The NEW ENGLAND JOURNAL of MEDICINE

Perspective

MAY 31, 2018

SHATTUCK LECTURE

Innovation for Pandemics

Bill Gates

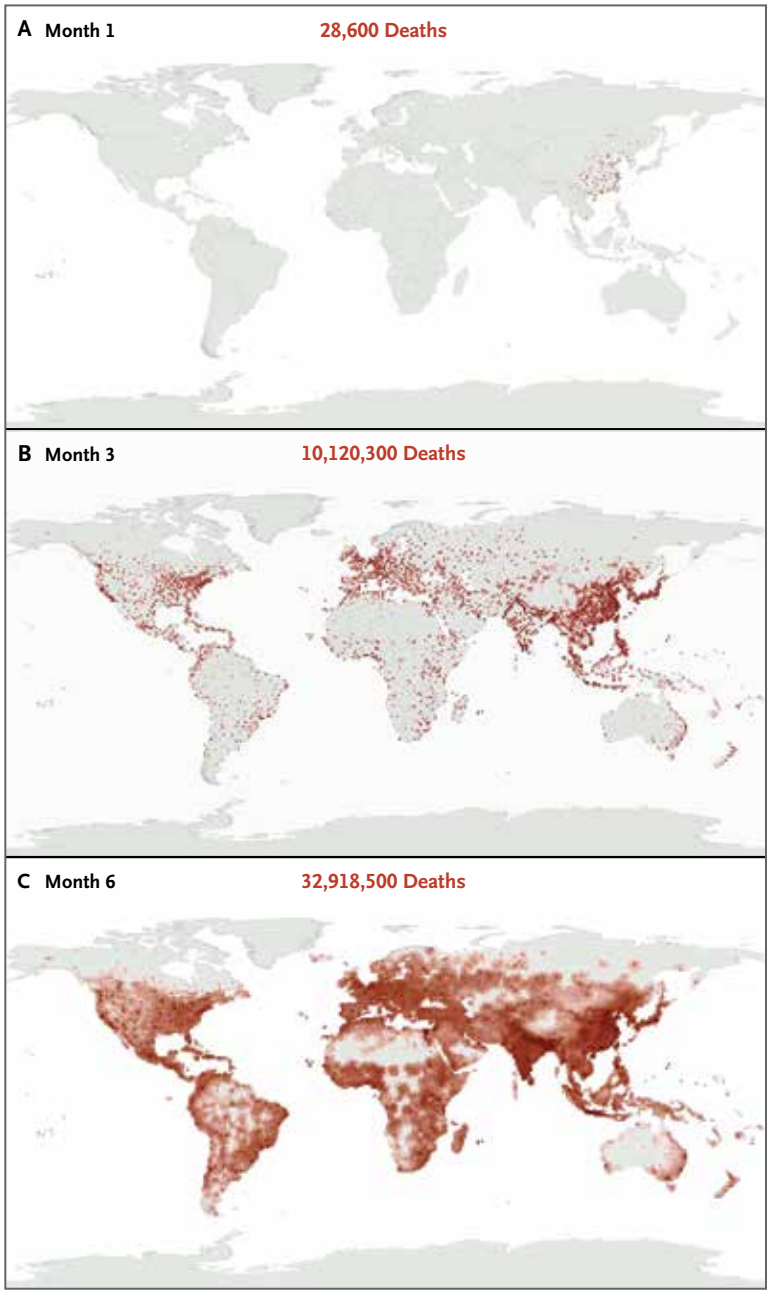
Over recent decades, the world has seen incredible progress in reducing child mortality and tackling infectious diseases. Thanks to better vaccines and other interventions, child mortality has decreased by more than 50% since 1990. We are on the verge of eradicating polio. HIV is no longer a certain death sentence. And half the world is now malaria-free.

Yet there is one area where the world isn't making much progress: pandemic preparedness. This failure should concern us all, because history has taught us there will be another deadly global pandemic. We can't predict when, but given the continual emergence of new pathogens, the increasing risk of a bioterror attack, and the ever-increasing connectedness of our world, there is a significant probability that a large and lethal modern-day pandemic will occur in our lifetime.

Several events in the past decade have made me pay close attention to the risk of future pandemics. One was the outbreak of swine flu in 2009. Although H1N1 influenza wasn't as lethal as people initially feared, it called attention to our inability to track the spread of disease and develop new tools for public health emergencies. The Ebola epidemic in West Africa 4 years ago was another wake-up call, as the number of confirmed cases climbed, the death toll mounted, and local health systems collapsed. Again, the world was much too slow to respond. And every year, advances in science make it easier for somebody to create a biologic weapon of mass destruction.

What the world needs is a coordinated global approach to pandemics that will work regardless of whether the next pandemic is a product of humans or of nature. Specifically, we need better tools, an early detection system, and a global response system.

This year is the centenary of the 1918 influenza epidemic, which killed an estimated 50 million people.[1] We have some better interventions than we had a century ago. We have a seasonal influenza vaccine, although it's not often fully effective, you have to get it every year, and the percentage of people who choose to get it is fairly small. We also have antibiotics that would help with the secondary infections from bacterial pneumonia. Yet despite these advances, a simulation by the Institute for Disease Modeling shows what would happen if a highly contagious and lethal airborne pathogen, like the 1918 influenza, were to appear today. Nearly 33 million people worldwide would die in just 6 months (see map).



Simulation of a Modern-Day Global Influenza Pandemic.

After 1 month (Panel A), there would be a total of approximately 28,600 deaths; after 3 months (Panel B), 10,120,300 deaths; and after 6 months (Panel C), 32,918,500 deaths worldwide. From the Institute for Disease Modeling. An animated map is available with the full text of this article at NEJM.org.

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The good news is that scientific advances and growing interest by a number of actors, including some in the private sector as well as philanthropic funders, make development of a universal influenza vaccine more likely than in the past.

Our foundation is involved in a variety of research partnerships, including a collaboration among the Icahn School of Medicine at Mount Sinai, GlaxoSmithKline, and PATH. Their work focuses on several vaccine candidates that did well in trials in animals and are now moving to human trials. We are also supporting efforts by others, including the National Institute of Allergy and Infectious Diseases, whose vaccine candidate is expected to advance to human trials in about a year.

To broaden these efforts even further, we launched a $12 million Grand Challenge in partnership with the Page family to accelerate the development of a universal influenza vaccine.[2] The goal is to encourage bold, cross-disciplinary thinking by the world's best scientists, including those who are new to the field.

However, the next threat may not be influenza at all. It may well be an unknown pathogen that we see for the first time during an outbreak, as was the case with SARS (severe acute respiratory syndrome), MERS (Middle East respiratory syndrome), and other recently discovered infectious diseases.

The world took a step to begin addressing this risk with the launch in 2017 of a public–private partnership called the Coalition for Epidemic Preparedness Innovations (CEPI). With funding commitments of more than $630 million, CEPI's first order of business is advancing the development of vaccines for three of the priority diseases on the World Health Organization (WHO) list for public health research and development: Lassa fever, Nipah virus, and MERS.

CEPI will also be working on rapid-response platforms to produce safe, effective vaccines for a range of infectious diseases. Later

this year, the coalition will announce grants to several companies, working with a variety of technologies, including nucleic acid vaccines, viral vectors, and other innovative approaches. The goal is the capability to develop, test, and release new vaccines in a matter of months rather than years.

But vaccines can't be the only answer when we have to respond immediately to a rapidly spreading infectious disease. Not only do vaccines take time to develop and deploy, they also take at least a couple of weeks after vaccination to generate protective immunity. So we need to invest in other approaches, such as antiviral drugs and antibody therapies that can be stockpiled or rapidly manufactured to stop the spread of pandemic diseases or to treat people who have been exposed.

There has been good work on specific antivirals in the past decade. For example, in the HIV field, the quality of the antivirals is phenomenal and suggests that broader-spectrum antivirals could be developed. For influenza, the Shionogi pharmaceutical company received approval in Japan for a new antiviral, Xofluza.[3] This single-dose drug inhibits an enzyme that influenza virus needs in order to multiply. Another approach, taken by PrEP Biopharm, a development-stage biopharmaceutical company, has demonstrated in challenge studies in humans that preactivating the immune response through internasal delivery of a double-stranded viral RNA mimic can help prevent both influenza and rhinovirus.[4] Since the innate immune response is non–virus-specific, this approach has potential for use against a range of respiratory viruses.

Over the past few decades, there has also been great progress in monoclonal antibody therapies, leading to new products for cancer and autoimmune diseases. During the Ebola outbreak in West Africa several years ago, researchers were able to identify and test a combination of monoclonal antibodies to treat infected patients. The overall estimated effect of the treatment appeared to be beneficial, though the result did not meet the prespecified statistical threshold for efficacy. And a growing pipeline of broadly neutralizing antibodies are being discovered in some people exposed to infectious diseases. For example, in a small percentage of people infected with HIV, antibodies with both high potency and broad coverage develop, sufficient to protect against most strains of the virus. The same is true for some people infected with influenza. Various combinations of these exceptional antibodies may be able to protect against pandemic strains of a virus even if it has evolved genetically from the time of its detection and identification. It is conceivable that we could create libraries of these antibodies and produce manufacturable seed stocks that would enable us to have the antibodies ready for immediate use in an outbreak — or to scale up manufacturing if a pandemic occurs.

If we can learn how to use RNA or gene delivery effectively, we may not need to make the antibodies at all. Instead, new methods of gene delivery could enable our own cells to produce these antibodies directly. These approaches are promising because the protection comes literally within hours after the antibodies are injected into the arm.

At the Munich Security Conference last year, I asked world leaders to imagine that somewhere in the world a new weapon exists or could emerge that is capable of killing millions of people, bringing economies to a standstill, and casting nations into chaos. If it were a military weapon, the response would be to do everything possible to develop countermeasures. In the case of biologic threats, that sense of urgency is lacking. But the world needs to prepare for pandemics in the same serious way it prepares for war. This preparation includes staging simulations, war games, and preparedness exercises so that we can better understand how diseases will spread and how to deal with responses such as quarantine and communications to minimize panic.

Earlier this year, the U.S. Congress directed the administration to come up with a comprehensive plan to strengthen global health security, both here and abroad. Such a plan could be an important first step if the White House and Congress use the opportunity to articulate a leadership role for the United States in global health security. Given the depth of U.S. scientific and technical expertise, our innovative biopharmaceutical industry, and our influence in international forums, the United States can and should play a leadership role in developing the kind of pandemic preparedness and response system the world needs.

The global community eradicated smallpox, a disease that killed an estimated 300 million people in the 20th century alone. We are on the verge of eradicating polio, a disease that 30 years ago was endemic in 125 countries and that paralyzed or killed 350,000 children per year. And today, nearly 21 million people

are receiving lifesaving HIV treatment, thanks primarily to the support of the world community.

The U.S. President's Emergency Plan for AIDS Relief (PEPFAR) was the key catalyst for world action on the AIDS crisis. It's an example of the kind of leadership that's needed for broader efforts to make the world safer from other infectious disease threats. Because of its strong bipartisan support, PEPFAR has saved millions of lives and shown that national governments can work together to address diseases.

We need a clear road map for a comprehensive pandemic preparedness and response system, because lives, in numbers too great to comprehend, depend on it.

Editor's note: This year's Shattuck Lecture was delivered at the annual meeting of the Massachusetts Medical Society as part of an educational event entitled Epidemics Going Viral: Innovation vs. Nature. Videos of the event, which included two panel discussions, the Gates lecture, and a Q&A session, are available at NEJM.org.

Disclosure forms provided by the author are available at NEJM.org.

From the Bill and Melinda Gates Foundation, Seattle.

1. Johnson NP, Mueller J. Updating the accounts: global mortality of the 1918-1920 "Spanish" influenza pandemic. Bull Hist Med 2002;76:105-15.
2. Bill and Melinda Gates Foundation. Ending the pandemic threat: a grand challenge for universal influenza vaccine development (https://gcgh.grandchallenges.org/challenge/ending-pandemic-threat-grand-challenge-universal-influenza-vaccine-development).
3. Single-dose flu drug approved for sale in Japan. Nikkei Asian Review. February 23, 2018 (https://asia.nikkei.com/NAR/Articles/Singledose-flu-drug-approved-for-sale-in-Japan).
4. PrEP Biopharm. Technology and pipeline (http://www.prepbiopharm.com/technology-and-pipeline.php).

DOI: 10.1056/NEJMp1806283

Beyond Legalization — Dilemmas Physicians Confront Regarding Aid in Dying

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"What do you think about physician aid in dying?"

Because 18.2% of the U.S. population lives in jurisdictions where physician aid in dying (PAD) is now legal, physicians need to anticipate that patients may inquire about or request it. Two decades ago, when PAD was illegal throughout the United States, 18.3% of physicians reported ever having received a request for assisted suicide[1]; inquiries are likely to be more frequent now. But physicians may feel unprepared, uncertain, and uncomfortable when confronting these conversations, even if they've thought through their own position on PAD legalization.

Physicians can start by clarifying what patients are asking and why. Some ways in which patients might raise the topic of PAD are listed in the box. Not every question about PAD is a request for assisted suicide. Patients might be seeking information, talking through concerns, expressing distress, or trying to ascertain the physician's views. To clarify the patient's motivation, physicians might say, "I'll be glad to answer that question, but first please tell me what led you to ask."

Next, physicians can explore patients' concerns and identify and address their palliative care needs,[2] regardless of the physicians' own views or the legal status of PAD where they practice. Discussions could cover patients' physical symptoms; psychosocial, existential, and spiritual suffering; hopes and fears; and goals of care. All options for end-of-life care should be discussed, including palliative and hospice care and palliative sedation.

It's also important for physicians to think through what actions they're willing to take. Both physicians who support PAD and those who oppose it should try to relieve patients' multidimensional concerns and distress. After comprehensive palliative care is intensified, 46% of patients who have requested PAD change their minds.[3]

Physicians who support PAD face several decisions regarding patient inquiries. First, are they willing to assist any patient who meets the legal requirements for PAD, or will they participate only in certain circumstances? Physicians are most likely to support PAD in cases of unremitting pain.[4] Many physicians who support PAD legalization may have cases of refractory physical suffering in mind. But perceived loss of autonomy and dignity is now a more common reason for requesting PAD than inadequate pain control.[1] Some physicians may decide they aren't comfortable assisting in a patient's death in such circumstances.[4]

Responses may also be influ-