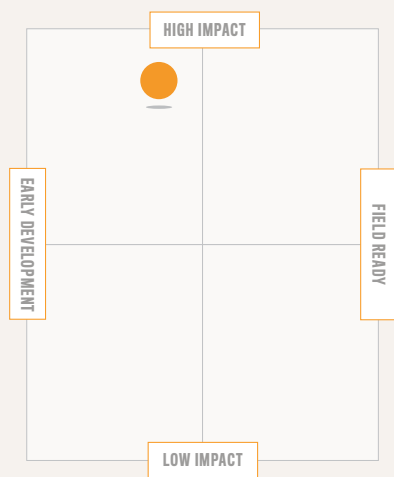
Success of this type of vaccine platform in an emerging epidemic would still depend heavily on improvements in timely identification of disease-specific antigens as well as having the necessary supportive regulatory environment in place. It is currently estimated that in a pandemic situation where the disease is known, optimistically a vaccine using this type of platform could be developed in about 2 months, plus additional weeks to scale up production. Advances in disease-specific antigen-identification platforms would expand the applicability of this technology to deal with emerging infectious diseases.

Medical Countermeasure Distribution, Dispensing, and Administration

In terms of the needed regulatory environment, a company working on related technologies, Synlogic, has recently had regulatory success with their

synthetic oral probiotic medicine through the FDA Fast Track Designation. Synlogic uses synthetic biology to engineer orally administered *E. coli* Nissle

to perform specific therapeutic functions to correct metabolic dysregulation in certain diseases. This success may help provide a path forward for similar technologies.



KEY READINGS

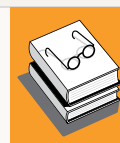
Prokarium. The Vaxonella® platform. <http://prokarium.com/vaxonella-platform/>. Accessed January 12, 2018.

Synlogic. Creating a Synthetic Biotic™ medicine. <https://www.synlogictx.com/synthetic-biotics/creating-a-synthetic-biotic/>. Accessed January 17, 2018.

Synlogic. Synlogic receives fast track designation in U.S. for lead candidate, SYN1020. June 26, 2017. <https://www.synlogictx.com/news/press-releases/synlogic-receives-fast-track-designation-u-s-lead-candidate-synb1020/>. Accessed January 17, 2018.

Vela Ramirez JE, Sharpe LA, Peppas NA. Current state and challenges in developing oral vaccines. *Adv Drug Deliv Rev* 2017;114:116-131.

World Health Organization. First mass campaign using a vaccine outside the cold chain is successful [press release]. February 19, 2014. http://www.who.int/immunization/newsroom/press/19_02_2014_meningitis_vaccine_outside_cold_chain/en/. Accessed January 12, 2018.



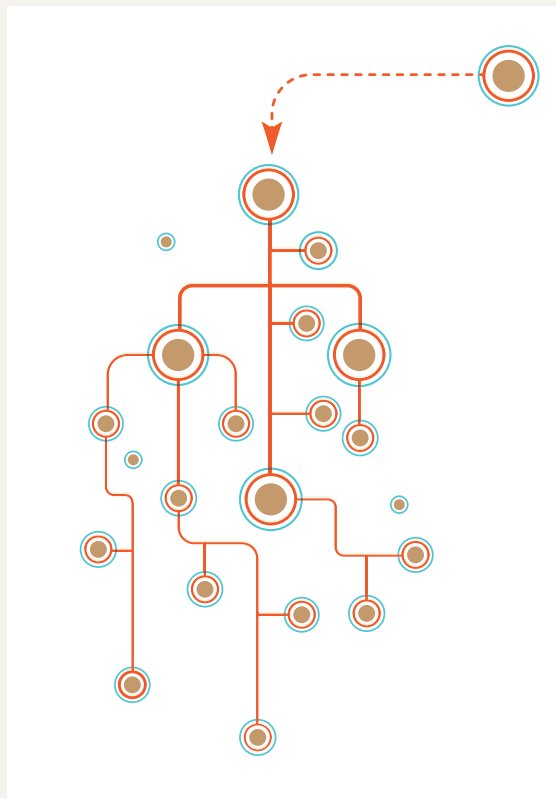
Synthetic Vaccinology: Self-Amplifying mRNA Vaccines

WHAT IS THE TECHNOLOGY?

The current time frame for vaccine licensure remains a major obstacle to flexible and rapid outbreak response. Novel vaccine platforms seek to shorten this time by providing flexible, timely, and cost-effective means for large-scale vaccine production. Recent research in synthetic vaccinology has highlighted **self-amplifying mRNA (SAM)** vaccines for their safety and excellent immunogenic response profiles.⁴⁴ Although the idea of RNA vaccines is not a novel concept, recent advances in potential delivery systems in combination with RNA vaccine have renewed interest in these products.

SAM vaccines use the genome of a modified virus with positive sense RNA. Positive sense RNA is recognizable to our human translational machinery, whereas negative sense RNA is not. Normally, once a positive sense RNA virus enters a human cell, it is translated by the cell into various structural proteins and a viral replicase (which creates copies of the viral genome).

The SAM vaccine platform works by enzymatically synthesizing a positive sense RNA strand from a complementary DNA template; however, the sequence that would normally code for the viral



structural proteins is instead replaced with a sequence that codes for an antigen of interest. Consequently, once inside a cell, the SAM is immediately translated and creates 2 proteins: the antigen of interest and the viral replicase. The viral replicase is then able to drive intracellular amplification by synthesizing a negative sense copy of the originally injected RNA, which will then result in production of additional positive sense viral RNA in a recursive process.

The use of a positive, single-strand RNA viral backbone for vaccine ensures self-amplification in a human host, while the removal of viral structural proteins

eliminates the production of viral particles, effectively preventing a potentially harmful infectious cycle.

WHAT PROBLEM DOES THIS SOLVE?

The safety, efficacy, and ease of manufacturing of mRNA vaccines make them potentially attractive alternatives to other vaccination methods. Using mRNA, which replicates in the cytoplasm and not in the nucleus, avoids the technical barrier of nuclear delivery (getting through the nuclear membrane). It also avoids the risk of **insertional mutagenesis**,⁴⁵ or integration into the host genome, which could potentially lead to

cancer and other problems, a common concern associated with DNA-based vaccines.

The ability of SAM to self-replicate results in a stronger, broader, and more effective humoral and cellular immune response than some other vaccines. Additionally, these vaccines can be produced through in vitro transcription reactions, which avoids the need for cell-based manufacturing and allows for rapid and highly scalable vaccine production. During the 2013 H7N9 outbreak in China, a **prototype SAM(H7)** vaccine was synthesized in only 8 days,⁴⁶ whereas other vaccines, using cell-based production, took between 6 and 12 weeks.

Additionally, studies have shown that SAM and other mRNA vaccines exhibited equivalent levels of protection against influenza strains. However, SAM proved to be more effective, requiring a **64-fold less dose**.⁴⁷ A SAM vaccine has also been created against the bacterial pathogen *Streptococcus*, thus highlighting the platform's versatility.⁴⁸

Recent advances in viral delivery methods such as lipid nanoparticle (LNP) packaging has further enhanced the delivery and immunogenicity of SAM vaccines.⁴⁹ Encapsulation of RNA in LNPs has been shown to protect from enzymatic degradation and to improve intracellular uptake efficiency after injection. Additionally, since LNPs do not express the vector surface proteins, they avoid anti-vector immunity. Cationic nanoemulsion (CNE) has also proven to be an effective biodegradable delivery vehicle that is well tolerated and immunogenic in various animal models.⁵⁰ Additional work is needed to test the various **other biodegradable vaccine delivery platforms** and vehicles to determine which is optimal.⁵¹

HOW DO WE DO IT NOW?

Current vaccine delivery technologies lack flexibility and require costly manufacturing processes. Recombinant viral vector technologies have the advantage of efficient delivery of the nucleic acid payload, but their utility is often hampered by anti-vector immunity, production limitations due to traditional egg-based culture methods, and safety concerns of reverting back to wild-type. Although a potentially safer alternative, subunit vaccines are less efficient and do not induce a cellular immune response, and thus they often require inclusion of adjuvants to make them more potent. Certain antigen protein folding patterns are difficult to create with current technology. Additionally, current protein purification methods are difficult, thus driving up manufacturing cost.

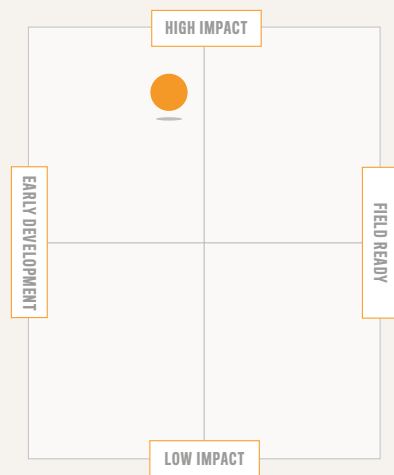
WHAT DOES SUCCESS LOOK LIKE?

Synthetic RNA vaccine technology has the potential to substantially shorten the time frame between pathogen sequence acquisition in the field to vaccine manufacturing. The speed provided by this platform could result in potential vaccine candidates just days after the discovery of a new virus, thus allowing responders to act much earlier in an unfolding epidemic.

In addition to the speed, the self-amplifying nature of the vaccine means that protective immunity may arise from a much smaller vaccine dose. In the context of a GCBR, the dose-saving potential of SAM vaccines would allow the initial batch of vaccine to reach a much wider population, potentially saving many more lives.

However, while this platform is promising, it will rely heavily on further refinement of vaccine delivery methods for the large RNA replicon (9kb). The use of lipid nanoparticle delivery systems is one of the most promising options to date due to biodegradability and potential for scalability. Several lipid-based formulations have already been approved for clinical use with different compounds, which might help speed up regulatory approval after efficacy trials.

While there is currently no specific regulatory guidance from either the FDA or the European Medicines Agency regarding mRNA vaccines, many of the same principles that guide DNA-based vaccines and gene therapy vectors can be applied to mRNA. As the mRNA vaccine field continues to expand, it is likely that specific guidance on production and evaluations of mRNA vaccines will be developed.



KEY READINGS



Brito LA, Chan M, Shaw CA, et al. A cationic nanoemulsion for the delivery of next-generation RNA vaccines. *Mol Ther* 2014;22(12):2118-2129. <https://dx.doi.org/10.1038%2Fmt.2014.133>. Accessed June 27, 2018.

Brito LA, Kommareddy S, Maione D, et al. Self-amplifying mRNA vaccines. *Adv Genet* 2015;89:179-233.

Dormitzer PR, Suphaphiphat P, Gibson DG, et al. Synthetic generation of influenza vaccine viruses for rapid response to pandemics. *Sci Transl Med* 2013;5(185):185ra68.

Lin CY, Lin SJ, Yang YC, Wang DY, Cheng HF, Yeh MK. Biodegradable polymeric microsphere-based vaccines and their applications in infectious diseases. *Hum Vaccin Immunother* 2015;11(3):650-656. <https://dx.doi.org/10.1080%2F21645515.2015.1009345>. Accessed June 27, 2018.

Magini D, Giovani C, Mangiavacchi S, et al. Self-amplifying mRNA vaccines expressing multiple conserved influenza antigens confer protection against homologous and heterosubtypic viral challenge. *PLoS One* 2016;11(8):e0161193. <https://doi.org/10.1371/journal.pone.0161193>. Accessed June 27, 2018.

Maruggi G, Chiarot E, Giovani C, et al. Immunogenicity and protective efficacy induced by self-amplifying mRNA vaccines encoding bacterial antigens. *Vaccine* 2017;35(2):361-368. <https://doi.org/10.1016/j.vaccine.2016.11.040>. Accessed June 27, 2018.

Pepini T, Pulichino AM, Carsillo T, et al. Induction of an IFN-mediated antiviral response by a self-amplifying RNA vaccine: implications for vaccine design. *J Immunol* 2017;198(10):4012-4024. <https://doi.org/10.4049/jimmunol.1601877>. Accessed June 27, 2018.

Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines—a new era in vaccinology. *Nat Rev Drug Discov* 2018;17(4):261-279. <https://www.nature.com/articles/nrd.2017.243>. Accessed June 27, 2018.

Vogel AB, Lambert L, Kinnear E, et al. Self-amplifying RNA vaccines give equivalent protection against influenza to mRNA vaccines but at much lower doses. *Mol Ther* 2017;26(2):446-455. <https://doi.org/10.1016/j.ymthe.2017.11.017>. Accessed June 27, 2018.

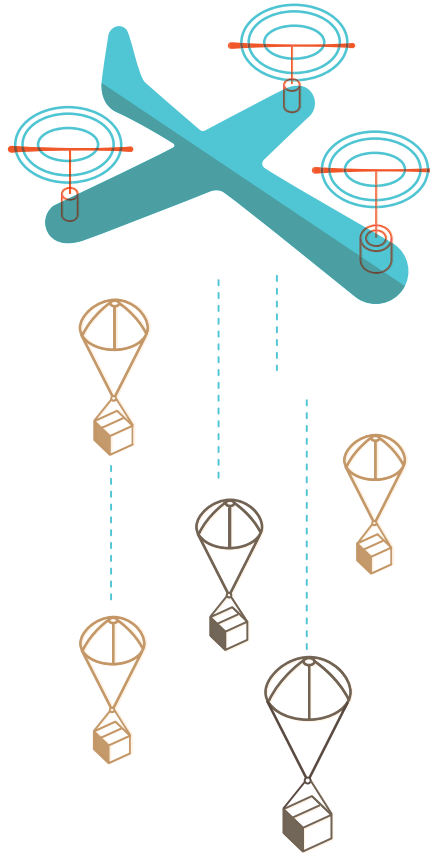
Drone Delivery to Remote Locations

WHAT IS THE TECHNOLOGY?

As discussed in a previous section, drones are unmanned vehicles—aerial, terrestrial, aquatic, or subaquatic—that can be directly controlled by a remote operator or operated autonomously. These vehicles can perform a wide variety of functions, depending on the specifications and purpose of the particular unit. In general, drone systems require the vehicle, a control system or operator, and a communication link between them. The recent availability of commercial off-the-shelf drones has facilitated an increase in their use in professional settings, leading to expanded roles for drones and drone operators during emergency responses.

WHAT PROBLEM DOES THIS SOLVE?

Drones are a platform technology that could support a wide variety of capabilities across the spectrum of GCB event detection and response. One of the most popular applications of existing drone systems is the airborne transportation of clinical



specimens, MCMs, or other supplies within or to remote areas. For example, a program in Rwanda operated by Zipline can deliver blood products from a central repository to hospitals nationwide, a trip that would take 4 hours by truck (under ideal conditions), in as few as 17 minutes by aerial drone. The principal benefit of these kinds of efforts is gaining ready access to remote or otherwise inaccessible areas.

Expanding on the scope and capabilities of these kinds of programs could allow for expanded range and payload for delivery and transportation systems.

Transportation of medical supplies would not be limited to the delivery of clinical specimens or supplies. In fact, these transportation networks could also be used to facilitate distributed manufacturing capabilities to support local outbreak response. Rather than relying on centralized, large-scale production platforms, on-demand delivery of specific active pharmaceutical ingredients, drug precursors, or genetic material could enable local production of MCMs, vaccines, or other products on a smaller scale, tailored to a particular pathogen.

Another significant advantage of using drones during infectious disease outbreaks, particularly those with global catastrophic potential, is that they remove humans from the affected environment and reduce or eliminate the potential for exposure to deadly pathogens. By reducing the risk to responders and the broader public, drones could reduce disease transmission without cutting off affected populations from clinical care, laboratory diagnostics, or other services, particularly in areas in which it is not possible for humans to operate safely.

HOW DO WE DO IT NOW?

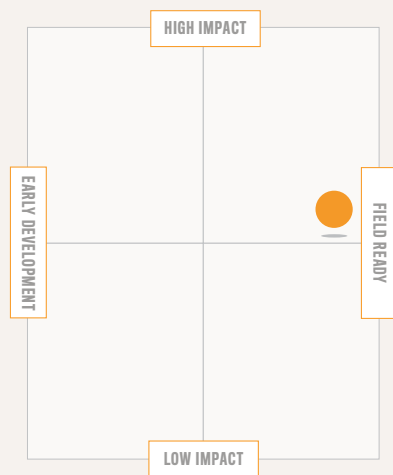
Current efforts to transport clinical specimens, countermeasures, and other medical supplies largely rely on human-operated, ground-based vehicles such as trucks. International shipping is conducted predominantly by airplanes and cargo ships, but local delivery is typically limited to ground vehicles, as helicopters are often too expensive. While trucks are effective in areas with well-established and maintained roadways and the infrastructure to provide the necessary fuel, these are not always available in developing areas that are often at the greatest risk from infectious diseases and natural disasters. Unpaved roads and mountainous terrain are difficult to traverse under ideal conditions, and inclement weather or destruction related to natural disasters or conflict can quickly make existing roads impassable,⁵² at least in a time frame in which the supplies would be beneficial. Delays in transporting medical materiel and clinical specimens can result in these supplies being unusable (eg, via an interrupted cold chain) or allow an outbreak to spread in the absence of effective diagnostics or MCMs.

WHAT DOES SUCCESS LOOK LIKE?

As a platform, drones could facilitate the expansion of services or the integration of other technologies into environments in which they currently are not available. Transportation and surveillance are likely the areas in which drones can make the most impact on GCB event preparedness, detection, and response. Transportation networks can enable the rapid delivery of clinical materiel and pharmaceutical supplies to areas that are difficult to access because of physical or topographical barriers or due to risk of infection for human responders.

The future of drones will be one of variety, with a wide range of units with varying capabilities (and cost) available to meet users' specific needs. The drones themselves will cease to be the limiting factor in their use. In the future, continued development will result in a variety of drones capable of incorporating any payload or function, further catalyzing innovation in sensors, communications systems, and other capabilities to meet changing requirements.

One of the challenges facing the expanded use of drones in many countries is regulatory limitations. Because commercial, off-the-shelf drones are a relatively new phenomenon, regulatory agencies, particularly at the national level, are struggling to classify and effectively oversee drone operations. In the United States, for example, drone use is limited to line-of-sight operations. While this is reasonable for most recreational use, it results in significant barriers to commercial or humanitarian use. Beyond-line-of-sight or over-the-horizon use of drones are likely required to make any impact on preparedness or response to potential global catastrophic biological events, particularly in remote geographic areas. Each country will have its own unique regulatory requirements, and they will evolve with varying speed and effectiveness.



KEY READINGS

Amukele T, Ness PM, Tobian AA, Boyd J, Street J. Drone transportation of blood products. *Transfusion* 2017;57(3):582-588.

Amukele TK, Street J, Carroll K, Miller H, Zhang SX. Drone transport of microbes in blood and sputum laboratory specimens. *J Clin Microbiol* 2016;54(10):2622-2625. <http://jcm.asm.org/content/54/10/2622.full>. Accessed February 14, 2018.

Haidari LA, Brown ST, Ferguson M, et al. The economic and operational value of using drones to transport vaccines. *Vaccine* 2016;34(34):4062-4067. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5547752/>. Accessed February 14, 2018.

Katariya M, Chung DCK, Minife T, et al. Drone inflight mixing of biochemical samples. *Anal Biochem* 2018;545:1-3. <https://www.sciencedirect.com/science/article/pii/S0003269718300046?via%3Dihub>. Accessed February 14, 2018.

Lichtman A, Nair M. Humanitarian uses of drones and satellite imagery analysis: the promises and perils. *AMA J Ethics* 2015;17(10):931-937. <http://journalofethics.ama-assn.org/2015/10/stas1-1510.html>. Accessed February 14, 2018.

Lippi G, Mattiuzzi C. Biological samples transportation by drones: ready for prime time? *Ann Transl Med* 2016;4(5):92. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4791341/>. Accessed February 14, 2018.



Medical Care and Surge Capacity

Surge capacity in medical care is a major limiting factor in responding to severe infectious disease events. Epidemics of highly transmissible pathogens like influenza, or highly lethal pathogens like Ebola virus, can quickly overwhelm not only a single hospital, but an entire healthcare system. In the case of Ebola, the US healthcare system has the capacity to provide high-quality care safely for only a few dozen patients. In the 1918 influenza pandemic, the breakdown of healthcare systems meant that many people died without adequate access to clinical treatment.

Since the 1918 influenza pandemic, health care has progressed in many ways: We now have more antibiotics and other treatment options and the capability to provide supportive care for critically ill patients, making infectious diseases more survivable. However, the past century of progress in health care has some downsides as well. Improved efficiency and cost-

effectiveness mean that hospitals are routinely filled nearly to capacity, and supplies are delivered using highly coordinated, just-in-time supply systems, eliminating the need for sizeable on-site stockpiles. This means that when we face the next pandemic, health care may not be able to keep pace with demand.



The 2017-18 influenza season threw these vulnerabilities into sharp relief: Even a severe seasonal influenza epidemic stretched hospitals thin. A severe pandemic would be much worse.

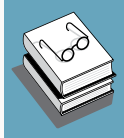
Efforts in the United States to improve healthcare preparedness, including the creation of healthcare coalitions and designated infectious disease resource hospitals, have begun to address these vulnerabilities. But in order to truly reduce these risks, access to quality clinical care during a pandemic will need to be expanded far beyond current capacity.

This section highlights technologies that have the potential to expand clinical care outside of traditional healthcare settings to provide greater surge capacity in a pandemic or GCB event.

KEY READINGS

Ferraro T. The United States is not ready for another flu pandemic. *Smithsonian* November 13, 2017. <https://www.smithsonianmag.com/science-nature/united-states-not-ready-another-flu-pandemic-180967177/>. Accessed June 27, 2018.

Osterholm MT, Olshaker M. We're not ready for a flu pandemic. *New York Times* January 8, 2018. <https://www.nytimes.com/2018/01/08/opinion/flu-pandemic-universal-vaccine.html>. Accessed June 27, 2018.



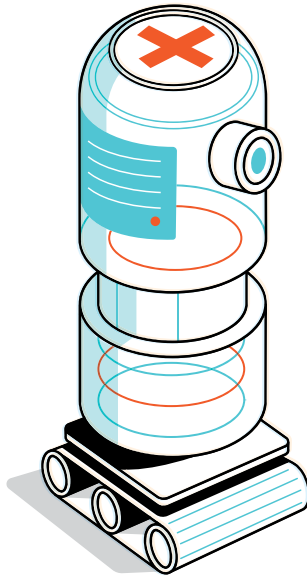
Robotics and Telehealth

WHAT IS THE TECHNOLOGY?

Robotics and telehealth are 2 broad categories of healthcare technologies that may be relevant during the medical response to a GCB event. Because of their common potential to extend the reach of healthcare providers to vulnerable, at-risk, or general populations, we've elected to consider them jointly in this section. Like most technological advances, they extend both the human sensorium and our ability to act over large distances. However, we recognize that they are distinct modalities whose healthcare applications have only recently been developed and are in the process of being refined.

As such, discussion of these technologies in the context of a GCB event is highly speculative.

The first technological category is the application of advanced robotics to the provision of health care. The field of robotics is not new, but its diffusion into the healthcare arena is a more recent development. Robots can currently be found in the halls of many hospitals,⁵³ where they are used primarily for transportation of lab samples, medications, and other essentials. They are also starting to be used to provide clinical care more directly. As typified by the da Vinci surgical robot, the dexterity of medical robots has improved dramatically, and advancements in autonomy and decision making are expected, given rapidly developing artificial intelligence and machine learning approaches.



The second category is the ability to remotely **connect healthcare providers to patients** through advanced information and communications technologies—a modality increasingly referred to as “telehealth.” Telehealth can facilitate the remote diagnosis, treatment, education, care, and follow up of a patient, and it is now used routinely for general infectious disease consults in the United States. This capability was **recognized by the US Congress** in the Pandemic and All-Hazards Preparedness Act of 2006 as a potential way to enhance preparedness and response capabilities, particularly for patients who reside in rural communities.⁵⁴ Recent public health **emergency declarations** have acknowledged the importance of telehealth in an

emergency and responded by loosening licensing restrictions on treatment and prescribing.⁵⁵ However, the effect of telehealth has been limited to date because of technical challenges and because it requires a treating physician on the other end of the line.

WHAT PROBLEM DOES THIS SOLVE?

The combination of robotics and telehealth could replace in-person medical expertise for some needs, yielding a number of potential applications during a GCB event. Infectious disease outbreaks generally take a significant **toll on medical providers** because of their close proximity to the sickest people.⁵⁶ These technologies could preserve medical expertise that would otherwise be lost, potentially replace providers who have been removed from the workforce, or act as a “force multiplier,” permitting one provider to have a greater reach than would otherwise be possible.

In the future, medical robots, operating either under the direction of a remote physician or autonomously, could collect biometric data and biological samples, test these samples, diagnose or treat patients, and dispense pharmaceuticals. Robots may also be able to replace more knowledge- or labor-intensive healthcare delivery activities, such as delivering intravenous fluids or medication.

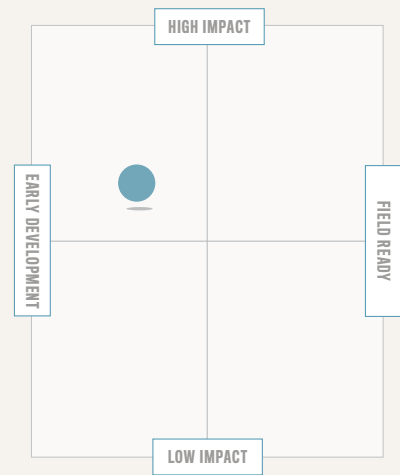
HOW DO WE DO IT NOW?

Although telemedicine and robotics are becoming increasingly intertwined with the delivery of health care, most medical diagnoses and treatments still result from face-to-face interaction between a patient and one or more healthcare professionals.

As it stands now, we can expect that individual healthcare providers, facilities, and systems will be overwhelmed in a severe pandemic.

WHAT DOES SUCCESS LOOK LIKE?

Integration and use of telemedicine and robotics into medical practice are already under way, but they would need to be dramatically expanded to be useful and protective at a population level during a GCB event. Although there are many possibilities for the actual application of these technologies, successful implementation during a GCB event would facilitate medical care being provided in nontraditional environments like the home. In such a scenario, more people could receive care and more lives could be saved.



KEY READINGS

PwC. What doctor? Why AI and robotics will define New Health. June 2017. <https://www.pwc.com/gx/en/industries/healthcare/publications/ai-robotics-new-health/ai-robotics-new-health.pdf>. Accessed February 28, 2018.

Macdonald K. A robotic revolution in healthcare. *BBC News* March 20, 2017. <http://www.bbc.com/news/uk-scotland-39330441>. Accessed February 28, 2018.

Keefe B. Robots/robotics in healthcare. Mayo Clinic Center for Innovation blog May 6, 2016. <https://blog.centerforinnovation.mayo.edu/2016/05/06/robotics-robotics-in-healthcare/>. Accessed February 28, 2018.

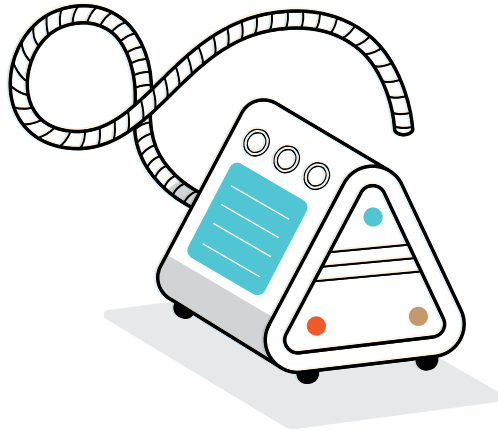


Portable, Easy-to-Use Ventilator

WHAT IS THE TECHNOLOGY?

In a severe outbreak of respiratory disease, ventilators will be needed for the sickest patients to support breathing during the worst of their illness and while they recover. An inexpensive, portable mechanical ventilator that is intuitive and largely automated—particularly if it did not require significant resources (eg, highly trained supervision, electricity, compressed gas) to operate—could allow for the care and survival of many more patients than would be possible if a pandemic emerged today. Mechanical ventilators work by supplanting a normal breathing pattern, enabling the inhalation of oxygen and exhalation of carbon dioxide to maintain body function.

Patients with hypoxemia due to severe pneumonia and acute respiratory distress syndrome (ARDS), where fluid builds up in the lungs, will still likely need to be treated in a hospital by a highly trained physician or respiratory therapist in order to survive. These patients will need to be sedated, intubated, receive compressed oxygen, and be monitored closely. However, patients who are recovering from their illness, or who are less severely ill but who still require ventilation to support breathing, may require less-



intensive care and could be ventilated outside of a hospital in an alternative care facility.

Two types of ventilation exist with the potential to be modified for applications outside of a hospital setting. The first is positive pressure ventilation, in which pressurized air is forced into the lungs, and the second is negative pressure ventilation, in which the chest cavity is mechanically expanded to lower the pressure inside the lungs and draw air in.

Simplified versions of positive pressure ventilators, like the **OneBreath** and **Ventec Life Systems** models, are made applicable to pandemic settings through a simple user interface that allows for easier control of breathing rate and volume. The air supply is provided using either an internal oxygen compressor or external compressed

air (depending on available resources), and they operate using long-lasting rechargeable batteries that make them adequately suited for austere environments without reliable power. They can also be less expensive, costing just a fraction of the price of a typical hospital ventilator.

Negative pressure ventilators, like the **Hayek** model, are basically modern versions of the iron lung. They work through the application of an airtight

outer shell around the chest. Using a mechanical pump, air is removed from the shell, creating a vacuum around the chest and allowing it to expand, subsequently lowering pressure in the lungs to draw air in. Pressure is then reintroduced to the shell, causing the chest to compress, increasing pressure in the lungs and forcing air out. Ventilators like the Hayek model are lightweight, rugged, and portable, with a rechargeable battery. They can be used by both clinical and nonclinical operators, requiring minimal supervision. This type of ventilation will be useful for patients with respiratory failure, when as with polio, muscles and nerves fail and breathing support is needed. It will be much less useful in cases of severe hypoxemia, when patients will need oxygen and suction due to fluid in the lungs.

WHAT PROBLEM DOES IT SOLVE?

In a major pandemic involving a respiratory illness, the healthcare system will quickly be overwhelmed by the large number of critically ill patients who need supportive care, including mechanical ventilation. In the United States and much of the world, ventilators are largely in use for routine medical care, without much surge capacity, due in part to their complexity and cost. Therefore, in many pandemic scenarios, ventilation will become a scarce resource. Recognizing this fact, US health officials have stockpiled a limited supply of additional ventilators to increase nationwide surge capacity. However, it is generally understood that despite planning and stockpiling efforts, ventilators would be in very short supply during a serious pandemic if it were to happen today.

A ventilator that can be used in alternative care facilities with less professional supervision, and fewer resource requirements like compressed air, may enable lifesaving supportive care for patients who are less severely ill or are recovering when hospital-level treatment is unavailable due to patient surge or other lack of access to care.

HOW DO WE DO IT NOW?

Most ventilators used in modern US healthcare settings are highly complex and require a trained physician or respiratory therapist to operate them to ensure that a patient receives the right mix of gases to maintain oxygenation and remove toxic carbon dioxide from the bloodstream. Hospital ventilators require a steady electrical power supply, have a narrow temperature band for use, and use large tanks of compressed oxygen—all resources that may be in short supply or unavailable during a severe pandemic. State-of-the-art hospital ventilators are also very expensive to purchase and operate, costing thousands to tens of thousands of dollars to purchase and \$500 to \$1,500 per day to operate for intensive care.⁵⁷ Patients are often sedated when they are on a hospital ventilator because of the need for intubation and the discomfort that causes.

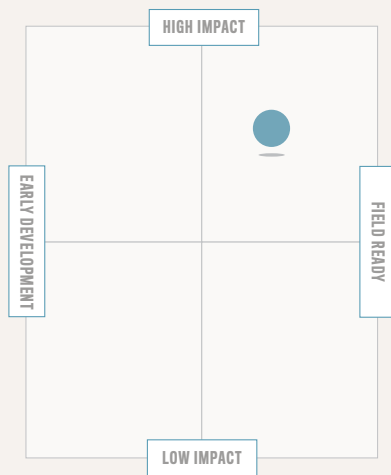
Transport ventilators—used mainly by emergency medical services (EMS) during patient transport—that are available on the market today have some but not all features that would be required in a major pandemic. While portable, they are largely intended for very short-term use, and their accuracy and sophistication vary widely. They are also expensive, costing as much as a hospital ventilator in some cases, and are intended for use by a medical professional, not a novice.

WHAT DOES SUCCESS LOOK LIKE?

In a major pandemic or GCB event, managing patients outside of the hospital can help preserve hospital capacity for the sickest patients. A significant stockpile of portable, easy-to-use ventilators that could be operated at alternative care facilities could help many people survive.

A large global supply of ventilators for pandemic scenarios could greatly improve the quality and efficacy of care available in a pandemic and thus improve survivability in a catastrophic event. These ventilators could also be used routinely in areas where healthcare resources are low and where hospital-level respiratory care is currently impossible.

Improvements in oxygen concentrators (as an alternative to compressed air tanks), noninvasive methods of ventilation, and continued simplification of operating systems and battery technologies will make these ventilators even more useful in a pandemic situation. In addition, regulatory agencies will need to see that these kinds of ventilators will be safe and effective, and cost per unit will still need to be lowered to enable mass stockpiling. However, these hurdles are not irreducible and may be worth the investment in preparation for a GCB event.



KEY READINGS

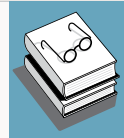
Abramovich MN, Toner ES, Matheny J. Panalysis: a new spreadsheet-based tool for pandemic planning. *Biosecur Bioterror* 2008;6(1):78-92.

Huang HC, Araz OM, Morton DP, et al. Stockpiling ventilators for influenza pandemics. *Emerg Infect Dis* 2017;23(6):914-921. https://wwwnc.cdc.gov/eid/article/23/6/16-1417_article. Accessed June 28, 2017.

L'Her E, Roy A, Marjanovic N. Bench-test comparison of 26 emergency and transport ventilators. *Crit Care* 2014;18(5):506.

Svoboda E. Invention awards: an inexpensive, portable ventilator. *Popular Science* May 28, 2010. <https://www.popsci.com/diy/article/2010-05/invention-awards-breathing-easy>. Accessed June 28, 2017.

Timenetsky KT, Aquino SH, Saghabi C, et al. High success and low mortality rates with non-invasive ventilation in influenza A H1N1 patients in a tertiary hospital. *BMC Res Notes* 2011;4:375. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3224397/>. Accessed June 28, 2017.



Major pandemic risks and global catastrophic biological risks are important and extraordinary challenges. The results of this analysis show that there are technologies that can be harnessed to respond to major pandemics and GCB events:

Conclusions

- ➔ • New approaches to disease detection and transformational surveillance technologies can improve the likelihood of identifying biological events with catastrophic potential.
- Field-deployable and handheld diagnostic tests that can be quickly manufactured and put into use can help support clinical care, isolation, and quarantine, lower morbidity and mortality, and flatten an epidemic curve through reduced disease transmission.
- Distributive manufacturing is one possible solution to facilitating global production of vaccines and drugs at scale and on a timeline sufficient to affect response operations.
- Novel approaches to medical countermeasure distribution, dispensing, and administration can ensure that drugs and vaccines reach the people who need them in time to save lives and reduce disease.
- Innovations in medical care that enable care at home will help people survive even if healthcare systems are overwhelmed and healthcare providers are unavailable.

The technologies highlighted in this report represent new possible approaches to addressing severe risks. Technologies that are democratized, distributed, field ready, user friendly, and globally attainable are essential.

To achieve the visions of success woven throughout this report will require dedicated effort and investment in the technology areas highlighted above. While this is occurring for vaccine development, and to some extent for surveillance, other needs for preventing and responding to pandemic and GCB events must be addressed if we are to confront these threats in a serious way.

This report highlights 15 technologies that, with further scientific attention and investment, as well as attention to accompanying legal, regulatory, ethical, policy, and operational issues, could help make the world better prepared and equipped to prevent future infectious disease outbreaks from becoming catastrophic events.

REFERENCES

1. US Agency for International Development; White House Office of Science and Technology Policy; US Centers for Disease Control and Prevention; Department of Defense. Fighting Ebola: a grand challenge for development. USAID website. 2015. <http://www.ebolagrandchallenge.net/>. Accessed May 29, 2018.
2. US Agency for International Development. Combating Zika and future threats: a grand challenge for development. USAID website. Updated January 26, 2018. <https://www.usaid.gov/grandchallenges/zika>. Accessed May 29, 2018.
3. Organisation for Economic Co-operation and Development (OECD). Futures thinking: overview of methodologies. OECD website. Undated. <https://www.oecd.org/site/schoolingfortomorrowknowledgebase/futuresthinking/overviewofmethodologies.htm>. Accessed April 18, 2018.
4. Norberg AL. An interview with George Heilmeier. March 27, 1991. Minneapolis: Charles Babbage Institute, Center for the History of Information Processing, University of Minnesota; 1991. <https://conservancy.umn.edu/bitstream/handle/11299/107352/oh226ghh.pdf?sequence=1&isAllowed=y>. Accessed May 29, 2018.
5. DARPA. Innovation at DARPA. July 2016. https://www.darpa.mil/attachments/DARPA_Innovation_2016.pdf. Accessed May 29, 2018.
6. Burke A. DNA sequencing is now improving faster than Moore's Law. *Forbes* January 12, 2012. <https://www.forbes.com/sites/teconomy/2012/01/12/dna-sequencing-is-now-improving-faster-than-moores-law/#3548c7615e4f>. Accessed February 28, 2018.
7. Internet Society. 2017 Global Internet Report: Paths to Our Digital Future. 2017:79. <https://future.internetsociety.org/wp-content/uploads/2017/09/2017-Internet-Society-Global-Internet-Report-Paths-to-Our-Digital-Future.pdf>. Accessed April 18, 2018.
8. Reingold AL. If syndromic surveillance is the answer, what is the question? *Biosecur Bioterror* 2003;1(2): 77-81.
9. Terry W, Ostrowsky B, Huang A. Should we be worried? Investigation of signals generated by an electronic syndromic surveillance system—Westchester County, New York. *MMWR Morb Mortal Wkly Rep* 2004;53 (suppl):190-195.
10. US Department of Homeland Security. BioWatch. Undated. <https://www.dhs.gov/sites/default/files/publications/BioWatch%20Factsheet.pdf>. Accessed May 31, 2018.
11. Mystery device in downtown San Francisco is air sampler to detect biological attack. *CBS SF Bay Area* January 28, 2016. <http://sanfrancisco.cbslocal.com/2016/01/28/mystery-device-in-downtown-san-francisco-an-air-sampler-to-detect-biological-attack/>. Accessed May 31, 2018.
12. Former navy chief presses U.S. to rework bioagent detection strategy. *Global Security Newswire* February 26, 2013. <http://www.nti.org/gsn/article/leading-expert-presses-us-rework-bioweapon-detection-strategy/>. Accessed May 31, 2018.
13. World Health Organization. *Guidelines for Environmental Surveillance of Poliovirus Circulation*. Geneva: WHO; 2003. http://polioeradication.org/wp-content/uploads/2016/07/WHO_V-B_03.03_eng.pdf. Accessed May 31, 2018.
14. Wolinski H. Biology goes in the air: unmanned aerial vehicles offer biologists an efficient tool for observation and sampling from a safe distance. *EMBO Rep* 2017;18(8):1284-1289.
15. Institute of Medicine. Forum on Microbial Threats. Board on Global Health. *Global Infectious Disease Surveillance and Detection: Assessing the Challenges—Finding Solutions. Workshop Summary*. Washington, DC: National Academies Press; 2007.
16. World Health Organization. Barriers to rapid containment of the Ebola outbreak. Ebola situation assessment. August 11, 2014. <http://www.who.int/csr/disease/ebola/overview-august-2014/en/>. Accessed May 23, 2018.
17. Luthra S. Lab constraints delay Zika test results. *Medical Xpress* October 10, 2016. <https://medicalxpress.com/news/2016-10-lab-constraints-zika-results.html>. Accessed May 23, 2018.

REFERENCES

18. Rohn J. First mass spectrometry diagnostic approved in US. *Nat Biotechnol* 2013;31(10):862.
19. Rollins G. The infectious diseases diagnostic revolution. *Clinical Laboratory News* May 1, 2014. <https://www.aacc.org/publications/cln/articles/2014/may/infectious-diseases>. Accessed June 5, 2018.
20. Zhang J, Rector J, Lin JQ, et al. Nondestructive tissue analysis for ex vivo and in vivo cancer diagnosis using a handheld mass spectrometry system. *Sci Transl Med* 2017;9(406):eaan3968.
21. Strickland E. Angry Kickstarter backers ask: where's SCiO, my pocket-size molecular sensor? *IEEE Spectr* September 14, 2016. <https://spectrum.ieee.org/the-human-os/biomedical/devices/angry-kickstarter-backers-ask-scio-wheres-my-pocketsized-molecular-sensor>. Accessed June 6, 2018.
22. Lu Y. Cell-free synthetic biology: engineering in an open world. *Synth Syst Biotechnol* 2017;2(1):23-27.
23. Ausländer S, Fussenegger M. Synthetic biology: toehold gene switches make big footprints. *Nature* 2014;516(7531):333-334.
24. Pardee K, Green AA, Ferrante T, et al. Paper-based synthetic gene networks. *Cell* 2014;159(4):940-954.
25. Pardee K, Green AA, Takahashi MK, et al. Rapid, low-cost detection of Zika virus using programmable biomolecular components. *Cell* 2016;165(5):1255-1266.
26. Lawrence J. Synthetic biology: microbes made to manufacture drugs. *Pharm J* 2015;295(7882). <https://www.pharmaceutical-journal.com/news-and-analysis/features/synthetic-biology-microbes-made-to-manufacture-drugs/20069575.article>. Accessed June 6, 2018.
27. The history of beer yeast. *ScienceDaily* September 8, 2016. <https://www.sciencedaily.com/releases/2016/09/160908130552.htm>. Accessed June 6, 2018.
28. Perez-Pinera P, Han N, Cleto S. Synthetic biology and microbioreactor platforms for programmable production of biologics at the point-of-care. *Nat Commun* 2016;7:12211. <https://www.nature.com/articles/ncomms12211.pdf>. Accessed June 6, 2018.
29. Luginbuhl RE. The commercial production of specific-pathogen-free eggs and chickens: the evolution of an industry. *Avian Dis* 2000;44(3):632-637.
30. Peplow M. Synthetic biology's first malaria drug meets market resistance. *Nature* 2016;520(7591):389-390.
31. Service R. You could soon be manufacturing your own drugs—thanks to 3D printing. *Science* January 18, 2018. <http://www.sciencemag.org/news/2018/01/you-could-soon-be-manufacturing-your-own-drugs-thanks-3d-printing>. Accessed June 7, 2018.
32. Hernandez D. Craig Venter imagines a world with printable life forms. *Wired* October 16, 2012. <https://www.wired.com/2012/10/printable-life-forms/>. Accessed May 28, 2018.
33. Atwell C. 3-D printing to the rescue of US military. Printing drones on demand is on its way. *Tech Times* January 3, 2018. <http://www.techtimes.com/articles/217341/20180103/3-d-printing-to-the-rescue-of-us-military-printing-drones-on-demand-is-on-its-way.htm>. Accessed June 7, 2018.
34. Murphy SV, Atala A. 3D bioprinting of tissues and organs. *Nat Biotechnol* 2014;32(8):773-785.
35. Vaidya M. Startups tout commercially 3D-printed tissue for drug screening. *Nat Med* 2015;21(1):2.
36. Mearian L. This is the first 3D-printed drug to win FDA approval. *Computerworld* March 28, 2016. <https://www.computerworld.com/article/3048823/3d-printing/this-is-the-first-3d-printed-drug-to-win-fda-approval.html>. Accessed June 15, 2018.
37. US Centers for Disease Control and Prevention. Final estimates for 2009-10 seasonal influenza and influenza A (H1N1) 2009 monovalent vaccination coverage—United States, August 2009 through May 2010. CDC website. Updated May 13, 2011. https://www.cdc.gov/flu/fluview/coverage_0910estimates.htm#modalIdString_CDCTable_1. Accessed July 5, 2018.
38. World Health Organization. Report of the WHO Pandemic Influenza A(H1N1) Vaccine Deployment Initiative. 2012. http://www.who.int/influenza_vaccines_plan/resources/h1n1_deployment_report.pdf. Accessed June 25, 2018.

REFERENCES

39. Röttingen JA, Gouglas D, Feinberg M, et al. New vaccines against epidemic infectious diseases. *N Engl J Med* 2017;376(7):610-613.
40. Taylor LH, Latham SM, Woolhouse ME. Risk factors for human disease emergence. *Philos Trans R Soc Lond B Biol Sci* 2001;356(1411):983-989.
41. Mähl P, Cliquet F, Guiot AL, et al. Twenty year experience of the oral rabies vaccine SAG2 in wildlife: a global review. *Vet Res* 2014;45(1):77.
42. Gomes-Solcki MJ, Brisson DR, Dattwyler RJ. Oral vaccine that breaks the transmission cycle of the Lyme disease spirochete can be delivered via bait. *Vaccine* 2006;24(20):4440-4449.
43. World Health Organization. First mass campaign using a vaccine outside the cold chain is successful [press release]. February 19, 2014. http://www.who.int/immunization/newsroom/press/19_02_2014_meningitis_vaccine_outside_cold_chain/en/. Accessed June 26, 2018.
44. Brito LA, Kommareddy S, Maione D, et al. Self-amplifying mRNA vaccines. *Adv Genet* 2015;89:179-233.
45. McDonnell WM, Askari FK. DNA vaccines. *N Engl J Med* 1996;334:42-45.
46. Dormitzer PR, Suphaphiphat P, Gibson DG, et al. Synthetic generation of influenza vaccine viruses for rapid response to pandemics. *Sci Transl Med* 2013;5(185):185ra68.
47. Vogel AB, Lambert L, Kinnear E, et al. Self-amplifying RNA vaccines give equivalent protection against influenza to mRNA vaccines but at much lower doses. *Mol Ther* 2017;26(2):446-455.
48. Maruggi G, Chiarot E, Giovani C, et al. Immunogenicity and protective efficacy induced by self-amplifying mRNA vaccines encoding bacterial antigens. *Vaccine* 2017;35(2):361-368.
49. Pepini T, Pulichino AM, Carsillo T, et al. Induction of an IFN-mediated antiviral response by a self-amplifying RNA vaccine: implications for vaccine design. *J Immunol* 2017;198(10):4012-4024.
50. Brito LA, Chan M, Shaw CA, et al. A cationic nanoemulsion for the delivery of next-generation RNA vaccines. *Mol Ther* 2014;22(12):2118-2129.
51. Lin CY, Lin SJ, Yang YC, Wang DY, Cheng HF, Yeh MK. Biodegradable polymeric microsphere-based vaccines and their applications in infectious diseases. *Hum Vaccin Immunother* 2015;11(3):650-656.
52. Dawson S. Rains complicate delivery of Ebola supplies in West Africa. Reuters September 29, 2014. <https://www.reuters.com/article/us-foundation-ebola-rains/rains-complicate-delivery-of-ebola-supplies-in-west-africa-idUSKCN0HO1SL20140929>. Accessed June 26, 2018.
53. Simon M. Tug, the busy little robot nurse, will see you now. *Wired* November 10, 2017. <https://www.wired.com/story/tug-the-busy-little-robot-nurse-will-see-you-now/>. Accessed June 26, 2018.
54. US Department of Health and Human Services. Pandemic and All-Hazards Preparedness Act: PL 109-417. <https://www.hsdl.org/?abstract&did=683164>. Accessed June 26, 2018.
55. US Department of Health and Human Services. HHS acting secretary declares public health emergency to address national opioid crisis [press release]. October 26, 2017. <https://www.hhs.gov/about/news/2017/10/26/hhs-acting-secretary-declares-public-health-emergency-address-national-opioid-crisis.html>. Accessed June 26, 2018.
56. World Health Organization. Unprecedented numbers of medical staff infected with Ebola [news release]. August 25, 2014. <http://www.who.int/mediacentre/news/ebola/25-august-2014/en/>. Accessed June 26, 2018.
57. American Association for the Surgery of Trauma. Mechanical ventilation in the intensive care unit. <http://www.aast.org/GeneralInformation/mechanical-ventilation.aspx>. Accessed June 26, 2018.

APPENDIX I. *Experts Interviewed*

Kate Adamala, University of Minnesota
Gregory Asmolov, Kings College London
David Baker, University of Washington Institute for Protein Design
Patrick Boyle, Ginkgo Bioworks
Matthew Callaghan, OneBreath
Rob Carlson, Bioeconomy Capital
Peter Carr, MIT Lincoln Lab
Brittany Hume Charm, Zipline
George Church, Harvard University
Lee Cronin, University of Glasgow
Mark Dredze, Johns Hopkins University
Drew Endy, Stanford University
Kevin Esvelt, Harvard University
Ted Fjallman, Prokarium
Jacqueline Fletcher, Oklahoma State University
Keiji Fukuda, University of Hong Kong
Dylan George, In-Q-Tel
Ariel Hecht, National Institute of Standards and Technology (NIST), US Department of Commerce
Matt Hepburn, DARPA
Kendall Hoyt, Dartmouth College
Joseph Jardine, Institute for Protein Innovation
Tiara Jones, In-Q-Tel
David Kong, MIT Media Lab
Joe Larsen, Biomedical Advanced Research and Development Authority, US Department of Health and Human Services
James Love, Institute for Protein Innovation
Tim Lu, MIT
Jason Matheny, IARPA
Piers Millett, Wilson Center and Future of Humanity Institute, University of Oxford
Michael Montague
Kelly Oakeson, Utah Public Health Laboratory, Utah Department of Health
Gene Olinger, Boston University School of Medicine
Sam Olof, OxSyBio
Kenneth Oye, MIT
Megan Palmer, Stanford University
Keith Pardee, University of Toronto
Rembert Pieper, J. Craig Venter Institute
Manu Prakash, Stanford University
Mark Prausnitz, Georgia Institute of Technology
David Rakestraw, Lawrence Livermore National Laboratory

Kunal Rambhia, University of Michigan
David Schmale, Virginia Tech
Carl Shulman, Future of Humanity Institute, University of Oxford
Andrew Snyder-Beattie, Future of Humanity Institute, University of Oxford
John Sotos, Intel Health & Life Sciences
Timothy Springer, Institute for Protein Innovation
Winston Timp, Johns Hopkins University
Alexander Titus, In-Q-Tel
Sanjay Vashee, J. Craig Venter Institute
Renee Wegrzyn, DARPA
Jennifer Weisman, Bill & Melinda Gates Foundation
George Whitesides, Harvard University
John Wilbanks, Sage Bionetworks
Paul Yager, University of Washington
Larry Zeitlin, Mapp Biopharmaceuticals

APPENDIX II. *Interview Questions*

Please think about the following questions in preparation for our discussion:

- If you could imagine 5-10 years in the future, what do you envision we should be able to do in controlling biological events with pandemic/GCBR potential?
- In your opinion, what is currently “too hard to do” but could have a large return on investment in terms of mitigating GCBRs were it to be solved?
- What technologies in your area of expertise do you think would be revolutionary for addressing GCBRs?
- What technologies or domains outside of your area of expertise do you think would be revolutionary for addressing GCBRs?
- Who else should we speak with? Who might have unique insight into applicable technologies?

APPENDIX III. *Reviewers*

The following individuals reviewed this report in its entirety and provided comments and suggestions, which were incorporated into the final report:

Amesh Adalja, Senior Scholar, Johns Hopkins Center for Health Security
Dylan George, B.Next, In-Q-Tel
Jason Matheny, Director, IARPA
Kunal Rambhia, doctoral candidate, University of Michigan



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