GOVERNANCE IN AN EMERGING NEW WORLD

PANDEMICS AND BIOSECURITY

George P. Shultz and
Milana Boukhman Trounce, MD

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Table of Contents

Foreword

On April 8, 2019, we gathered around the circular table in the Annenberg Conference Room at the Hoover Institution for another discussion from our research project on Governance in an Emerging New World. This session was led by Dr. Lucy Shapiro, a professor of biology at the Stanford University School of Medicine.

One featured speaker was Dr. Milana Boukhman Trounce. One of Hoover's great assets is our ability to draw on the wealth of expertise surrounding us across the Stanford campus, and our interaction with Dr. Trounce exemplifies that. A Stanford professor and emergency medicine physician, policy scholars here were introduced to Dr. Trounce through an even earlier cross-disciplinary Hoover policy panel on the threat of pandemics, organized by Hoover National Security Affairs Fellow Conny Arvis, representing the US Department of State. For our 2019 Governance Project discussion, Dr. Trounce presented a paper on potential pandemics. She described in detail in her paper how "the threat of infectious disease is making a comeback. Unfortunately, at this point, we are ill equipped to deal with a number of scenarios, particularly those involving large-scale infectious disease outbreaks—pandemics." She explained how human activities, including increased contact between humans and wild animals and global transportation networks, have increased the threat of new infectious diseases. She explained why drugs for the treatment of a new disease such as this and vaccines to prevent its spread would not be available in time to prevent a public health crisis. The principal countermeasures would be the same public health measures that have been used for centuries—isolation and quarantine.

We learned that the word "quarantine" is derived from an Italian term for the forty days that all ships were required to be isolated before passengers and crew could go ashore during the fourteenth-century Black Death plague epidemic. We learned about "social-distancing" measures, such as closing schools, public gatherings, businesses, and transport, and the possibility that internet commerce might facilitate implementation of isolation and quarantine. We learned that rapid diagnostic testing, if available, might help a lot. Later in the day, we heard from Stephen Quake, a professor of bioengineering at Stanford, about the potential of modern gene-sequencing technology to rapidly recognize the causes of infectious disease outbreaks.

Overall, the panelists argued that "the public sector is not sufficiently preparing for this." While local public health departments have protocols, do drills, and receive guidance from the federal Centers for Disease Control and Prevention (CDC), "there are too many cooks in the kitchen." A large-scale disease outbreak is not just a medical event but also one of public safety and security: "It's chaos every time, and it is always reactive." Looking at how warehousing and logistics technologies are developing, panelists considered how the US private sector might end up delivering many needed services in such an outbreak, and the market incentives and coordination that governments could consider to help enable that.

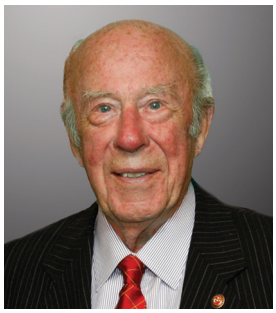
In response, Dr. Shapiro observed, "If you don't push the boundaries of understanding this world that we are living in . . . without new kinds of understandings of how living beings, living organisms, can survive changes in their environment—we are being, if not short-sighted, then we are being criminal."

One year later, project participants found themselves discussing pandemics one again, but not in a circle around Hoover's Annenberg Conference Room on Stanford campus. Instead, we were all in our own squares, meeting virtually over online videoconferencing, each discussant in his or her spare bedroom—three months after a novel coronavirus became capable of infecting and spreading among humans in Wuhan. The potential threat was known, but we were not prepared for it when it became real.

An early retrospective of the US governance and civil society response to the COVID-19 pandemic of 2020 changes little from these warnings. It has simply made them clearer. We understand that political realities make proactivity—fully preparing for every small-chance, large-impact risk ahead of time—infeasible. No one celebrates the mitigation of the outcome that never occurred. One could say that the American way of dealing with the problem of prioritization is instead to react, swiftly and effectively, to the reality that has been made present to everyone. The whole-of-society approach to the 9/11 attacks exemplifies this sort of mobilization. But the COVID-19 pandemic calls that approach into question for the sorts of risks we see coming over the hinge of history and into the rest of the century: though small circles of experts knew exactly how the problems of a pandemic were likely to unfold, their technical foresight described a scenario so foreign to many of our institutions that once it actually happened, attempts to respond to an unrolling crisis fell flat. It took too long for them to internalize the novel nature of the crisis they faced. This was true across many

organs of government. And it highlights the need to not just better prepare for pandemics but better prepare to react to anything, and to be flexible, so as to effectively function while under duress.

The virus shows that we are part of an interconnected world. And a pandemic is a clear example of a problem whose solution would benefit greatly from international cooperation and US leadership. The global response to COVID-19 could have been more effective with better international cooperation—and better US leadership. This is a recurring theme. International cooperation is part of the solution to the transformational challenges before us, including advancing technology, changing demographics, large-scale migration, global warming, and nuclear proliferation, not to mention the potential for infectious diseases far more lethal than COVID-19. Knowledge can lead to assessment of risk and appropriate preparations, and the following (unfortunately needed) sequel to Dr. Trounce's earlier analysis points to steps that we can still take today for a better American recovery from this pandemic—and resilience against other health crises that are sure to come. Informed US leadership here is crucial at this time in our history.



George P. Shultz[1]
Thomas W. and Susan B. Ford Distinguished Fellow
July, 2020

[1] Adapted from George Shultz and James Timbie, *A Hinge of History: Governance in an Emerging New World* (Stanford, CA: Hoover Institution Press, forthcoming [late 2020]).

COVID-19 and Future Pandemics

By Milana Boukhman Trounce, MD | July, 2020

The COVID-19 pandemic shook the world and made humans' vulnerability to infectious organisms apparent to all. When we wrote on potential pandemics in April 2019, as part of Hoover's Governance in an Emerging New World publication series, the notion of a pandemic crippling society and spurring lockdowns and social distancing all over our nation and in much of the world seemed fantastical, something from a hundred years ago—which it was.[1] The last time there were such sweeping infection-control measures in the United States was during the Spanish flu pandemic of 1918.

Yet what has transpired over the past few months followed a pattern remarkably similar to numerous other infectious-disease outbreaks. As such, our views on the management of pandemics, as discussed in the spring of 2019, remain unchanged. We will therefore revisit those ideas in light of the COVID-19 pandemic.

The Increasing Threat of Infectious Disease

Not only is our vulnerability to infectious disease not a new phenomenon. Throughout human history, it has in fact been the most frequent cause of human death. More people have died from infectious disease than from any kind of violence, including war, by at least one order of magnitude.

Infectious organisms have destabilized societies and governments, determined the outcome of wars, and otherwise shaped history. Europe was not the same after over half its population, by some estimates, was wiped out by bubonic plague in the fourteenth century. The course of American history, too, might have been quite different had 90 percent of the native populations not succumbed to the viruses brought by Europeans. Moreover, more people died from the Spanish influenza pandemic of 1918 than in the fighting in World War I. In more recent history, the destabilization due to the Ebola virus outbreak in West Africa caused the United Nations Security Council to declare it a "threat to international peace and security" in September 2014. It was the first resolution of the Security Council to deal with a public health crisis.

Now, we are witnessing the disruption of societies across the world brought on by SARS-CoV-2—the virus responsible for COVID-19. Given the numbers of lives lost in past infectious disease outbreaks, dedicating a level of effort and resources to fighting this pandemic similar to what we expend to win a war seems appropriate.

Although the twentieth century saw a retreat of infectious disease due to the advent of antibiotics, the notion of our species "conquering" them is misleading.

Why, especially now? Since the 1980s, we have seen a threefold increase in the number of global epidemics. Globalization, urbanization, the increased pace of commerce, climate change, and other factors enable viruses to spread faster across the world than ever before, and organisms that historically caused relatively small outbreaks are now able to launch epidemics.

For example, there were more than twenty Ebola outbreaks from 1976 to 2014. They were limited to either one or a cluster of villages in Africa. By contrast, the outbreak of 2015 claimed tens of thousands of lives all across West Africa and terrorized the entire world—the largest outbreak caused by a viral hemorrhagic fever virus in history. Other novel coronavirus outbreaks such as MERS and SARS have been significantly smaller, and coronaviruses causing relatively mild symptoms commonly circulate in human populations. Yet, in recent history, we have seen new types of pathogens causing damage of increasingly ominous proportions. What is driving that, besides urbanization and globalization?

Greater human encroachment on wild animal habitats, climate change, and different patterns of land use have resulted in closer contact between wild animal populations and humans. That increases the risk of viruses moving from animals to human beings. And *that* matters because most infectious disease outbreaks, including pandemics, are caused by viruses that originate in animals.

Viruses are small packages of genetic material—DNA or RNA—that cannot replicate on their own. To do so, they must find their way into an animal or human cell and take over the host's genetic machinery. The viruses often mutate and reassort while they circulate in animal populations. They then challenge human immune systems with novel strains.

SARS, MERS, and the yearly flu pandemics are all examples of this, and the current pandemic is no different. It was sparked by a coronavirus that originated in bats. There are thousands of varied strains of viruses lurking in the wild, all with seemingly infinite potential for change within their DNA and therefore a seemingly infinite number of potential challenges to the human immune system.

At the start of the COVID-19 pandemic, there were concerns about SARS-CoV-2 escaping from the level-4 biosafety (BSL-4) lab in Wuhan, China. Although it is now believed that that was not the case with SARS-CoV-2, with the recent advances in biology, such considerations are not unreasonable. In fact, our growing ability to manipulate biology increases our pandemic risk. Despite efforts to regulate and secure biology through the National Science Advisory Board for Biosecurity, plus other advisory and governmental organizations, perfect control is not possible.

The Challenges of Preparedness and Response

Medical Countermeasures

With respect to the availability of vaccines and drugs to fight COVID-19, right now we are in a similar place to where we were over a hundred years ago during the Spanish flu pandemic. Despite massive global efforts, the goal of producing medical countermeasures capable of saving most lives is still many months away, even in the best-case scenario. This is hardly a surprise. It was also the case during early Ebola outbreaks. By the time there was a vaccine for Ebola, the outbreak was over and there were insufficient numbers of subjects on which to run trials. However, those efforts were helpful with the subsequent outbreaks, during which the vaccine was used successfully.

The development of Remdesivir, which was initially conceived to fight MERS, was paused after the MERS outbreak ended. It was restarted for COVID-19. Unfortunately, it is only partially effective in mitigating the disease, and the COVID-19 mortality rate, even with the use of Remdesivir, remains high.[2]

The US government's typical course of action in response to anxiety-provoking disease outbreaks has been to pour resources into vaccine and drug development. While politically popular, this strategy generally fails, due to the timelines required for vaccine or drug development. To develop, clinically test, produce, and distribute a vaccine or a drug typically takes years, not weeks or months. Therefore, the medical countermeasures that have resulted have usually been used for subsequent outbreaks, not the ones that are then in effect. With advances in technology, the timelines have shrunk somewhat, and we hope that a vaccine for COVID-19 will be available at some point during the current pandemic, perhaps in 2021. In the meantime, we must rely on other tools.

Thinking beyond COVID-19 to future pandemics, the idea of developing universal vaccines for influenza and coronaviruses—not simply ones for individual strains—has a great deal of appeal, since these viruses rapidly mutate and can cause pandemics. However, millions have already been invested in the effort to develop a universal flu vaccine, and it has yet to bear fruit. Now the attempt to develop one for coronaviruses will continue.

Until universal vaccines are developed, there is a possibility we will begin getting a yearly coronavirus shot in addition to the yearly flu shot—both based on the best estimates of which strains will circulate. Some studies have suggested that a mutant and apparently more infectious version of the original SARS-CoV2 virus is now the predominant one.

Even if we were to come up with a vaccine for COVID-19, many in the United States would not agree to be vaccinated. With the yearly flu pandemic, which consistently claims tens of thousands of lives in this country and for which we have decades of vaccine-safety data, only 40 percent of the population gets vaccinated in most years. That number would likely be significantly lower for a COVID-19 vaccine, which would have to be approved under the Food and Drug Administration's "emergency use authorization," with limited clinical-safety data. With the anti-vax movement, we have seen outbreaks of measles and pertussis, which are reliably prevented by vaccinations with proven high rates of safety and efficacy. This is one of the more unfortunate consequences of lack of trust in our government and the increasing politicization of public health. Thus, even with the availability of a COVID-19 vaccine, it is not a given that we would reach herd immunity levels—i.e., 70 percent.

We might also consider repurposing existing drugs for COVID-19 or taking partially developed drugs to completion. Many efforts by esteemed research teams have been designed to do just that, so far with only modest success because such endeavors take time. As we look ahead to preventing or minimizing future pandemics, it would be particularly helpful to develop drugs that are safe and effective against a broad spectrum of viruses, particularly ones known to cause pandemics, such as flu and coronaviruses. Despite the predictable devastation caused by flu each year in this country, to treat it we only have Tamiflu, which shortens the duration of symptoms by half a day and has no effect on mortality for a vast portion of the population, excluding those at very high risk.

Lack of availability of these types of drugs is in large part due to market failure, since it is far more profitable for pharmaceutical companies to develop and produce drugs for chronic diseases rather than ones used at most once a year, if at all. In cases involving market failure but significant public benefit, it is necessary for the government to step in, which has happened to a degree, and provide funding via the Department of Health and Human Services' Biomedical Advanced Research and Development Authority and other means. Now that society is more aware of the vulnerability to pandemics, public and policy support for these efforts should be expanded.

Surge Capacity

With COVID-19, as well as other viral infections such as Ebola and flu, supportive hospital care saves lives, even in the absence of antiviral drugs. The treatments applied there include fluid resuscitation, breathing assistance with the help of oxygen and ventilators, and other measures designed to support vital functions while the body's immune system mounts a response to an infectious organism.

Medical surge capacity—the ability to respond to an increased number of patients—is limited, as was seen with the heart-wrenching crush of early COVID-19 cases in New York, Italy, and other hot spots around the world. Hospital business models do not allow for slack; it is expensive to maintain staffed but unoccupied hospital beds. Although numerous hospitals, including Stanford's, have significantly expanded intensive care units and other inpatient capacity, the ability to address the pandemic is still limited and will likely be outstripped if SARS-CoV-2 is insufficiently mitigated. Meeting the demands of an unmitigated pandemic would require surge capacity to be expanded by one or even two orders of magnitude, which would be prohibitively expensive to maintain.

If Not Drugs, Vaccines, or Increased Surge Capacity, Then What?

Interrupting Transmission

Ultimately, control of any pandemic boils down to one step: interruption of the spread of particles containing infectious organisms. No spread, no pandemic. This is simple in principle, challenging in practice—but not impossible. How can it be accomplished? With tried and true public health methods such as isolation, quarantine, and good hygiene. Additionally, we can use modern technology to develop tools that will interrupt transmission. That will be our strongest leverage point. And we must innovate to develop tools which work with every bug and also do not require the expense or time lag associated with developing specific medical countermeasures. If done well, this approach will not require significant expansion of hospital surge capacity.

Cybersecurity Analogy

To make this approach more relatable, we can offer an analogy to cybersecurity. Since the 1980s, when cybersecurity was a nascent concept, it moved from "debugging" individual computers to protecting computer networks by building firewalls. Similarly, with infectious disease outbreaks, we can move beyond the emphasis on individual medical treatment and focus on building barriers to interrupt the spread of pathogens. We are now witnessing the broad realization of the importance of biosecurity, in which the connection to our lives and health is more direct.

Thinking about pandemic control from a biosecurity standpoint reframes it as an engineering and management problem and positions it for innovation and, ultimately, the development of solutions. This can happen at various levels—global, national, state, county, organizational, and even that of individual households. In this country, the decentralized response by state and local governments and independent organizations has contributed significantly to filling in glaring gaps in the national response.

Hierarchy of Controls

How do we interrupt transmission of infectious organisms? According to COVID-19 guidelines provided by the Occupational Safety and Health Administration (OSHA), a framework called the "hierarchy of controls" is used to select ways of controlling workplace hazards. Although OSHA focuses on workplace safety, the same principles can be utilized in a variety of settings and levels discussed above. According to the hierarchy of controls framework, the best way to control a hazard is to "systematically remove it from the workplace, rather than relying on workers to reduce their exposure."[3]

During the COVID-19 outbreak, the most effective protection measures, according to OSHA, are engineering controls, which involve physically isolating susceptible individuals from SARS-CoV-2. After that, there are administrative controls, with personal-protective-equipment (PPE) controls being the least effective. Each type of control measure has advantages and disadvantages involving ease of implementation, effectiveness, and cost. In most cases, a combination of control measures is necessary. What follows is an outline of these controls, illustrating how they have been or can be used for the SARS-CoV-2 and future pandemics.

Administrative Controls

Administrative controls require human action and include changes in policy or procedures to reduce exposure. Examples include encouraging sick people to stay home; minimizing face-to-face contact by instituting telework; tele-education; telemedicine; limiting the number of people in a building; discontinuing nonessential travel; and educating the public about risk factors, safe behaviors, and the correct use of PPE. Safe work practices such as maintaining an environment and procedures that reduce the duration, frequency, or amount of exposure to infectious organisms also fall within this category. At the county, state, national and international levels, various forms of administrative control such as lockdowns and school closures have generated controversy and social angst and continue to do so.

Containment: Surveillance, Rapid Diagnostics, Quarantine, Isolation

The deployment of aggressive surveillance, testing, quarantine, and isolation measures in combination with lockdowns has been shown to effectively control the COVID-19 pandemic in a number of countries in Asia, including China, where in June 2020 there were fewer than five thousand deaths. Over that same period, the United States, which has a quarter of China's population, recorded more than triple the number of deaths from COVID-19.

As we have witnessed, closing down the economy has massive economic and social consequences. However, a number of countries, including South Korea, have contained the pandemic without lockdowns by establishing a coordinated governmental response. That has included testing on a massive scale, contact tracing through the use of digital technologies, isolation of infected individuals, and quarantining those who may have been exposed. Additional social distancing measures also played an important role, notably the intermittent closures of schools and select businesses where outbreaks were detected.

It took South Korea about a month after the detection of its first cases in January to start testing 10,000 people daily through a variety of means. One was to set up 600 testing sites throughout the country, including more than sixty drive-through locations.[4] Given the fact that a significant proportion of transmissions involve asymptomatic individuals—as much as 35 percent, according to the Centers for Disease Control and Prevention (CDC)—testing widely is key.[5] Other countries, such as Germany, have borrowed from this experience. In general, countries that previously experienced epidemics, such as Taiwan, Singapore, South Korea, and China, were better prepared to contain SARS-CoV-2.

Can the United States Follow Suit with Rapid Containment?

Replicating South Korean success in containment will be far more difficult in the United States. Although ramping up testing here has been significantly delayed and erratically attempted, achieving sufficient capacity is an attainable goal, particularly if there is significant funding by the government. Also, testing does not have to be driven by the CDC. Local, decentralized response offers enhanced efficiency and resilience. For example, Stanford was one of the first institutions in the nation to develop its own polymerase chain reaction, or PCR, test. That enabled wider testing and more efficient allocation of resources. The FDA's emergency use authorization, created after the Ebola outbreak, helped develop these kinds of approaches nationally.

Although readily accessible testing is critical, it is also insufficient unless test results are acted upon quickly and aggressively. South Korea employs mandatory surveillance of its population, in which geolocation data from personal mobile devices is shared with public health authorities.[6] That enables rapid and accurate contact tracing and communication.

Individuals who test positive are informed as soon as possible, usually via text message. They are then isolated and educated. Their contacts are identified and notified. Contacts who may have been exposed are asked to self-quarantine. More than a thousand people who worked in one building in South Korea where an outbreak was detected were tested within twenty-four hours.[7]

South Koreans who test positive go to the hospital if they are sick enough to warrant admission. They go into isolation in a dormitory-style environment with medical monitoring if they are moderately symptomatic. If they are asymptomatic or mildly symptomatic, they self-isolate at home.

Public health officials check on those at home twice a day via a mobile tracking app. If the self-quarantine has been violated, a prompt visit by a governmental representative typically follows, resulting in significant fines and other legal recourse.

Although the South Korean system is highly efficient for pandemic containment, in the United States, privacy concerns, legal constraints, and general distrust of the government make such a system unlikely to succeed. There are two primary impediments.

First, the US Constitution makes a mandatory system of digital contact tracing a high hurdle, so versions now in place rely on manual means, along with a small but growing opt-in digital systems. The manual system

includes an "army" of contact tracers. As many as 300,000 are needed.[8] This approach is expensive, slow, and inefficient, which increases the time lag between potential exposure and isolation. Another complicating factor is that people who are contacted by one of the tracers sometimes withhold information. Modeling studies suggest that to achieve effective containment, contacts must be quarantined within twenty-four hours of a positive test. Manual contact tracing may simply be too slow to keep up with that standard.

Second, legally mandated isolation is also an enormous challenge. Although public health officials in this country have the legal power to do it, it has never been carried out on the scale required in a pandemic.

Enforcing isolation and quarantines in the United States was challenging enough with Ebola, which involved relatively few cases and a mortality rate of 30 percent—far higher than COVID-19. Lawsuits were filed and bad publicity followed. Given the backlash against wearing facemasks, one can imagine the level of resistance, including social and political unrest, that is apt to take place. Although most sick or exposed Americans would likely follow a directive to self-isolate or voluntarily quarantine, the likelihood that they would do so consistently is much lower.

Nonetheless, even at reduced efficiency, this approach should be pursued aggressively, and it is. In theory, the efficient application of containment can be effected without lockdowns and the associated economic and social consequences. In practice, however, the US population tends to dig its heels in over heavy-handed governmental interventions. The politicization of public health evident in the anti-vax movement has real costs. Those costs are financial as well as biological and spiritual, taking the form of human lives.

The level of government oversight that has played out in South Korea during the COVID-19 pandemic may be inconceivable in a democracy. The South Korean population believes the temporary loss of a specific civil liberty is a worthwhile price for protecting the economy and human health. They trust their government, which has demonstrated commitment and competence in containing the pandemic. One reason may be that South Korea learned lessons from the SARS and MERS coronavirus outbreaks. With MERS the mortality rate was nearly 30 percent. The illness terrorized the country in 2015, affecting people of all ages. At the time the government drew criticism for the shortcomings in its response, particularly an unwillingness to share information on the location of infected individuals with the public.[9] This fueled new legislation, new policies, and enhanced pandemic preparedness and arguably decreased politicization of public health, allowing for a more "technocratic" approach.[10]

As a result, during the COVID-19 pandemic, South Korea has "acted like an army," and the entire country has been much better prepared on the legal, policy, and public health fronts. Perhaps the United States will develop policy and legal instruments that will help contain and mitigate the current and future pandemics. It will need to learn from its own mistakes and perhaps South Korea's as well.

Mitigation: Lockdowns and Other Social Distancing Infection Control Measures

Given the challenges of containment in this country, mitigation measures such as lockdowns, school closures, travel restrictions, and other forms of social distancing need to become the dominant strategy. Many countries have moved from containment to mitigation during the SARS-CoV-2 pandemic, and the strategy has saved lives during this pandemic, just as it did during the influenza pandemic of 1918.[11]

While highly effective, mitigation measures such as lockdowns are blunt tools that impose heavy economic and social costs. To determine an optimal approach, we should refine these tools by using data-driven analysis.

Data-Driven Approach to Nonpharmaceutical Interventions (NPIs)

With increasingly available data about the current pandemic, we can move beyond estimating the effectiveness of large-scale NPIs to understanding their individual effects and burdens. The largest and most recent aggregate study found that schools play a "surprisingly" significant role in the containment of COVID-19, with closures responsible for a 58 percent decrease in the rate of spread.[12] This strategy was significantly more impactful than all the others and contributed to the ongoing debate about the necessity of school closures during the pandemic.

Additional reductions came from limiting gatherings to ten people (24 percent), closing nonessential businesses (23 percent), closing high-risk businesses (19 percent), issuing stay-at-home orders (17 percent), and conducting symptomatic testing (18 percent). The study also found that symptomatic testing, closing high-risk businesses, and limiting gathering size had significantly higher effectiveness-to-burden ratios compared with closing nonessential businesses and issuing stay-at-home orders.

While no policy decisions should be based on one study, the increasing availability of data and research will contribute to the debate about ending lockdowns

and will reveal the increasing potential for data-driven decision making.

Countries have differed significantly in their choices of NPIs. For example, Sweden took a relatively relaxed approach by choosing not to institute strict lockdown policies. Elementary schools and businesses remained open, although secondary schools and universities were closed for in-person instruction, and social gatherings of fifty or more people were banned. Instead, Sweden relied largely on education about social distancing and hygiene. As of mid-June 2020, the country had reported more than 4,500 deaths, and was eighth in the world in per-capita mortality—39.6 per 100,000 in May, compared with 6 in neighboring Finland and Norway, and 30 in the United States.

While there is much debate in the research literature about which NPIs should be adopted, some principles are clear.

Cellularizing

The concept of cellularizing involves limiting the size of groups that can potentially be exposed to an infectious vector. At the most basic level, we have seen the application of this principle when people are kept isolated within their homes during lockdowns. This principle can and is being expanded to varying degrees in other settings, such as day-care facilities, schools, workplaces, and social groups, where small groups can remain constant for long periods of time and function in a manner similar to households when it comes to social distancing and isolation methods. Cellularizing also makes effective contact tracing and isolation of potentially exposed individuals easier.

Limiting the size of gatherings is particularly beneficial since the spread of SARS-CoV-2, like its cousins SARS and MERS, is largely mediated by super-spreader events, at which 10 percent of the individuals in attendance may contribute to over 80 percent of the spread.[13]

Much of the discussion has focused on the average number of new infections caused by each patient, which is reflected in the reproduction number (R). For COVID-19 without social distancing, R is about three. In reality, in the case of SARS, MERS, and SARS-CoV-2, most people do not transmit at all. The dispersion factor (k) for SARS-CoV-2 is estimated to be 0.1, although some studies have cited slightly higher numbers.[14] In this regard, coronaviruses behave differently from influenza viruses, for which transmission is more uniform.

The fact that SARS-CoV-2 transmission is largely mediated by super-spreader events is encouraging, because if one can predict the circumstances giving rise to these events, one can quickly squelch the spread of the disease, as the math shows.

Unfortunately, super-spreader events are difficult to study, and why coronaviruses cluster significantly more than other viruses is still an open scientific question. The mode of transmission appears to be a critical factor. Although SARS-CoV-2 transmits through both touch and aerosol spread, most large transmission clusters appear to involve aerosol transmission.[15] Individual factors such as higher shedding of virus by some people also appear to play a role, as some healthy people breathe out many more particles than others when they talk or sing.[16]

The Great Outdoors

There is clearly a much lower risk outside than in enclosed spaces. This may be driven by both the interruption of airborne transmission by superior ventilation and the inactivation of SARS-CoV-2 by sunlight.[17] A Japanese study found that the risk of infection outdoors is almost nineteen times lower than indoors.[18] Japan, which has kept the epidemic under control, has built its response strategy explicitly around avoiding clusters and advising citizens to avoid closed spaces and crowded conditions. This is consistent with a study out of China that identified 318 clusters of the coronavirus outside Hubei Province, only one of which originated outdoors.[19]

This supports allowing and encouraging people to be outdoors. So long as social distancing can be maintained, measures such as closing state parks, beaches, and other large, open, outdoor public spaces appear to be of limited benefit, while imposing a significant burden on the public. This data also supports moving group activities, such as children's summer camps or work meetings, outside.

Information Technology Enablers for Administrative Controls

Information technology has become the backbone of our resilience as it has enabled us to carry on during the pandemic and has helped compensate for a number of governmental shortfalls. The internet and the ability to shop for food and supplies online makes it far easier to shelter in place. The ability to telework, tele-educate, and tele-entertain makes lockdowns and school closures far less costly and disruptive. And telemedicine has allowed us to conduct over 80 percent of visits virtually during the pandemic. Technology has enabled our population, particularly our vulnerable population, to self-isolate in the safety of homes and has empowered individuals and organizations to continue despite the new normal.

Personal Protective Equipment, Including Face Coverings

Although engineering and administrative controls are considered more effective in protecting people from exposure, PPE is a useful adjunct.

Although face coverings play a significant role in decreasing the spread of SARS-CoV-2, they are, unfortunately, less protective for the wearer than for others in the vicinity.[20] Medical-grade respirators such as N95s, which require yearly fittings to ensure a proper seal, or powered air purified respirators, or PAPRs, which don't, are appropriate for protecting the wearer from airborne viruses in high-risk settings. N95-like respirators are currently not recommended for use by the general public in order to preserve them for high-risk workers.

Airborne transmission is mediated by particles smaller than 5 microns, which can remain suspended in the air for hours and are not filtered by most face coverings. There may be opportunities to create better PPE that everybody, not just medical personnel, can safely and easily use. Innovations to make the equipment capable of interrupting all forms of transmission more affordable and available to the public, particularly those in the high-risk category, would save lives. Given the increasing risk of infectious disease outbreaks, there may come a time when having this kind of PPE as part of one's home emergency preparedness kit will be as basic as having a flashlight.

Another issue involved in face coverings and PPE is compliance. While face masks clearly play a large role in decreasing transmission, there has been significant resistance to measures mandating this. Public health professionals have even received death threats, causing them to step down from their jobs. Compliance and enforcement in social settings have proved to be even more challenging, becoming highly charged political issues in this country. Wearing face coverings is not nearly as strong a social norm in the United States as in many countries in Asia, where nonwearers suffer strong governmental and social repercussions.

Engineering Controls

Engineering controls involve physically isolating susceptible individuals from hazards.

Optimizing Ventilation, Airflow, Air Filtration

With SARS, MERS, and SARS-CoV-2 coronaviruses, super-spreader events have been responsible for the majority of the spread, with transmission through air (droplets or airborne) implicated as the key driver.[21] Thus, engineering controls involving enhanced ventilation, air filtration, and optimally directed airflow can be deployed to decrease or prevent this critical mode of transmission.

The benefits of engineering controls in this regard are perhaps best illustrated by a few examples. According to a report by the Institute of Medicine's Forum on Microbial Threats, "a global outbreak of SARS was seeded from a single person on a single day on a single floor of a Hong Kong hotel," where one person infected at least sixteen others.[22] Airborne spread was implicated, although the exact mechanisms are unknown. In another super-spreader event in Hong Kong involving SARS, one person infected 187 out of 300 people living in a building. According to the epidemiologic and airflow simulations, poor ventilation and airflow resulted in plumes of virus-laden air being transported from the bathroom of the infected person to the entire building.[23] Finally, a research letter to the CDC described an incident in which 1 patient infected several family groups seated relatively far away in a restaurant. The "droplet transmission was prompted by air-conditioned ventilation. The key factor for infection was the direction of the airflow."[24]

In health care settings, installing high efficiency air filters and creating negative-pressure rooms for high-risk areas and positive-pressure rooms to protect the vulnerable are among many possible steps that can be taken. Far more simply, droplet spread can also be reduced by installing physical barriers such as clear plastic partitions, an engineering control that has been widely deployed during this pandemic. Reducing droplet and airborne transmission by optimizing airflow, filtration, and ventilation can be widely deployed in buildings and in transportation settings.

Using Ultraviolet Light

Ultraviolet (UV) light effectively kills germs. More specifically, simulated sunlight has been shown to inactivate 90 percent of SARS-CoV-2 in under seven minutes.[25] Ultraviolet germicidal irradiation, or UVGI, is not a new concept. It has been used extensively in public health to decrease the transmission of infectious organisms. In the 1930s, upper-room, or high-overhead, UV light fixtures were found to effectively decrease the transmission of smallpox, measles, and mumps in schools, and they have also been effective in decreasing transmission of airborne tuberculosis.[26] Unfortunately, UVA, UVB, and most wavelengths of UVC light are harmful to the skin and eyes. However, recent research into far-UVC light (207 to 222 nanometers) has shown that it efficiently kills coronaviruses without harming exposed human cells or tissues.[27] Engineering controls using the sterilizing effects of UV light could be used in public transportation, offices, schools, and other settings.

Optimizing Temperature and Humidity

Humidity and temperature have been shown to have synergistic effects in deactivating coronaviruses as well as influenza viruses.[28] This can be creatively used in devising engineering controls, as for example was done by Ford Motor Company. The automaker produced police SUVs that could be heated to 133°F for 15 minutes, thus eliminating 99 percent of viable SARS-CoV-2 viruses even in hard to reach areas of the vehicle.[29] The American Society for Refrigerating and Air-Conditioning Engineers (ASHRAE) asserts that relative humidity in the 40 percent to 60 percent range is least conducive to microbial growth.[30]

Utilizing Antimicrobial Materials

The stability of SARS-CoV-2 on surfaces varies significantly, depending on the type of material. Utilizing antimicrobial surfaces, which rapidly deactivate SARS-CoV-2 and other infectious organisms, is another promising approach for devising engineering controls. This could be particularly useful for frequently touched surfaces, such as bathroom fixtures, doorknobs, and keyboards. Viable SARS-CoV-2 was found on plastic and stainless steel after seventy-two hours, but none was found on copper after just four hours.[31] A research group at an Australian university devised a way to use a wet etching technique to corrode aluminum surfaces, thus imbuing them with antiviral and antibacterial properties. This can have significant applications in both medical and nonmedical settings by interrupting transmission arising from physical surfaces.[32]

Advantages of Engineering Controls

Engineering controls are considered to be the most effective means of making workplaces safe and may also be most the cost effective, according to OSHA.[33] The same logic can be expanded to places of public gathering, such as schools, transportation hubs, parks, community spaces, and houses of worship, and also to homes.

The advantage is that they can help decrease reliance on administrative controls, which tend to entail heavy economic, social, and political costs. Engineering controls also tend to be less expensive and burdensome, as they do not rely on changes in human behavior or compliance and thus create less controversy and resistance. Finally, they are typically market rather than policy driven and therefore more decentralized and resilient.

A longer-term advantage of engineering controls is that they have broad applicability. They can be reused in future pandemics—unpredictable catastrophes as well as predictable annual outbreaks, such as those caused by the influenza virus. Flu claims 12,000 to 60,000 lives in the this country every year and, in addition, results in significant economic losses, with the estimates ranging from $11 billion to $26 billion in medical costs and projected lost earnings.[34] Engineering controls can help interrupt the transmission of other infectious organisms that normally circulate in the population, such as other types of viruses that cause symptoms of common colds, thus making the return on investment more attractive. Finally, they help build resilience to threats of bioterrorism and therefore enhance our biodefense capabilities. Unfortunately, engineering controls take time to develop and operationalize, as compared with administrative controls, which can be enacted almost immediately. Engineering controls also require up-front investment, whereas administrative controls may have no associated costs or only minimal prior investment. They can, however, have massive economic costs postimplementation.

Once the engineering controls are in place, they can be "switched on" quickly just like administrative controls and without the time lag necessary for medical countermeasure development and testing. Although the United States has by necessity relied heavily on administrative controls, such as business and school closures, it is time to shift the focus toward investing in and deploying engineering controls to rein in SARS-CoV-2 as well as future pandemics.

Who Should Develop and Pay for Engineering Controls, and What Is the Proper Role of Government and Organizations?

Like the Amazons and the Zooms of the world, which currently help enable our pandemic resilience, most of these solutions will come from the private sector and will be market driven. But governments and organizations also need to play a role.

Similar to the role of the CDC in the provision of medical and public health guidance, government agencies such as OSHA should be the central source for information and the vetting of technologies for their claimed effectiveness. Nonprofit and industry organizations such as ASHRAE and the International Ultraviolet Association can also contribute. Both governmental and nongovernmental organizations can also play a part by raising awareness of the potential benefits of appropriate technologies and educating the public and various organizations on their applicability, safety, and correct use.

Research funding can be directed through governmental mechanisms for basic science, engineering, and translational efforts in order to help develop effective engineering controls.

Finally, organizations that may otherwise not be able to afford expensive engineering controls should be

subsidized with grants. Particular attention ought to be paid to reducing social disparities and enabling equal access. In addition to the obvious ethical and social considerations, the decreased transmission of infectious organisms will have a ripple effect through the entire society and help protect everyone as a result.

Future Directions

With COVID-19 cases on the rise, a second wave is of high concern. As containment and mitigation measures are being loosened across the country, we should remember the devastating lesson that was learned by lifting controls too early during the Spanish flu pandemic of 1918. Back then, San Francisco reduced the mortality rate by 25 percent, but 90 percent of the deaths occurred during the second and third waves, from September 1918 to May 1919. Tragically, that might have been avoided had the initial controls been kept in place.[35] Throughout the United States, in fact, most of the deaths happened during the second and third waves.[36] According to the CDC and the National Institutes of Health, during the Spanish flu pandemic, cities that used aggressive measures ended up losing significantly fewer lives compared with those cities that did not, and cities that instituted control measures early did best of all.[37]

We may be dealing with this pandemic for many more months, until herd immunity is developed naturally or through the introduction of a vaccine.[38] Given the availability of modern tools enabling mitigation and containment, particularly the ability to function remotely, it would not be surprising if the time to develop herd immunity to SARS-CoV-2 is significantly longer than it was a hundred years ago. On the flip side, we are likely to have pharmaceutical tools such as vaccines available, a capability that did not exist one hundred years ago.

We need to figure out how to live with this new reality in ways that limit the burden on our society and economy while still optimizing disease control. We should shift the balance from administrative to engineering controls, and this investment has the potential to significantly decrease social disruption and economic burden while still maintaining a sufficient level of disease control.

However, until effective engineering controls are devised and implemented, we will need to rely on administrative controls and the use of PPE. A rigorous data-driven approach should be used to select measures that optimize effectiveness while minimizing the burden. Particular attention should be paid to protecting vulnerable populations, minimizing social disparities, and enabling equal access to protective measures and technologies. Besides the obvious ethical and moral considerations, this will help protect everyone, as infectious diseases know no social or national bounds.

As we consider ways of strengthening our pandemic resilience capabilities, we would be well advised to revisit the recommendations of the 2015 Blue Ribbon Study Panel on Biodefense.[39] It was the only bipartisan high-level body to comprehensively assess the state of US biodefense efforts and make concrete recommendations. Its assessment revealed systemic challenges in protecting Americans from a biological event, so our suboptimal response to the COVID-19 pandemic should not come as a surprise.

The recommendations provided a systematic way of addressing biological threats, enhancing national biosurveillance capabilities, improving public health emergency response capabilities, and incentivizing innovation in point-of-care diagnostics. Although much progress on the panel's recommendations has been made—particularly in the last few months—most of the recommendations are still as current and their value is far more obvious today.

A strategic, innovative, and collaborative approach to mobilizing the response to the COVID-19 pandemic across medical, technological, policy, legal, social, and ethical arenas will not only save lives now but also lay the foundation for enhanced safety, security, and resilience to the inevitable future pandemics in our nation and the world.

Dr. Milana Boukhman Trounce *is a clinical professor at the Stanford University School of Medicine and an emergency medicine physician. She serves as biosecurity chair for the American College of Emergency Physicians.*

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Potential Pandemics

By Milana Boukhman Trounce, MD | April, 2019

The Threat of Infectious Disease and the Evolution of the Threat

Infectious disease has been a formidable force in shaping human history. In the times past, most people died from two causes: violence and infectious disease, with deaths from infectious disease being many times more common. Bubonic plague killed between a third and a half of the population of Europe in the Middle Ages, thus changing the course of Europe and the world forever. Smallpox killed half a billion people in the 20th century alone before being finally eradicated in 1982.

Oftentimes more people die from infectious disease than from combat even in times of war. Napoleon started the war with over half a million soldiers and only a few thousand staggered back. Most died from trench fever, typhoid and other infections, with immune systems of soldiers weakened by malnutrition, cold and other stressors during movement of the Napoleonic troops through Russia. More recently, more people died due to the Spanish flu pandemic of 1918 than died in combat in World War I.

In the mid to late 20th century, with the advent of antibiotics and dramatic advances in the biological sciences, it seemed that we have conquered infectious disease–and, at least in the western world, we largely have for some period of time. We can now treat, have eradicated or decreased the incidence of infectious diseases. We can now effectively treat plague, cholera and numerous other infectious. We have eradicated smallpox, are close to eradicating polio, and have dramatically decreased the occurrence of other historical killers such as diphtheria, whooping cough, measles, and others through vaccination campaigns. Despite the many remaining challenges including antibiotic resistance and global access to curative drugs, we have developed drugs to treat many infectious diseases.

But now it is time to rethink the notion that we have conquered infectious disease. Due to human activity, the threat of infectious disease is making a come-back. Unfortunately, at this point we are ill equipped to deal with a number of scenarios, particularly those involving large-scale infectious disease outbreaks–pandemics. Pandemics pose some of the biggest threats to humanity, both as far as infectious disease risks as well as overall existential threats more broadly. In terms of impact on human population, this threat is as high as nuclear annihilation, climate change, and global instability for a variety of reasons. Pandemic risk is closely tied to climate change, technological disruption, as well as other factors relating to human activity.

Pandemics challenge our society's ability to withstand them. Severe pandemics can lead to mass panic and disruption of society and governments. In September 2014, the United Nations Security Council declared the Ebola virus outbreak in the West Africa a "threat to international peace and security". The resolution was the first in the history of the Security Council to deal with a public health crisis. In response, the United States sent in troops to assist in disaster response. The prowess of U.S. military in logistics and operations proved critical in helping to stabilize the region during this societal disruption.

Different Patterns of Spread of Infectious Diseases

The risk of pandemics has been increasing and accelerating significantly over the last several decades. Since the 1980s, we have seen a three-fold increase in the number of global epidemics. Climate change has been driving increased risk as mosquitos and other vectors spreading diseases such as dengue, chikungunya, zika moved up north. Also, different ways of using land, increased contact between humans and wild animal populations, urbanization and global travel have all contributed. As a result, we have seen a change in the pattern of spread of infectious organisms: some organisms which historically spread only locally have spread in ways we have never seen before, with dire consequences.

One example of this is the Ebola outbreak of 2014-2015. Historically, Ebola outbreaks involved tens to a few hundred people, and have been limited to one or a few remote villages in Africa. For the first time in history, we have seen this disease affect a continent, claiming tens of thousands of lives and wrecking fear and havoc on the entire world. Notably, this Ebola outbreak was caused by the same Ebola virus as the previous 20 outbreaks of Ebola occurring in Africa between 1976 and 2014. Why was this outbreak different? The difference in 2014-2016 outbreak is attributed to the fact that people are no longer isolated in remote villages–they travel. And when they do, they travel to cities, which, with the rise of urbanization, are now more heavily populated, but still lack the needed health infrastructure. Furthermore, people travel by planes

at higher rates. All of this contributed to the number of people infected. It is also an example of a trend which is bound to continue. Although Ebola outbreak was the most recent dramatic example, the same dynamics also apply to the spread of flu and other infectious organisms.

With humans encroaching on traditionally animal habitats, there has also been an increase in the emergence of new infectious diseases affecting humans. This is significant since most pandemics stem from infectious organisms typically infecting animals becoming capable of infecting and spreading between humans.

The Challenges of Preparedness and Response

Medical Countermeasures

Pandemics pose a number of unique challenges to our society's ability to withstand them. One of the challenges is our ability to develop medical countermeasures. Since we know how to develop vaccines and drugs, why can't we just develop drugs and vaccines to control pandemics? To examine this question, let's start with the most common pandemic which predictably happens every year–seasonal flu. In 2018 seasonal flu claimed about 80,000 lives in the United States alone. It would seem that for a pandemic which happens yearly, claims thousands of lives yearly, and results in billions of economic costs predictably every year, we would by now have great medical countermeasures. However, despite the fact that much effort is expended every year in designing and making a flu vaccine, the effectiveness of this vaccine varies significantly year to year.

There are a number of factors which can make creation of good flu vaccine challenging.

Influenza virus is remarkable for its high rate of mutation, compromising the ability of the immune system to protect against new variants. As a consequence, new vaccines are produced each year to match circulating viruses. Currently, vaccine production takes, on average, six months from the selection of seed strains to the final vaccine product. The decision of which influenza antigens to include in the vaccines is made in advance of the influenza season and is based upon global surveillance of influenza viruses circulating at the end of the prior influenza season. In some years certain influenza viruses may not appear and spread until later in the influenza season, making it difficult to prepare a candidate vaccine virus in time for vaccine production. This can make vaccine virus selection very challenging. As a result, sometimes there are mismatches between the vaccine strain and the circulating strain that result in reduced efficacy of the vaccine. Can we come up with a vaccine which would be effective against all flu viruses? Ongoing research is focused on developing a universal vaccine that would elicit protective antibodies directed against conserved viral proteins.

What is the effectiveness of the flu vaccine? It depends on the type of the vaccine and it also varies every year and depends on how good a match is between the viral strains used to make the vaccine and the viral strains actually circulating in the population. During the 2004 to 2005 influenza season, the antigenic match was only 5 percent compared with 91 percent during the 2006 to 2007 season, which resulted in vaccine effectiveness of 10 versus 52 percent, respectively.[1] During the 2014 to 2015 influenza season in the United States, influenza A H3N2 viruses predominated and more than half of these viruses contained H3N2 antigen that was antigenically different (drifted) from that included in that season's influenza vaccines. The adjusted overall vaccine effectiveness for the 2014 to 2015 influenza season was 19 percent; for H3N2-associated illness, the vaccine effectiveness was only 6 percent.[2]

Despite the fact that flu vaccine has varying effectiveness, vaccination does reduce mortality from influenza significantly, and yet only 40% of the population gets the vaccine. The resistance to vaccinations is not unique to influenza. With the rise in anti-vaccination movement, we have recently seen outbreaks of measles and pertussis, both of which are prevented by vaccines with long standing record of safety and efficacy. Given this, what vaccination rates can we expect for newer, less tested vaccines? What percentage of the population would be comfortable getting vaccinated with a vaccine which was developed quickly in response to a novel viral pandemic? What if this vaccine was approved by the FDA under Emergency Use Authorization, which is a legal means for the FDA to approve new therapeutic and diagnostic tools during a declared emergency with more limited testing than it would normally require? How many people would feel comfortable getting immunized with a vaccine with an incompletely understood safety profile? This is one of the many challenges unique to pandemic preparedness and response.

And what about drugs? For immunocompetent population, antivirals like Tamiflu only shorten flu symptoms by a day and offer no mortality benefit. Despite the public panic of trying to get Tamiflu during some of the more severe influenza seasons and the pharmacies running out of Tamiflu, the benefit of Tamiflu and other influenza antivirals is marginal in immunocompetent populations. It does offer more potential benefit to people whose immune systems may be compromised.

How about medical counter-measures such as drugs and vaccines for other viruses and what would it take for us to be prepared for a pandemic due to an emerging infection? Most pandemics caused by emerging infectious diseases are due to organisms which have recently appeared within a population or whose incidence or geographic range is rapidly increasing or threatens to increase in the near future. Most of these arise from human interaction

with animals. There are over 200 species of viruses and 500 species of bacteria capable of infecting humans. Focusing on viral infections which are far more likely to cause a pandemic than bacterial infections, there are numerous strains of viruses within each of the specie. This leaves us with thousands of various strains of viruses capable of causing a pandemic. Also, viruses mutate, some very frequently, which increases this number significantly. Additionally, with advances in synthetic biology, it is possible to manipulate viruses to make them more lethal and infectious–those can be released accidentally or nefariously. Although numerous measures have focused on prevention of this occurrence including attempt to regulate biology more tightly and secure it through the NSABB (National Science Advisory Board for Biosecurity) and other governing or advising organizations, ultimately perfect control is not possible. Unless specified beforehand in a grant application or another form of disclosure, it is exceedingly difficult to monitor what kinds of biological experiments one is setting up in their lab or garage, or what kinds of samples one may store in their lab freezer.

This leaves us with a virtually infinite number of viruses to which our population is vulnerable. It costs hundreds of millions of dollars to develop a vaccine or a drug. It would therefore take infinite amount of resources in an attempt to have a vaccine or a drug for every possible pathogen. While it is sensible to have drugs or vaccines to some more commonly occurring organisms, this quick calculation makes it apparent that this strategy will leave large gaps in our preparedness.

How about developing a drug or a vaccine at the very start of an epidemic in order to quickly control it? This reactive approach is politically tempting, and one frequently tried in the past, but which generally fails. The reason is simply the timeframe. It takes years to develop, test, and produce vaccines or drugs. While in an emergency this time may be shortened, it will still likely take a few years to develop and produce a new drug or a vaccine, by which time the epidemic would have already ran out and claimed the lives it was going to claim. It is hard to speed up drug or vaccine development by spending large amounts of money in response to an outbreak. In the past when U.S. Government has reacted to outbreaks by spending large amounts of money, as happened during the Ebola outbreak of 2014-2016, it has not made significant difference. We are still limited by what is possible as far as the speed of development, clinical testing, and production. We still don't have an FDA approved Ebola vaccine, although numerous ones have been developed and some are used, apparently with success, in Africa. Despite significant advances in the biological sciences over the past century, ironically, in the scenarios involving pandemics due to emerging infectious diseases, we are not in a dramatically different place as far as availability of specific countermeasures compared to where we were a century ago.

Surge Capacity

Thanks to the advancement in the medical sciences, even without having specific drugs or vaccines to treat infections, patients today are far more likely to survive thanks to the availability of supportive medical treatments such as fluid resuscitation, ability to help patients breath with the help of respirators, and other medical measures designed to support vital functions while the body's immune system mounts a response to an infectious organism. This is why Influenza or Ebola patients, for example, are far more likely to survive with supportive medical treatment than without it.

In a pandemic scenario, however, the availability of supportive medical treatment is not a given. This has to do with limited ability of hospitals or the medical system more broadly to handle a sudden influx of patients, which is known as surge capacity. In an event of a significant pandemic, our surge capacity will likely be outstripped given limited amount of hospital beds and medical personnel to staff the beds, as well as limited equipment, medications and other supplies needed to care for additional patients. Managing an infectious disease outbreak can also be more complicated since it may require additional kinds of resources such as negative pressure rooms and quarantine facilities.

We have experienced limited surge capacity at Stanford first hand. A number of times over the past several years, for weeks to months at a time, we had to open "The Tent". The Tent is a portable medical tent without running water which Stanford purchased in order to accommodate the influx of patients in disaster situations. We would open the Tent right outside the Emergency Department on the lawn by the parking lot at Stanford hospital in order to accommodate the increase in the number of patients during the flu season. Thus, Emergency Department created extra capacity with 8 additional patient chairs, and an additional physician as well as nurses and techs to take care of patients. We have the luxury of the benign weather in California to be able to operate part of an Emergency Room in a tent during the winter. Given that Stanford hospital has been operating close to capacity, as many hospitals throughout the country do in order to optimize operations and be fiscally responsible, during those times we had insufficient amount of space in the Emergency Department to accommodate the yearly influx of patients. Part of the reason for this is that we had numerous admitted patients being boarded in the Emergency Department due to a lack of availability of inpatient beds. If we have to set up our disaster Tent during the predictable yearly flu season, one can imagine that an influx of patients which is significantly beyond those experienced during the yearly flu season will be

challenging and potentially impossible to accommodate as far as medical surge capacity.

We have plans to operate in disaster situations and flex our surge capacity, but the capacity to flex is limited. Our flexing involves putting admitted patients in the hallways, in addition to placing them in rooms, and discharging borderline patients who might be able to be reasonably discharged under these circumstances. Treating patients in the hallways and discharging patients who might be better served in the hospital under normal circumstances puts a stress on the system as well as on the patients. These disaster plans are generally supposed to last for hours to days following disaster, not months, as would be required in a case of a significant pandemic. This does not only apply to Stanford hospital, but is a typical situation in many if not most hospitals throughout the nation.

Another example of the limited medical surge capacity specifically around high consequence infectious disease became apparent during the Ebola outbreak of 2014-2015. During the outbreak, hospitals throughout the country including Stanford were rapidly preparing to receive and treat Ebola patients. Per CDC guidelines, the treatment area for such patients, in addition to the patient rooms, needed a "warm zone" as well as the "cold zone". The "warm zone" is an area right outside the patient room where providers would take off personal protective equipment (PPE) and which may be contaminated with infectious organisms. The "cold zone" is a zone right outside the "warm zone" where providers would put PPE on, where clean supplies would be contained and where medical charting and other duties not directly involving direct patient contact can take place. The patient rooms themselves would need to have the capacity to suck the potentially infected air out of the rooms and release it into the atmosphere–these are called negative pressure rooms. There are only two such places at Stanford hospital: two rooms in the Emergency Department which are part of the Pediatric area, and the Stanford's Critical Care Unit for cardiac patients.

If Stanford was to receive one or two suspected Ebola cases, those patients would be placed in the pediatric zone rooms, and if three or more patients would need to be cared for, Cardiac Intensive care unit would be converted into an Ebola care ward. To the chagrin of the cardiologists at Stanford, this would necessitate cancelling all cardiac catheterizations and heart surgeries. Thus, merely three suspected Ebola cases would significantly disrupt Stanford's normal hospital operations and ability to provide medical care. The Cardiac Intensive care unit could accommodate additional 8 patients. Thus, Stanford as a whole was prepared to accommodate 10 suspected Ebola patients. One can imagine that in an outbreak of highly pathogenic flu or another emerging infection, the number of patients seeking medical care would be hundreds or thousands of times higher, thus overwhelming the system.

Many are under a hopeful impression that in a disaster situation involving pandemic with high consequence infectious organisms Federal Government through agencies like FEMA would step in and provide the medical surge capacity required. While indeed FEMA and other governmental and non-governmental organizations have been instrumental in responding to various disasters in the past such as earthquakes and floods, pandemics are not localized events. We would expect that most if not all areas of the country would be affected, far outstripping the federal and state resources required to provide additional medical capacity. Most of disaster response takes place on a local level, using local resources.

If Not Drugs, Vaccines, or Increased Surge Capacity, Then What?

If we are unlikely to have drugs or vaccines to counter infectious organisms during a pandemic, and if our medical surge capacity may be outstripped, what are we left with? We are left with an approach we have used for centuries to counter infectious disease, namely public health measures such as isolation, quarantine and other forms of infection control. This will be our strongest leverage point and our biggest opportunity. This strategy has a track record of success in a variety infectious disease outbreaks in the past. Despite the fact that it is a centuries-old approach, it makes sound sense to put resources behind it and innovate around it using modern tools.

Rapid Diagnostics and Surveillance: Lessons from Ebola

Rapid diagnostics and surveillance have been challenging for most outbreaks in the past for a variety of reasons, but this is one of our biggest points of leverage in controlling infectious disease outbreaks, and also most realistically doable given the state of technology and the cost/benefit equation. Although this was not available at Stanford hospital during 2014–2015 Ebola outbreak, a time is close when rapid and accurate point of care diagnostic testing for emerging infections will be widely clinically available. This will be very helpful in optimizing utilization of the scarce medical resources and patient outcomes, since a determination could be made quickly whether a patient is infected and therefore whether or not they need to be isolated.

During the 2014–2015 Ebola outbreak, the plan at Stanford was to send samples from suspected Ebola patients to the Center for Disease Control (CDC) lab for confirmation. If the patient was confirmed positive for Ebola, the plan was to transfer the patient to an Ebola-designated treatment hospital—at that time it was

UCSF. And, if the patient could be medically managed at home, to discharge them. The turnaround time given specimen travel and analysis time by the CDC lab was expected to take several days to a week. That would mean that a patient with suspected Ebola would have to be quarantined and treated in the Emergency Room for up to a week, taking up valuable medical resources. Due to high containment, Ebola patient would take up several times more resources than a regularly admitted patient, potentially disrupting provision of intensive cardiac care since the Cardiac Care Unit would be converted to an Ebola ward. All of this could be avoided by having a rapid and accurate point of care diagnostic test. For other kinds of lab testing for clinical purposes, a policy was made by Stanford hospital to only use point-of-care bedside testing for suspected Ebola patients. A rapid point of care diagnostic test which could be used at the bedside would optimize resource allocation.

During the Ebola epidemic in Africa, suspected patients were often quarantined together. Given limited resources, separate rooms were generally not available. Patient with malaria and other viral or bacterial diseases and patients with Ebola were often in the same living quarters: in the beginning of the illness, these diseases can be indistinguishable from each other clinically. This unfortunately made possible transmission of Ebola to patients with non-Ebola infections. A rapid and accurate test which could be used in the field would have precluded this from happening.

This is applicable not only to Ebola outbreaks but to most scenarios involving pandemics. In pandemic scenarios, it is likely that large numbers of patients will present to Emergency Departments and clinics. It would be very helpful to be able to rapidly distinguish between those who are sick due to a dangerous pathogen from those who are not and make treatment and quarantine decisions rapidly and accurately. This is key to getting an outbreak under control.

Quarantine, Isolation, and Other Infection Control Measures

Quarantine has been used extensively in the past during epidemics. The word quarantine comes from an Italian term "quaranta giorni", meaning forty days, the period that all ships were required to be isolated before passengers and crew could go ashore during the Black Death plague epidemic. A quarantine is used to separate and restrict movement of people who may have possibly been exposed to an illness or to restrict transport of possibly contaminated goods; quarantine is designed to prevent the spread of communicable diseases. Quarantine is different from medical isolation, which is to separate ill persons who have communicable disease from those who are healthy.

Outbreaks have been avoided in the past using the above measures alone. One example of this involved SARS. On March 7, 2003, two patients with SARS arrived in Canada and both promptly presented to the local hospitals—one in Vancouver and the other one in Toronto. No outbreak resulted in Vancouver. Toronto had a SARS outbreak with 247 probable cases and 44 deaths. Half of these were in healthcare workers. Vancouver is a useful point of reference for Toronto's response to SARS. Main difference? Immediate medical isolation upon presentation to the hospital in Vancouver, which included respiratory isolation and the use of N95 respiratory masks.

This decision was not only a result of a good call by an ER doctor in Vancouver—this was a team effort and no accident. This decision stemmed from months of monitoring, careful planning, and excellent communication by the local public health department, which was on a lookout for a highly pathogenic form of bird flu coming out of Asia and communicated these alerts to the local medical providers. As a result, although SARS and bird flu are caused by different viruses, a sick patient with flu-like symptoms with recent travel to Asia immediately got isolated with respiratory precautions. In Toronto, medical isolation with respiratory precautions was delayed and numerous medical and non-medical staff were exposed, got infected, and died due to a resulting SARS outbreak.[3]

Another example involved using infection control measures in non-medical settings, which were instrumental in mitigating infection rates during the Spanish flu pandemic of 1917–1918. This entailed the loss of civil liberties, especially in U.S. cities. As demonstrated by the research through the National Institute of Health (NIH) and the Centers for Disease Control (CDC), cities using aggressive measures had significantly lower infection and mortality rates.[4,5,6] As documented by numerous historians, the first line of defense was educational campaigns regarding hygiene, such as spitting and coughing into handkerchiefs, and banning common cups and utensils.[7]

The use of more aggressive interventions required the closing of schools, the restriction of large gatherings, and isolations and quarantines.[7,8] While some have argued that cities with rigorous closings and illegal gatherings fared no better than other cities, the examples of positive effects resulting from aggressive interventions are compelling.[7] Cities that implemented social measures within a few days of the first few cases of flu did better than cities that waited a few weeks to respond; the peak weekly death rates of the former were halved compared to the latter.[7,9] St. Louis had implemented measures within 2 days of their first reported cases, which resulted in a death rate I/8 the number of fatalities in Philadelphia, the worst hit city. The City of Brotherly Love failed at keeping people apart by allowing a city-wide parade to be thrown. The results show a necessity for isolation measures. Other examples of

these interventions include Kansas City banning weddings and funerals with greater than twenty persons, New York City staggering factory shifts to reduce the waves of commuter traffic, and Seattle ordering its constituents to wear face masks in all public places. A clear negative correlation between the time of implemented measures and mortality can be observed, along with another negative correlation between the number of measures and mortality. The statistics are publicly available and can be found on the CDC's website.

Even with initial control measures, the second and third waves of Spanish flu caught cities that ended their nonpharmaceutical interventions off guard, demonstrating the importance of not lifting nonpharmaceutical interventions prematurely. For example, San Francisco reduced their mortality rate by 25%, but 90% of their deaths occurring between September 1918 to May 1919 could have been avoided if they had kept their initial controls in place.[4,9] They had previously closed schools and theaters and boasted their law mandating the use of masks in all public places. Catchy sayings, such as "protect your jaws from septic paws," were promoted by the Board of Health, the Red Cross, and the mayor himself; violators of public mandates faced jail time. After signs of the flu waned, sirens wailed on November 21st, 1919; masks came off, schools resumed session, and theaters reopened their doors. This also highlights the need for situational awareness and surveillance–the earlier we are aware of a potentially dangerous outbreak, the earlier we can institute infection control measures including isolation and quarantine, thus giving us a chance to prevent or curtail an outbreak. The premature celebrations left members of the public volatile and the next two cycles of flu once again ravaged the city.

While in retrospect it may seem obvious that rapid implementation of these sweeping measures saved lives, they were met with considerable opposition. Significantly, this resistance did not come from specific ethnic or racial groups being made scapegoats for the outbreak, as had happened in previous epidemics. The Spanish influenza moved so quickly and so indiscriminately among the population that it could not easily be blamed on immigrants or the poor.[10] Instead, the lines of resistance reflected divisions between the public health departments and the communities they served.

Implementing social-distancing measures in these big cities presented a massive public health challenge.[11] They had complex economies dependent on both industry and commerce that could easily be damaged by quarantines and closures. As had happened in earlier epidemics, businessmen resisted the idea of mass closures of transportation and businesses that would cause economic distress both to owners and workers. Some employees filed lawsuits to recover lost wages due to such a closure. Big cities also had large public-school systems, flourishing commercial entertainment districts, and extensive systems of mass transit, all of which formed fertile ground for the spread of influenza. School closures left parents with children to provide for during the day. Shutting down saloons and theaters meant not only lost revenue for owners but also lost pleasures for their customers. To inflict such economic damage on a city's economy required a public health emergency without precedent.

Hence, a number of cities including New York felt that the most practical strategy was to move quickly to isolate the acutely ill in hospital wards or at home and to direct an intensive public education effort about personal hygiene to everyone else.

Public-gathering bans also exposed tensions about what constituted essential vs. unessential activities. Those forced to close their facilities complained about those allowed to stay open. For example, in New Orleans, municipal public health authorities closed churches but not stores, prompting a protest from one of the city's Roman Catholic priests. Theater owners often voiced the "why us and not them" argument. In many cities they were the first, and sometimes the only, businesses to be shut down. In response, some of them asked that the closing order be extended to department stores and public transport.[11]

Perhaps the most important "lesson" taught by the Spanish flu pandemic was the realization that those measures that worked the best to control a highly infectious disease—bans on public gatherings, school closures, and strict quarantine and isolation—were precisely the ones most difficult to implement. In the modern times, the amount of resistance to these measures will likely be no different. Also, in an event of a serious pandemic, some measures such as those involving closure of county or state borders in a quarantine may be impractical since they will not be able to be enforced. The manpower required to do so will outstrip the need. Even more so due to the fact that a significant proportion of law enforcement personnel may themselves fall ill or be taking care of their own ill family members or providing for the safety of their families in an event of societal disruption secondary to a massive pandemic. The mandatory quarantines will also likely fuel public distrust in the government and may even fuel public unrest and societal disruption, as we have seen happen in the most recent Ebola outbreak in Africa.

In light of all this, a combination of select public health control measures with empowering individuals and organizations to self-quarantine or use other measures to decrease or stop the transmission of infectious organisms may be the most practical and effective approach.

Other Infection Control Measures and Opportunities for Innovation

As discussed above, due to the fact that we are unlikely to have drugs or vaccines available in time to counter an emerging infection in a pandemic, we will instead need to rely on infection control measures to get ahead of it. This does not mean we cannot utilize modern technology, however—quite the opposite. This is an area which is currently underinvested but which holds much promise and opportunity if we innovate around it. What might this look like? If we are able to keep everybody home for a month or two, we would stop the cycle of transmission and illness and be done containing a pandemic.

How do we enable that? Perhaps people can work or study remotely from home while they get automated delivery of food, water, and basic supplies via driverless cars or drones. Keeping everybody home for a month at this point in time may be an unrealistic goal given the current state of technology, but it may be more achievable as technology advances. Even if part of the population can be isolated in this way for a period of time, this may help us get ahead of an outbreak. Also, perhaps people would prefer to self-quarantine if they face a possibility of catching an infection with high mortality rates if they leave their homes. They would just need to be enabled to self-quarantine, either with the use of technology or simple personal disaster preparedness. If we are prepared in this way, we are also likely to decrease the chances of public chaos and breakdown of society in an event of a deadly pandemic and will significantly decrease the burden on hospitals and medical infrastructure as a side-effect.

How about creative use of UV lights, which we know effectively kill germs? Those could be used in public transport, offices, and schools. Or the use of germicidal ozone? Air filters? Wider use of negative pressure rooms, to remove air with germs and replace it with the one without? Or altering humidity and temperature in hospitals and buildings, since both have been shown to affect the spread of some infectious organisms including influenza?[12] Or creating better personal protective equipment that everybody, not only medical personnel, can safely and easily use? The opportunities to innovate are numerous. The attractiveness of these approaches is that they can be used for every bug or at least a large group of bugs, unlike the traditional pharmacologic countermeasures, which generally use a one bug per drug approach.

Are We Prepared for Pandemics, and What Should Be the Next Steps?

Are we prepared to withstand pandemics due to organisms with high mortality rates? According to the Blue Ribbon Study Panel on Biodefense (BRSPB) in 2015, we are not.[13] The Blue Ribbon Study Panel on Biodefense is a privately funded entity established in 2014 to provide a comprehensive assessment of the state of U.S. biodefense efforts, and to issue recommendations that will foster change. It is the only body of bipartisan high-level policymakers to do so.

The study covered human-generated (terrorist and accidental) and naturally occurring biological threats. The study culminated in a report to the public that Congress released on October 28, 2015. BRSPB's final report had 33 recommendations and over 80 specific items associated with those recommendations. The study assessed biological threat awareness, prevention and protection, surveillance and detection, and response and recovery. Current and former members of Congress, former administration officials, state and local representatives, thought leaders, and other experts provided their perspectives on current biodefense efforts, including strengths, weaknesses, and opportunities. While much good work has been achieved toward biodefense, these meetings have revealed systemic challenges in the enterprise designed to protect Americans from a biological event.

Some of the challenges highlighted include lack of senior national leadership to centralize efforts of the various governmental agencies working on issues related to biosecurity. The Panel proposed empowering the vice president with jurisdiction and authority over biodefense responsibilities. Other recommendations included measures to enhance national biosurveillance capability, improving public health emergency capabilities and hospital preparedness, incentivizing innovation in countermeasure development and deployment, and rapid point-of-care diagnostics, leading the way toward establishing an agile global public health response apparatus. In 2018, the Blue Ribbon Study Panel also issued their budget recommendations to increase return on investment in biodefense.[14] Much is left for us to do to enhance our ability to withstand serious pandemics. Concerted effort with an innovative and collaborative mindset will save lives and enhance our nation's safety, security, and resilience to pandemic threats.

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About

New and rapid societal and technological changes are complicating governance around the globe and challenging traditional thinking. Demographic changes and migration are having a profound effect as some populations age and shrink while other countries expand. The information and communications revolution is making governance much more difficult and heightening the impact of diversity. Emerging technologies, especially artificial intelligence and automation, are bringing about a new industrial revolution, disrupting workforces and increasing military capabilities of both states and non-state actors. And new means of production such as additive manufacturing and automation are changing how, where, and what we produce. These changes are coming quickly, faster than governments have historically been able to respond.

Led by Hoover Distinguished Fellow George P. Shultz, his Project on Governance in an Emerging New World aims to understand these changes and inform strategies that both address the challenges and take advantage of the opportunities afforded by these dramatic shifts.

The project features a series of papers and events addressing how these changes are affecting democratic processes, the economy, and national security of the United States, and how they are affecting countries and regions, including Russia, China, Europe, Africa, and Latin America. A set of essays by the participants accompanies each event and provides thoughtful analysis of the challenges and opportunities.

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

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

HOOVER INSTITUTION