CHAPTER

9

Strengthening Preparedness for Pandemic Influenza

How able are we to respond to a pandemic?
How can people protect themselves and their families
when a vaccine is not available?

When H5N1 avian influenza emerged in Hong Kong in 1997, public health officials around the world were alarmed. Of eighteen people reportedly infected, six died.[310] Although it appeared that H5N1 could not be transmitted from one person to another, and that all known infections had occurred through contact with infected birds, experts worried about the future of the virus. Influenza viruses routinely evolve and combine with other influenza viruses, creating new strains. If the H5N1 virus were to evolve to become contagious, it could spark a global pandemic. Worse, the greater than 30 percent mortality rate seen

in the 1997 outbreak would vastly exceed the devastation caused by the 1918 pandemic virus that killed approximately 2.5 percent of those infected.[311]

In years after the 1997 Hong Kong outbreak, there were major outbreaks in poultry, but the virus rarely crossed over to humans. When it did, it was deadly: By 2005, nearly one hundred people had been diagnosed with confirmed cases of avian influenza, and half had died.[310] With every case, there were more opportunities for the virus to adapt and to become both contagious and more deadly. In 2012, H5N1 continues to cause human infections in a number of countries around the world, including Indonesia, Vietnam, Bangladesh, and Cambodia. The case fatality rate for the more than 600 WHO confirmed cases is greater than 50 percent.[312] Fortunately, the virus has not evolved to become transmissible between people.

By 2004, the possibility of an avian influenza pandemic appeared to be increasing, and pandemic planning in national governments and the WHO took on new urgency, focused mostly on the problem of how to get vaccine made as quickly as possible.[313] If the H5N1 influenza virus started spreading from person to person, there would be a race to develop, test, and manufacture a new vaccine, but there was not nearly enough manufacturing capacity to produce vaccine for everyone who would need it. An assessment of the time needed to produce a new vaccine suggested that the maximum number of H5N1 vaccine doses that could be hoped for globally was only 300 million, a little less than the population of the United States.[314] A lack of vaccine manufacturing capacity was not a new problem, but in a lethal pandemic, it could have especially damaging consequences.

What a vaccine shortage could look like in the United States became clear during the 2004 05 flu season. The UK based company Chiron, one of the

two manufacturers that supplied vaccine to the US market, had contamination problems and was barred from exporting its vaccine. Other nations, including the United Kingdom, had contracted with additional vaccine manufacturers to avoid severe shortages. In the United States, supply was cut by nearly 50 percent.[315] Elderly and chronically ill people waited in line for hours for the chance to be vaccinated, and some people in vaccine priority groups were turned away. In some places, vaccine distributors became price gougers, charging $800 for a $60 vial of vaccine.[316]

Without vaccine, our main defenses will be non pharmacological interventions.

Thankfully, the flu season was moderate that year. Some people in priority groups did not receive the vaccine as they had in previous years, but the consequences of the shortage were not as bad as they could have been.[315] However, if the prevailing flu strain that year had been H5N1 or another pandemic virus that put more of the population at risk of serious illness, the flu season could have been disastrous. The best option for protection was vaccination, but it would have been available to relatively few people.

The fact that vaccine might not be widely available in a pandemic was the point of a 2006 *Science* magazine editorial by Stephen Morse from Columbia University, Richard Garwin from IBM Research Laboratories, and Paula Olsiewski, who argued that, without vaccine, "our main defenses will be non pharmacological interventions, such as hand washing, 'respiratory etiquette,' face masks, school closure, and social distancing or isolation [which] are ironically similar to the measures used in 1918 to combat the greatest of all known influenza pandemics."[317] The authors called for more research on actions that individuals could take to reduce their risk of infection.

The Sloan Foundation's funding for pandemic influenza related work expanded understanding of how influenza epidemics unfold, how well the public health system can respond, and what measures people can take to protect themselves. Sloan supported efforts to learn more about how the 1918 epidemic came about and to assess both the effectiveness of public health measures during the 2009 H1N1 pandemic and the value of nonpharmacological measures, including surgical masks, school closures, and social distancing. The work that resulted provides insights important for managing not only the next flu epidemic, but also for informing public health responses to many other contagious biological threats, whether emerging or intentional.

Learning from the 1918 Influenza Pandemic

John Barry's Historical Study of the 1918 Flu Pandemic

The catastrophic influenza pandemic of 1918 took place before there were vaccines to prevent infection, before genetic analysis existed to determine how the virus was mutating over time, and before events could be preserved in real time for future analysis. Understanding the genetic makeup of the virus could be important to understanding what makes some influenza viruses especially dangerous and, potentially, to predicting new pandemics as

they are emerging. Understanding what worked to slow transmission in the absence of vaccine such as quarantine or school closures may help today's decision makers develop sensible plans for managing an epidemic when it occurs. Remarkably, genetic study is possible because researchers have a handful of viral samples retrieved from victims buried in the Alaskan permafrost and some samples stored for decades at the Armed Forces Institute of Pathology.[311] However, answers to questions about what worked to slow transmission are to be found only through study of the historical record, an effort undertaken by acclaimed author John Barry.

Flu vaccine production cannot beat the speed of a pandemic.

Barry, a distinguished scholar at Tulane and Xavier universities, raised public consciousness of the events of 1918 in his bestselling 2004 book, *The Great Influenza: The Epic Story of the Deadliest Plague in History*.[318] With Sloan Foundation encouragement and funding, he then turned to the historical archives to uncover more information that could inform modern pandemic planning. His research, still ongoing, has informed the scientific debate about what made the 1918 influenza virus so dangerous and how a future flu pandemic could emerge.

It has long been understood, for instance, that there were three different waves of influenza infections in 1918; that is, three distinct outbreaks occurred in the span of one year, all caused by the same virus. However, the first wave outbreak was mild, while the second and third waves were deadly. The stark difference has led some researchers to hypothesize that the first wave of illness may have been caused by a different virus altogether.[311,319]

This debate cannot be settled in the laboratory because there are no known samples of the first wave virus, so Barry undertook a comprehensive

quantitative analysis of 1918 records from thirty seven US Army camps as well as some British military and civilian records. He found that populations that experienced first wave outbreaks were largely protected from illness and death in the second wave. That finding strongly suggests an immunizing effect that would occur only if the same virus caused all of the influenza like illnesses in all three waves.[320]

The implications of this finding are important. In a modern pandemic, a mild first wave might protect much of the population from a deadlier version of the same virus. The time between discovery of a first wave and emergence of a deadlier second wave may be enough to produce a protective vaccine for those not infected in the first wave, who may be susceptible to the second wave virus.

Sustained change in people's normal behavior is less reliable than the protection of a vaccine.

On the social front, Barry's examination of the use of quarantine, the most extreme form of nonpharmacological intervention, continues; however, he notes that "the data strongly suggest it's useless except under very special circumstances."[321,322] His historical research also yielded important lessons for leaders who may hesitate to be completely candid in communicating risks to the public. Barry has argued that the modern notion of risk communication "implies that the truth is being managed," and that "the truth should not be managed, it should be told."[321] History supports this notion. During the 1918 pandemic, panic resulted when authorities offered no information or, worse, false reassurances. As Barry has explained, "Although a false alarm can be damaging, it is not nearly as damaging as silence the type of silence that makes people believe the truth

is being withheld. That is how trust disintegrates and how rumors passed in the streets in 1918, passed over Internet blogs today take hold and grow."[323]

Barry's work indicates that direct public communication and some nonpharmacological interventions may have an effect, but sustained change in people's normal behavior is less reliable than the protection of a vaccine. Unfortunately, flu vaccine production cannot beat the speed of a pandemic. Recent research suggests, though, that it may be possible to produce a vaccine that will protect against all influenza viruses, thus eliminating the need to produce a new vaccine for each outbreak.[324] "Had influenza been taken seriously for the past thirty years, we would probably have one by now," Barry lamented. "No matter what happens over the next year or two, that's one history lesson we need to learn."[325]

A Billion Decision Makers

A Fresh Look at Pandemic Modeling Assumptions

In 2003, concerns about an H5N1 avian influenza pandemic and the likelihood of vaccine shortages led the US government to look in earnest for data about nonpharmacological methods to prevent the spread of flu. Through the mathematical modeling work of the Models of Infectious Disease Agent Study (MIDAS), supported by the NIH, important public health policy questions were explored, such as the likely effectiveness of administering antivirals, isolating the sick at home, reducing work contacts, cancelling community events, or closing schools.[326] The MIDAS work influenced policy decisions and formed the basis for some CDC flu guidance.

On the premise that some of the underlying assumptions for pandemic planning should be examined independently, in 2007 the Sloan Foundation funded Richard Larson of MIT to take a fresh look at flu preparedness and modeling. Larson is an expert in operations research, a field that combines mathematics, engineering, and management sciences to find the best solutions to complex decision making problems. Over the course of his career, Larson has sought answers to such diverse questions as how can a city make police patrols by car more effective, and what is the science of waiting in line. The

search for commonsense solutions to everyday problems shapes the research questions of Larson's field.

Flu is not a simple problem. As Larson put it, "With pandemic influenza, we are dealing with a worldwide problem involving decisions by literally billions of people."[327] In the early days of a pandemic, disease spread may be determined by the scientific characteristics of the virus. How well can it spread? How long can it remain infectious on a person's hand? Once the danger of the illness is recognized, many decision makers come into play, such as government officials who may cancel public gatherings or close schools, and people who change their behavior to see fewer friends, wear face masks, or cough into their elbows. Meanwhile, the scientific characteristics of the virus change as the virus evolves. Simple mathematical models cannot account for such a complex, stochastic global system, as "disease dynamics are partly under our individual and collective control. Any engineered system in anticipation of the flu must take this into account."[327]

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From complex models that iteratively reflect changes in people's behavior, Larson extrapolated some lessons for decision makers. First, travel restrictions during a pandemic are futile because if they are not 100 percent effective, they will not stop the spread of disease. Second, nonmedical behavior changes are probably going to be effective, so social distancing something people will do anyway as they reduce nonessential personal contacts, but which should be actively encouraged by officials may limit the number of infected people and lower the peak of an epidemic.[328]

Larson's work has been incorporated into the BLOSSOMS (Blended Learning Open Source Science or Math Studies) Initiative, also funded by the Sloan Foundation, to educate high school students all over the world.[329] Larson's students have gone on to apply these modeling techniques to such diseases as malaria and polio.[329] His work on flu continues as well. In a 2010 article, Larson emphasized that it is not just public health authorities who should work to limit the spread of disease. Those authorities ". . . must recognize that ordinary people at the individual, family, workplace, school, neighborhood, and community levels must be engaged in meeting the threat."[330] Social distancing, increased hygiene, and other nonmedical interventions "are key to empowering our citizenry to be the authors of their own survival in the event of a pandemic."[330]

Preventing Flu Transmission in Families

A Controlled Study of Flu Prevention Measures in Families

Influenza spreads fairly easily among strangers, coworkers, and friends, but it spreads especially well in families. Estimates of the risk of household spread of flu have ranged from 10 percent to 40 percent in various epidemics.[331-333] When flu spreads within households, illness leads to missed school days for children and missed work days for adults who may be caregivers or patients

themselves. Without an effective vaccine, nonpharmacological measures must be taken to reduce transmission in families, prevent broader spread of flu, and minimize the disruption it causes.

Manfred S. Green, along with Michal Bromberg and Adi Libling, all from Tel Aviv University, Ramat Aviv Israel Center for Disease Control, wanted to explore ways in which family members could stay well, even when caring for a sick child. With support from the Sloan Foundation, Green and his collaborators conducted a randomized, controlled, unblinded study to test the effect of nonpharmacological methods, such as using surgical masks, washing hands, and isolating sick family members. Sick children were not asked to wear masks, but household members older than six were. If Green and colleagues could prove that these methods reduced flu transmission within a family, health agencies could recommend them for entire populations. Most important, perhaps, these measures could be implemented by anyone as safe, easy, inexpensive ways to reduce flu transmission. That could, theoretically, reduce reliance on drug development or vaccine supplies.

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Green's study was inconclusive. The number of families who agreed to participate was small, and not many participants used the masks.[334] This is a common problem when studying influenza transmission. Even the surgical mask the simplest nonpharmacological intervention has never been proven to actually reduce transmission, and the CDC acknowledges there is little concrete evidence to support its use.[335] Researchers have had a hard time proving the effectiveness of nonpharmacological measures in general, which may be the most important conclusion stemming from this study. The authors

explained that "the two main reasons given for non feasibility were the difficulty in isolating patients, especially young children, from their mothers and siblings, and the burden of following all the hygiene instructions."[334] In follow up conversations, participating families indicated that, even though they believed the preventive measures would help stop the spread of flu, they still did not follow the researchers' instructions.[334]

As we prepare for the next influenza season, or the next pandemic, this conclusion is important. Even though parents may be convinced that wearing masks, washing hands, and isolating sick children from other household members will make a difference to their own health and the health of their families, such seemingly easy prevention methods may be difficult to put into practice. For influenza at least, such measures may not be practical for families, and other tools to prevent transmission need to be developed.

Evaluating the Nation's Response to the 2009 H1N1 Flu Pandemic

CIDRAP's Assessment of Flu Vaccine Efficacy

By the time a new influenza pandemic emerged in spring 2009, the US government had already done a great deal of planning and preparing for

pandemic vaccine production, allocation, and distribution. HHS put forth strategic plans in 2005 to define the roles of federal, state, and local public health agencies.[336] The government invested in domestic cell based vaccine manufacturing capacity, although it did not come online until 2011.[337] The pandemicflu.gov website was established as a one stop shop for the public to find flu resources and information.[338]

When the 2009 H1N1 influenza pandemic put those plans to the test, there were surprises among them, the emergence of the pandemic in Mexico, instead of East Asia, as was expected. The timing of the pandemic made the US public health system go into overdrive. The seasonal influenza vaccine was already in production when a pandemic vaccine was needed, so two separate influenza vaccine campaigns were launched, each with its own public health messages. Finally, the estimates for how much vaccine could be available by October 2009 turned out to be overly optimistic.[339] The H1N1 vaccine was initially in short supply and recommended only for specific priority groups.[340]

The H1N1 vaccine was delayed and did not work as well as expected.

By the time the WHO declared the pandemic over in August 2010, some experts thought the response was a tremendous public health success, particularly because the vaccine development process was accelerated as much as possible and the H1N1 vaccine that was produced had the same safety profile as other flu vaccines.[341] Others thought public health officials stoked fear in the face of what was perceived as a mild pandemic,[342] even though the pandemic was anything but mild for children, young adults, and pregnant women, who disproportionately suffered from the disease.[343,344] The mean age of death in the 2009 pandemic was estimated to be thirty

seven years, which is considerably closer to twenty seven years, the mean age of death in the 1918 pandemic, than to the mean age of death in other pandemics sixty five years in 1957, sixty two years in 1968, and seventy five years in normal flu seasons.[345,346]

While the 2009 H1N1 pandemic was still occurring, the Sloan Foundation moved quickly to support an evaluation of US response to the outbreak. The project's goals were to document the public health response and identify lessons to improve planning and to apply in the next pandemic response. The University of Minnesota Center for Infectious Disease Research and Policy (CIDRAP) spent three months collecting real time information on vaccine manufacturing, allocation, distribution, and impact during the H1N1 pandemic in the United States and followed that effort with a one year Sloan funded project to review all aspects of pandemic influenza vaccine preparedness and response. Leading the study was CIDRAP's director, Michael Osterholm, who has a distinguished career in public health and has written extensively about influenza vaccine preparedness.[347-349]

Although Osterholm and CIDRAP set out to assess the response to H1N1 influenza, their animating question shifted dramatically during the course of the project. They found, for instance, that despite accelerated production, the H1N1 vaccine was delayed and did not work as well as expected. A large, multicenter study found that the overall effectiveness of the 2009 H1N1 vaccine in the United States was just 56 percent.[350] Most public health experts consider a flu vaccine successful if it is 70 percent to 90 percent effective.[351] The 2009 H1N1 vaccine fell short of that measure, even though, as Osterholm noted, "This was the most closely matched strain in decades."[352]

That dubious success rate led the CIDRAP team to delve more deeply into the historical efficacy of flu vaccine. What they discovered surprised them. Their effort began with a search for randomized controlled trials that assessed "a relative reduction in influenza risk" after vaccination.[353] They used more stringent inclusion criteria than had been used in the past by considering only studies of patients with laboratory confirmed flu (RT PCR or viral culture) as opposed to serology confirmed flu because serology is less accurate.[354] Of the 5,707 articles they identified in their initial Medline scan of publications from the years 1967 to 2011, only thirty one met the CIDRAP team's criteria for studies measuring vaccine efficacy.[353]

No company will invest the $800 million needed to bring a new vaccine to market as long as the current vaccine is so wholeheartedly endorsed by public health officials.

Osterholm's team found that the efficacy of flu vaccines is about 59 percent in adults younger than sixty five years. With 83 percent efficacy, live attenuated vaccine works well in children aged six months to seven years. Surprisingly, there is not much evidence in either direction of the efficacy of flu vaccine for older children and young adults or for the elderly. The team concluded that "current influenza vaccines can provide moderate protection, but it is greatly reduced or absent in some seasons."[355]

Until recently, a major hurdle in assessing flu vaccine effectiveness has been methodology. Osterholm argues that many previous studies used erroneous outcome measures: "They were using serology for the trivalent vaccine, when we now know that serology grossly underestimates the number of infections among vaccinees."[355]

In 2010, the US Advisory Committee on Immunization Practices (ACIP) established the first national universal seasonal influenza vaccination

recommendations, which advocate either annual trivalent inactivated vaccine for all people aged six months or older or live attenuated vaccine for healthy people aged two to forty nine years who are not pregnant.[356] Even though Osterholm believes that, with such recommendations, public health officials have pushed universal flu vaccination in spite of mixed data, he does not want his criticisms to fuel anti vaccine sentiment because, on an individual level, some protection is better than no protection. However, he does not want people to lose sight of the need to develop better vaccines that are more effective for individuals and populations. It will be a real problem, he explained, "if 'some protection' gets in the way of developing better vaccines. People should still get vaccinated, but we have to understand that the impact will be limited."[355]

Osterholm advocates greater investment in new vaccines, including further research into a universal vaccine that protects against all influenza viruses. There are several candidates in early stages of development, but, according to Osterholm, no company will invest the $800 million needed to bring a new vaccine to market as long as the current vaccine is so wholeheartedly endorsed by public health officials.[137,352] Ultimately, Osterholm believes that "we have to demonstrate the shortcomings of the current vaccine to be in a position to motivate, financially and otherwise, research on better vaccines."[355]