Supplementary Appendix

This appendix has been provided by the author to give readers additional information about his work.

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The Next Epidemic

Lessons from Ebola

The ongoing Ebola epidemic in Guinea, Sierra Leone, and Liberia is a huge tragedy. The impact on the 22 million people who live in those countries goes far beyond the Ebola deaths. The health systems and the economies of the three countries have been largely shut down during the outbreak. The world has a lot of work to do to make sure the case rate drops to zero—in the week leading up to March 1, 2015, there were 132 new confirmed cases reported. It will also need to make sure a good health care system is built and enough food and other basics are available. Without catch-up vaccination for the children who have not gotten vaccines during the epidemic, for example, the increase in measles deaths alone could outnumber the deaths from Ebola.

The only good news from this epidemic is that it can serve as a wake-up call to help us prepare for a future epidemic that spreads more effectively than Ebola does. There is a significant chance that a substantially more infectious epidemic will come along over the next 20 years; after all, we saw several of them throughout the 20th century, including the Spanish flu of 1918-19, which killed at least 30 million people, and the ongoing HIV pandemic. In fact, of all the things that could surprise people in a negative way by killing more than 10 million people, by far the most likely is an epidemic, from either natural causes or bioterrorism.

Ebola is far from the most infectious disease we know about. During the epidemic, almost all of the secondary infections have taken place after the patient was very sick. Most people are infected while taking care of a patient at home or in a hospital, or by touching the body of someone who died from Ebola. This means there has been very little spread to strangers other than health care workers and those providing emergency transportation. This factor has helped keep the number of cases below 0.5 percent of the general population, and it allowed a few tactics—such as persuading infected people to get isolated and treated—to slow the epidemic.

By contrast, other disease agents (measles and flu, for example) are far more infectious because they can spread through the air, rather than by direct contact. People may not even be aware that they are infected or infectious. These agents make it possible to infect lots of strangers in the marketplace or on a plane, so the number of cases can get large very quickly. And successive waves of infections can come just days apart, leaving little time to mount an effective response.

When I heard that the Ebola epidemic had reached urban areas, I had a dreadful feeling that we might not be able to keep it from spreading to many more countries with weak health systems. It was only when I got a chance to start looking at the case data with colleagues at the Institute for Disease Modeling that I saw the relatively confined pattern of the infections and began to think the geographic spread could be controlled.

I am concerned that as the intensity of the problem fades from the world's attention, we will miss the opportunity to learn from the Ebola epidemic and be better prepared for the next one. Even if the system we have today worked perfectly, it would not contain a more infectious disease.

It's useful to compare our preparations for epidemics with our preparations for war. Defense budgets and investment in new weapons dwarf investments in epidemic preparation. NATO has a mobile unit that is ready to deploy quickly. Although it's not a perfect system, they do joint exercises where they work out basic logistics like how fuel and food will be provided, what language they will speak, what radio frequencies will be used. When soldiers sign up to serve, they know what the risks are and who will take care of them if they're injured or killed.

Few if any of these things exist for an epidemic response. The world does not fund any organization to do the broad set of coordinated activities that are needed for the next epidemic. The last serious simulation of an epidemic in the United States, the Dark Winter exercise, took place in 2001. The International Health Regulations (IHR), adopted by the United Nations after the SARS outbreak of 2002-03, were intended to improve the world's ability to prevent and contain outbreaks. But few countries have met their commitments under the IHR. Nor have most countries established an Emergency Operations Center that can be activated within 2 hours of identifying an outbreak, a commitment made under the 2014 Global Health Security Agenda.

Because there was so little preparation, the world lost a lot of time trying to answer fairly basic questions about how to deal with Ebola. In the next epidemic, these delays could cause a global disaster.

The problem does not lie solely with any single institution—it is a global failure. The world needs a global warning and response system for outbreaks. (WHO has a group with a similar name—the Global Outbreak Alert & Response Network—but it is severely understaffed and underfunded.)

In this essay, I describe what I think that system might look like, based on lessons learned from the Ebola response. Many details will need to be worked out. I have not seen a rigorous projection for what a complete system like the one I describe would cost, but the World Bank has made some projections that give a sense of the cost of inaction. For example, it has <u>estimated</u> that a worldwide flu epidemic would reduce global wealth by \$3 trillion. It has also <u>projected</u> that Guinea, Sierra Leone, and Liberia will lose 12 percent of their GDP this year because of Ebola; if a global epidemic were as costly, the worldwide impact would be more than \$7 trillion, not to mention the immeasurable misery caused by millions of deaths.

The key point is that the world is not nearly as prepared for a massive epidemic as it needs to be. While Melinda and I remain committed to our work on improving the health of the poorest, I hope this paper—in spite of whatever shortcomings it has—helps spark conversation and action to prepare for an epidemic that could have global consequences.

Public Health and Primary Health-Care Systems

There is a critical need to reinforce basic public health systems. These are fundamental systems that include primary health care facilities, laboratories, surveillance, critical care facilities, etc. As many commentators have pointed out, Ebola has spread much faster and more widely in countries whose health systems, and especially primary care systems, were severely weakened by years of conflict and neglect. Countries with stronger health systems have been able to respond more quickly.

Strengthening primary health-care systems provides a double benefit. One, it improves our ability to prevent, detect, and respond to epidemics. The other benefit is to health more broadly. Primary health-care facilities are where women go to seek preventive services like family planning and vaccinations for their children, and to get treatment for a sick child. Without a functioning health system—including adequate numbers of trained health workers, good supply chains, disease surveillance, information systems, and policies that enable access by the poor—it is very hard for a country to end the cycle of disease and poverty.

Good health is so fundamental to well-being and development that even if there were no chance of another epidemic ever occurring, health care systems would be a worthwhile—and life-saving—investment. The fact that they also bolsters our ability to deal with the next epidemic is all the more reason to invest in them.

Disease Surveillance

There is no systematic disease-surveillance process in place today in most poor countries, which is where a natural epidemic seems most likely to break out. The Zaire strain of Ebola had not previously been seen in West Africa, so the region wasn't as prepared as central Africa, where it has shown up more than 20 times over the past several decades. Although Médecins Sans Frontières (MSF) reported a rise in Ebola cases in Guinea last spring, there weren't adequate resources on standby to go into the area and do the requisite sampling to determine how widespread the outbreak was. Even once the crisis was recognized, there weren't resources to effectively map where cases were occurring and in what quantity.

We need to invest in better disease surveillance and laboratory testing capacity, for normal situations and for epidemics. Routine disease surveillance systems should be set up so they can detect early signs of an outbreak beyond their sentinel sites and be efficiently and quickly scaled up during epidemics. They should be tied in to the national public health laboratories to enable robust monitoring and response as part of a country's health-care system. The data derived from the testing needs to be made public right away. A lot of the laboratories in developing countries have been financed by the polio eradication campaign, so there should be a plan for what capacities we need once that campaign is over.

Personnel

Once it became clear that a serious emergency was under way, recruitment of local clinicians and the flow of trained personnel into the affected countries should have been very high. It wasn't. There was no comprehensive plan for what was needed. No training centers were standing by. The United States, Cuba, China, and other countries stepped forward with volunteers, but few of them were trained in what treating Ebola patients effectively would entail. All of this happened over two to three months, when it needed to happen within days. It is fortunate that MSF was able to mobilize volunteers faster than any of the governments.

We need trained personnel ready to deal with an epidemic quickly. One approach is to think of them in three tiers: 1) an incident manager for each Emergency Operations Center (EOC), in charge of coordinating efforts by the medical care providers, military, volunteers, and others at the country level; 2) experts in epidemiology, surveillance, outbreak response, social anthropology, and other areas who can provide surge capacity for the response; and 3) respected community leaders who can lead the local engagement efforts and community workers who can implement programs and give accurate information to the public in local dialects.

There should be updated lists of people at all levels—especially the first two—documenting their availability and capabilities. There should be standby training centers and a plan to quickly recruit community leaders as soon as the EOC is activated. There should be an explicit understanding about how to compensate and insure the volunteers, and information about what is expected of them so they can decide very rapidly whether to sign up. Countries should commit to manage a pool of volunteers and send a certain number of people with various skills and equipment within a week of an emergency, with plans for evacuating them if they are exposed. We should also leverage the talent at schools of public health around the world. The earliest people to go in should be surveillance experts, logistics experts, and clinical staff. Finally, countries should have plans in place for supporting volunteers when they come back. In this epidemic, returning health workers have lost their jobs and experienced discrimination, which may have made others reluctant to sign up.

Transportation and Equipment

When an epidemic strikes, transportation will be a critical problem. Roads and airports in affected areas will be overwhelmed by swarms of people trying to get out. Volunteers will be more likely to sign up if they know they will be able to get out when their duty is done or if they get sick.

There are very few organizations in the world that can move thousands of people to different locations on the globe with a week's notice—especially given that, in an epidemic, some of the transport needs onboard isolation so that passengers can't infect each other or the crew. The United Nations has to borrow transportation equipment to support its military missions. The World Food Programme can move people and food during a famine but has nowhere near enough capacity for an epidemic.

The Ebola epidemic might have been a lot worse if the U.S. and U.K. governments had not used military resources to help build health centers, manage logistics, and fly people in and out of the affected countries. The militaries also provided command and control capacity to help organize the different groups working on Ebola. It is fortunate that they were not too busy with other emergencies to help out, and that the Ebola epidemic is happening in countries that are open to working with them. We should not assume that this will always be the case.

The world should identify trained military resources that will be available for epidemics. In a severe case, almost every middle-income and rich-world military would have to come together with their resources. Countries might hesitate to deploy resources abroad that might be needed at home, which could create a paradox where the world allows an epidemic to spread from the primary sites and reach lots of countries.

Transportation is not the only critical resource. Severe epidemics also require tents, protective suits, bleach, portable power sources, portable air conditioning, medical supplies, and more. We should have a list of supplies needed to stop an epidemic that reaches 10 million people, which would be 100 times what we experienced in the Ebola epidemic. Because face masks, protection suits, medical tents, and other medical supplies could see extreme demand, there should be an analysis of which items need to be stockpiled or subject to being commandeered so we don't run out. Militaries and agencies that deal with humanitarian crises stockpile items like these for natural disasters and refugee crises, and they should get support for expanding their supplies to what is needed for epidemics.

I have experience with one item that—although it wasn't critical—shows how unclear the decision making process is. By early September, it was apparent that health workers in protective suits would get so hot that it was difficult for them to care for their patients. I asked a group of people who work for me on technology for keeping vaccines cold to refocus on keeping the medical workers cool. Within days, they had found existing commercial and military technology that could help. But there was no unified mechanism for getting this equipment to the treatment centers. The team had to create new distribution channels by working directly with local treatment centers and organizations like Partners in Health and MSF. I am not saying this was a critical issue, but it illustrates how there was no coordinated process for getting new equipment designed and distributed to the people who need it.

Data Systems

Given all of the actors involved in an epidemic and the importance of allocating resources quickly and efficiently, it is critically important to have good data about what's going on. Unfortunately during the Ebola epidemic, the case database has not always been accurate or up to date. Some of this is because of the chaos of the situation, but it is also because there isn't good technology and training available or clear rules about making the data accessible.

Today the default is that countries must sign off on making data about their citizens available, but because that process is unclear, it happens slowly or not at all. For future epidemics it should

be possible to have a system to digitally enter information like suspected cases, locations, survivors, etc. into a database that is instantly accessible to organizations engaged in the response and the agencies coordinating their work. The rationale for not waiting for each country to release the information is clear: An accessible database would be a critical global public good. The groups that work on the Ebola data—including WHO, the CDC, and others—could write up a specification or revise the International Health Regulations for what we need next time. Based on what we've learned with Ebola and polio, I think some combination of foundations and technology companies can find the resources to make sure a robust system, including the training materials and back-end systems, comes together within the year.

Experts will also need computer models to predict what might happen and which interventions should be prioritized. The ideal is to have multiple strong modeling groups who can focus full-time attention on an outbreak. They should have access to satellite photography and analysis so they can understand how people are moving in the region. And with appropriate privacy safeguards in place, cell phone records can help modelers understand population counts, social connections, and movement.

If the data systems are going to work, we also need to improve Internet and cell phone connectivity. During the Ebola crisis, there has been a lot of discussion about enhancing the Internet and cell phone networks in the affected areas, but there was far too little progress. As a result, much of the case reporting has been done on paper and then sent to a central location for data entry. We should be able to use cell phone systems to get messages out to everyone and to poll people about what they are seeing. Key centers should have high-bandwidth Internet capacity via satellite, and wi-fi capacity should be added in key areas so that digital tools can help with reporting data and coordinating personnel. Rapidly deployable systems should be available to quickly increase capacity in crisis areas.

Medical Tools

Among the pathogens we know about, flu is the most likely to cause a big epidemic. But we could also encounter one we have never seen before. In 2003, for example, no scientist had seen SARS. That year it infected some 8,000 people and killed 800.

Making sure that prophylactics and treatments are available for key personnel (police, health workers, pilots, etc.) and volunteers could make a gigantic difference in stopping an epidemic and limiting the damage it does. The good news is that there is a lot of scientific work that can be done that is not specific to a particular pathogen and enables faster response to a wide variety of infectious agents. It should be possible to have general capabilities to make diagnostic tests as well as drugs, and vaccine platforms that could be adapted for use against various pathogens. Today, with the possible exception of flu, we do not have nearly enough capacity to do this.

One problem is a lack of incentives. Pharmaceutical companies and others in the private sector face an opportunity cost in shifting resources (including their researchers) away from more

commercially viable projects to work on drugs or vaccines for epidemics that may not happen. Their work represents a kind of insurance policy against the next epidemic, and there may need to be an international system for funding it that factors in these opportunity costs.

There are three key areas of medical tools that will be important for the next epidemic: diagnostic tests, therapeutics, and vaccines.

Diagnostic Tests

When a new epidemic breaks out, one of the most urgent tasks is to obtain and analyze biological samples—including blood, saliva, nasal swab, and stool—to determine what is causing the disease. Those samples start the process of figuring out how to make diagnostic tests, drugs, and vaccines. The samples will be tested, the pathogens sequenced, and all of that data should be immediately published digitally for the world's scientists to study. Fairly quickly it should be possible to see the signature of the disease and determine whether the pathogen is a virus, bacterium, or something else.

It's extremely important to have an accurate diagnostic test that can determine whether someone is infected. The ideal test, which is being developed, will be one where you take a sample and get a definitive result within 20 minutes. People who are infected can be sent to treatment centers so they are isolated from the uninfected. If getting results takes more than a day—because the testing capacity is overloaded, or the transport of the sample to the testing service is slow, or the test process itself takes a lot of time—then holding people while you wait to get the answer is very difficult.

Other than watching for symptoms (which are a clinical diagnostic test, albeit a bit late), most of the diagnosis during this Ebola epidemic has been done by taking a blood sample and sending it off for quantitative polymerase chain reaction (qPCR) analysis. Availability of these expensive qPCR machines is limited and centralized, so on average it has taken one to three days for test results to come back after a sample is collected and sent out. For the next epidemic, we should make sure adequate qPCR machine are made available or mobilized in the first few weeks (with trained technicians and supplies), while novel diagnostic methods are rapidly developed. A number of diagnostic companies have technologies that are cheaper, more portable, and faster and requires less expertise than qPCR. When you move to a new format, though, you have to be sure that the biomarker and your sensitivity to that marker are not compromised—otherwise you could miss early disease and allow infected people to be identified as uninfected.

In the future there should be a clear process for taking the information about disease signature and then developing and manufacturing accurate diagnostic tests very rapidly. A focused effort to accelerate this process and establish a rapid approval and procurement process would be worthwhile. The science of bio-diagnostics is advancing rapidly, so there is a good chance that a proven test could be produced at scale within weeks of an outbreak.

Therapeutics: Antivirals, Antibodies, RNA, Transfusion

It is hard to overstate the value of having a drug that reduces the duration and degree of infectiousness and saves lives. Infected people are more likely to come to a treatment center if doing so will increase their odds of surviving, rather than just preventing them from infecting others. Survivors from the treatment center would likely be immune from getting sick again, so they could go back to the affected regions to help inform people about the importance of seeking treatment.

There are drugs that work against viruses that are similar to Ebola, and in various test assays, a number of them show an effect against Ebola. Unfortunately, they were not tested in Ebola patients until after the peak of the epidemic. This was partly because there wasn't a clear decision process to approve a novel trial format and to provide indemnity against legal liability. The role of the local governments relative to the global actors remains unclear, but it is not hard to imagine local authorities being inundated with suggested therapies, as happened with this epidemic. There should be a clear set of guidelines (and testing and regulatory pathways) for figuring out whether existing drugs could be re-purposed to help stop a particular epidemic. This testing should be carried out as soon as possible—we can fill the pipeline now with the best options so they are ready to be used in a future outbreak.

We also need to invest in more research on antiviral drugs and have either stockpiles or rapid manufacturing capacity for those that might be effective in an epidemic. The search for drugs against HIV, which started in the 1980s, has contributed a lot to the field of antiviral drugs. The number of antiviral drugs that perform well against HIV is quite impressive. Since the next epidemic will probably be caused by a virus, general work on broad-spectrum antiviral drugs is a global public good that needs more research than is being done.

There is a special class of therapies that are based on antibodies. For example, Zmapp was specifically designed for treating Ebola patients. This is another intervention that was given to many of the patients who were treated in the United States and Europe, but it was not made in sufficient volume quickly enough to help in Africa.

Because of the small number of treated patients and lack of an adequate control group, we don't know which interventions were key to the higher survival rates in the United States and Europe. Still, the evidence suggests that antibody-based approaches will probably be valuable for the next epidemic. We need to improve our ability to design an antibody against a new pathogen and make sure that it is applied along with new rapid manufacturing techniques and a clear regulatory pathway to maximize the chance of success. Manufacturing capacity for making antibodies at scale will have to be set aside or subject to being commandeered during an epidemic. We should also leverage approaches like adeno-associated virus (AAV) vectors, which use a harmless virus as a backbone to explore generating robust antibody levels.

Another special class of drugs involves giving patients a set of particular RNA-based constructs that enables them to produce specific proteins (including antibodies). Although this is a very new area, it is promising because it is possible that a safe therapy could be designed and put

into large-scale manufacture fairly rapidly. More basic research as well as the progress of companies like Moderna and CureVac could eventually make this approach a key tool for stopping epidemics.

There is one approach that should have been applied for this Ebola epidemic, but it wasn't approved and scaled up until it was too late to have a large impact. It involves taking the blood of survivors, extracting the plasma from it (plasmapheresis), and giving the plasma—or the immunologically potent parts of it—to people who have early symptoms of disease or who are at high risk of contracting it. Depending on the disease, a single survivor should be able to provide protection for at least one person every two weeks.

This process is quite effective for a number of diseases. It was very effective with smallpox and viral hemorrhagic fevers, including treating a patient in the United States who had Lassa fever in 1969. It has a reasonable chance of working for Ebola as well. It was used to treat 8 patients during an Ebola outbreak in Zaire in 1995, but because it wasn't done as an organized trial, we don't know for sure whether it worked. Subsequent animal experiments had mixed results.

The Gates Foundation started working to get plasmapheresis units going in early September and quickly found partners with equipment ready to take it into the affected countries. Unfortunately, the effort was hampered because there was no clear process for approving new approaches, or for exporting plasma to other countries to be processed and then getting it back to the patients who needed it. By the end of 2014, only a few patients in West Africa had been treated with convalescent plasma, which means the sample size is too small to determine whether it was effective. (This treatment was given to some of the Ebola patients who were lucky enough to be treated in rich countries.)

For future epidemics, there need to be rules in advance for all medical interventions and a clear assignment of responsibility for approving studies and treatments, including experimental ones. One of the critical elements would be to obtain specimens (e.g., blood) from infected individuals to isolate samples of the pathogen and also to fish out high-affinity antibodies. Then we should be able to quickly leverage the sequence information of the antibodies to test novel approaches and determine what might work quickly and be safe. A Global Epidemic Drug Approval process could avoid long delays by indemnifying companies working on new approaches and enabling decision-making around "permission to use" of investigational medical products.

For transfusion in particular, there needs to be ample equipment easily available, as well as a process for quickly getting donor plasma to facilities for processing and then returning the finished product to the affected populations. There is a good chance that the plasma transfusion could work as a therapeutic and have a dual impact on the potential disease as well as empower local populations to engage in the outbreak responses.

Vaccines

Three different Ebola vaccine constructs were being developed in the summer of 2014, but all were in early stages and had not reached Phase 1 safety testing. The normal process for going from Phase 1 to full approval for sale and use would have taken at least another 5 years. Even the accelerated process adopted for the epidemic will require more than 9 months. Ironically, by the time of the final phase of testing—which measures effectiveness in a large population—there will likely be too few people still being exposed to Ebola virus to know reliably how effective these vaccines are.

Because of this early work, we were more prepared for Ebola virus than we would be for a new pathogen. If the pathogen hasn't been seen before, at least another year of work would probably be needed. And the issues of how quickly to move and who should finance the final research and the manufacturing are not as clear as they should be.

With the seasonal flu, we know how to make vaccines against specific antigenic forms of the virus, but even the relatively minor season-to-season variations are significant enough that we have to design a new vaccine each year. When a very different antigenic variant like H1N1 (the swine flu of 2009) comes along, there is no clear process for getting resources applied to creating a new vaccine. In fact, after the swine flu scare—where WHO worked with pharmaceutical companies to create and buy a stockpile of vaccines—some people criticized WHO for doing too much, a stark contrast with the complaints that it did too little on Ebola. Given that flu is the most likely single known pathogen to cause a large epidemic and that even the seasonal variations likely cause several hundred thousand excess deaths each year, it is disappointing that we don't have a vaccine that works on all variants of flu. There is work being done toward this goal, but with nowhere near the resources that it deserves.

I have a bias towards vaccine research because of the impact I see from vaccines in the Gates Foundation's work on preventing disease. Many of the same legal and regulatory barriers that slow down the approval of therapeutics also apply to vaccine candidates. We should establish clear guidelines to avoid these hurdles during emergencies. The ideal would be to fund vaccine research so that a vaccine can be designed, tested for safety, and ready for manufacture in large volumes in a matter of a few months. There is no guarantee of success, but given enough time—probably no more than a decade—and enough resources, I think this effort could produce an invaluable contribution to both promoting overall health and preventing epidemics.

Quarantine and Communications Plans

During the Ebola epidemic there was a lot of discussion about quarantine. Should commercial flights into and out of the affected countries be stopped? Should people returning from the affected region be forced into quarantine? For this epidemic, given the limited infectiousness of Ebola in the early stages of the disease, most of these proposals would have been counterproductive. Banning travel from affected areas to the United States, for example, would have forced people to take an indirect route, making them harder to track once they arrived. Forcing people into quarantine would have discouraged volunteers from working in the

affected countries. Basic monitoring procedures were adequate to determine whether patients were developing Ebola and get them into isolation before they infected others.

But when a far more infectious agent comes along, quarantine will be one of the few tactics in the early stage of the disease that can reduce the spread of contagion. Travel today is so common that an infection can spread across the globe far faster now than in 1918, when the Spanish Flu epidemic swept across the world. During the SARS epidemic, China eventually did a good job of curtailing travel and public gatherings in affected areas. I doubt every country would have handled this aspect as well as China did, because in normal situations the system is designed to avoid abridging individual rights to travel and assemble freely. I worry that in the early stages of an epidemic, democratic countries might be too slow to restrict activities that help spread the contagion.

Part of the process should include a plan for effective public communications. There will be lot of panic and thirst for information when the epidemic hits. Many people will be tempted to tie up health and transport assets when they should not. Well-designed quarantine plans need to be part of an overall outreach plan that coordinates all the different voices people will hear: governments, U.N. agencies, news media, bloggers, etc. The ways that people communicate digitally can be used to great advantage, but unless a plan is in place ahead of time, they will just spread confusion and panic faster than in the past—perhaps at the cost of many lives.

Bioterrorism

I chose to focus this essay on the lessons from a natural epidemic. But an epidemic could also be engineered intentionally. As biological science and technology advances, it is getting easier to create (or re-create) pathogens with only modest effort and technical knowledge. Over the next few decades it will be even more feasible to synthesize, mass-produce, and disseminate pathogens that are highly infectious and largely fatal. (Because Ebola doesn't spread very effectively, it would not make a highly effective bioterror weapon.) Everything I have described in this essay would also be worthwhile in preparing for bioterrorism. Nathan Myhrvold discusses these challenges in his essay on strategic bioterrorism, which I highly recommend—although it is sobering to read.

A Global Call to Action

The world spends a great deal of money—hundreds of billions of dollars a year—getting ready for war. I am not saying this is a mistake, but given that an epidemic is more likely to kill millions of people than a future war, I believe we should build on these efforts so we can be more prepared for a severe epidemic. Some of the capabilities, like transport and some personnel, overlap and can play a dual purpose if properly planned. Other elements, like research on diagnostic tests, vaccines, and treatments, will require specific investments.

A serious epidemic would also raise a lot of questions about global governance. What body would bring sovereign nations together and ask them to make decisions about limiting travel

and allocating scarce resources like vaccines or drugs? All of the epidemics we have seen so far have shown that we desperately need processes for making tough decisions fast.

One technique that we should borrow from the military is the idea of a war game. Once we have taken action on the basics, countries should come together every few years to simulate different types of epidemics so they can understand what is missing from the response.

I worry that many people do not think a serious epidemic is a problem for them to worry about. They may think that the United Nations system, and especially WHO, has it covered. In fact, WHO has not been clearly chartered or funded to handle most of the things required in an epidemic. Or they may think their government has a plan already in place. While the United States, the United Kingdom, and others are working on many of the things described in this memo, there are still big holes in the world's ability to respond.

There should be a rigorous study of the cost of building a global warning and response system for epidemics, including greater investments in research and development, preparing military resources for epidemic response, and maintaining a reserve of paid responders who go through regular training exercises. There would need to be a plan for how much each country would contribute and for coordinating the spending so it is used effectively. I think other countries need to step up, but they are more likely to do so when they see an overall plan and understand their role in it. Rich, technically advanced countries should invest far more in the key research and manufacturing capacities than they do today. Most of the others can contribute to the crucial surveillance work.

Through the United Nations, some global institution needs to be empowered and funded to coordinate a global warning and response system—including systems for sharing data, managing personnel, setting an R&D agenda, and other key areas. At the request of WHO's Executive Board, Director-General Margaret Chan is evaluating the organization's response to the recent Ebola outbreak. U.N. Secretary-General Ban Ki-moon is commissioning a high-level panel to recommend ways to improve international crisis management, with a special focus on health based on the lessons learned from the Ebola response. These evaluations would be a good place to start a much-needed conversation about how to strengthen WHO's capacity and about which pieces it should lead and which should be led by others (including the World Bank and G7) in close coordination with it. The conversation should include military alliances such as NATO, which should make epidemic response a priority when they are designing strategies, training troops, and buying equipment. The final arrangement should include a reserve corps of experts with the broad range of skills needed in an epidemic.

In my view, an epidemic is one of the few catastrophes that could set the world back in a huge way in the next few decades. Severe epidemics have struck many times in the past, and they are only more likely as the world becomes more closely connected. By building a global warning and response system, we can prepare for the next epidemic and avoid millions of deaths.

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Recommendations

The world needs to build a warning and response system for outbreaks. This system should:

- Be coordinated by a global institution that is given enough authority and funding to be effective.
- Enable fast decision-making at a global level.
- Expand investment in research and development and clarify regulatory pathways for developing new tools and approaches.
- Improve early warning and detection systems, including scalable everyday systems that can be expanded during an epidemic.
- Establish a reserve corps of trained personnel and volunteers.
- Strengthen health systems in low- and middle-income countries.
- Incorporate preparedness exercises to identify areas for improvement.