Trends That Will Affect Your Future . . .

DEATH ON THE WING

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The SchwartzReport tracks emerging trends that will affect the world, particularly the United States. For EXPLORE *it focuses on matters of health in the broadest sense of that term, including medical issues, changes in the biosphere, technology, and policy considerations, all of which will shape our culture and our lives.*

I was 45 years old before I really grasped the Spanish flu. My entire family is medical, and medicine has been a family profession for generations. I mention this because one would expect that, in such a family, the occurrence of major medical events and trends would be discussed. Yet I have no memory from when I was a child of hearing anyone speak of the pandemic of 1918. They talked about the medical impact of the First World War, the Depression, the Second War, and Korea, often in what nonmedical friends called "clinical detail." They talked about polio and smallpox and measles. As I grew older, the conversations around me shifted to "Civil Rights," the "60s," "the War"–Viet Nam–the pill, women's rights, gay rights, and abortion.

But nowhere in this mix, across what for me is now four generations, was there much about an event that killed an estimated 675,000 Americans, and as many as 30-50 million people worldwide, all in the course of a single year, 1918 and 1919.[1,2] Nor, as far as I can tell, have there been many such conversations on this subject in the lives of my friends and their families. I had to learn about the Spanish flu in a book bought at a jumble sale early one Sunday morning.

My mother, then in her late 80s, who became a nurse not long after the Spanish flu swept through America, when its effects were still palpable, never mentioned it to me, and, when I went to her appalled at what I had just read, she didn't really want to talk about it. "I remember men went to the edges of towns, and stood there with shotguns to keep strangers out. They wouldn't let the trains stop, and they put out the dead like cordwood for the carts to pick up." To her, it was "an awful time best put away."

It made me wonder whether this cataclysmic event was so awful– in the original sense of that word–such an act of God, a sort of ultimate legal *force majore*–that, as a culture, we edited it out of our collective memory.

I ask this question because our societal response to the potential lethality of the flu strain H5N1 seems almost pathological at the political and social level, while the research community, in the vernacular of the day, is running around "with its hair on fire" as they see a trend emerging.

In a rare coordinated publishing event, both *Nature*[3] and *Science*[4] simultaneously published major papers on the avian flu strain H5N1. The *Nature* team headed by Dr. Neil Ferguson from Imperial College London modeled the potential spread should an outbreak occur among Thailand's population of 85 million. Dr. Ira Longini of Emory University, in Georgia, led the team that published in *Science*; their focus was the effect of an outbreak occurring in Thailand's Nang Rong region, with a population of 500,000.

These papers stress that the relevant question about an outbreak of H5N1 is no longer "if" but "when." For the researchers, the focus shifted then to "what might an outbreak be like?"

How lethal is this virus? If H5N1 mutates into an aerosol form that can be easily transmitted among humans and an outbreak crosses the "40 infected people" line, it could lead to a global pandemic.[3,4] Within a year, 50% of the world's population would be infected. With a projected mortality rate of 50%, 25% of our species, roughly one-and-a-half billion people, could perish.[3,4] In contrast, the Spanish flu was far milder and less contagious. Only 28% of the U.S. population became infected, with a worldwide mortality estimated to have been between 2.5 and 5%. Still, the effects were so profound that the 1918 pandemic reduced the average life span in America by 10 years.[1]

The *Science* and *Nature* studies looked at every scenario the researchers could conceive. Each simulated how the virus would move should H5N1 mutate so that human-to-human contact was possible. They considered every method of migration. They modeled how prophylactic treatment would affect the virus' spread: what treatment might achieve and the power of quarantine to impede human-to-human infection. They looked at how things would develop should the viral strain change. They considered the effect of different rates of detection in different countries.

The critical assumption in both studies, used for all modeling scenarios, was very conservative. Because the H5N1 virus has low virulence, both Ferguson and Longini assumed its basic reproduction number, R (the number of people that each infected person, in turn, infects = R), was just two. That is, each person would only infect *up to* two others.

Both researchers seem to repose confidence that they have overestimated the R value of H5N1 as it currently exists, that it is actually lower. Why do epidemiologists care about this arcane statistic? Because if the international response can push the reproductive number below one, each vic-

tim will infect less than one other person, the disease cycle will be broken, and a nascent pandemic will quickly die out.

But their fear is that H5N1 could combine with an extant, much deadlier, human flu, or mutate itself so that its *R* number dramatically increases. Instead of just two people infected, its virulence could go up several or even many times. Imagine one sick person on a crowded train or an airplane or attending a wedding or a funeral.

What endows the *Science* and the *Nature* studies with a peculiar gravity is that they concur in their conclusions:

- The virus needs to be detected within 21 days and before 40 people contract it.
- Good surveillance techniques are the best first line of defense and are in the world's interest to create and maintain.
- Accurate diagnosis by symptoms is a critical skill healthcare professionals must develop because, by the time genetic confirmation is returned, it will almost certainly be too late to stop a pandemic—the same virus appearing on several continents simultaneously and affecting a substantial percentage of the population.
- Following diagnosis of a cluster of infected individuals, a system must be in place to stop the virus from spreading. Healthcare professionals and governments must be prepared to impose what Ferguson, principal in the *Science* study, calls "social distancing"—closing schools, establishing travel restrictions, and imposing quarantine.
- Particularly in less developed Asian countries, where an outbreak is most likely to occur, international intervention must be prepared to move immediately, which requires massive and detailed preparation.
- Each new case must be isolated and treated with antivirals within two days.

It is at this point that the models begin to veer toward catastrophe. The studies conclude that to stop a pandemic three million courses of *oseltamivir* (Tamiflu; Hoffmann-La Roche Inc, Nutley, NJ) need to be available to the World Health Organization (WHO) with which to treat individuals with the flu or to prevent illness in those exposed. In fact, WHO has stockpiled only 120,000 courses of the antiviral drug. An additional 2.4 million doses have been stockpiled by the United States. And Tamiflu, which is a Roche Pharmaceuticals product, is presently produced by a single plant in Switzerland, and requires eight months to produce. An international debate is underway about waiving patent rights, and generic pharmaceutical companies in several countries, notably India, are prepared to go into production. But the matter is far from settled, not least because it establishes a precedent in international patent law. It could take months of negotiation to settle. And this class of antiviral drugs only protect, they do not provide immunity. For that, there must be a vaccine.

Happily, using the new genetic engineering, such a vaccine has just been announced. The vaccine, which is grown in chicken eggs, proved efficacious in a small study of less than 65 years of age adults, producing a strong immune response.

Dr. Anthony S. Fauci, the director of the National Institute of Allergy and Infectious Diseases made a public statement amplifying the announcement and saying that, although the vaccine had passed its preliminary trials and could be used on an emergency basis, it will take months of further testing before an approved vaccine is commercially available. However, he pointed out, that, in spite of his caveats, this was "good news" because at least now "We have a vaccine."[5]

On the strength of this announcement the government is ready to begin stockpiling millions of doses. Presently, the vaccine industry can produce approximately 300 million flu shots each year. The usual yearly flu vaccine addresses the three most prevalent flu strains. If the entire global capacity were redirected to produce only the H5N1 vaccine, the output could be about 900 million injectable doses, a number that is already inadequate. But the reality of the moment is worse.

Virologists who have studied H5N1 believe that people will need two injections administered approximately a month apart to stop successfully a pandemic. That cuts the number of individuals who could be vaccinated worldwide to 450 million. Many medical researchers believe that an entirely new virus such as H5N1 would require a dose each time larger than the usual "flu shot," which would further decrease the number of people who could be vaccinated. Is it possible to increase world production to the levels required to meet the threat?

Fauci himself is far from sanguine. "The critical issue now," he said, "is, can we make enough vaccine, given the well-known inability of the vaccine industry to make enough vaccine?"[5] And, even with bulk vaccine to hand delivery down to the individual patient still only partly accomplished. In his statement, Fauci explained "we cannot put it in vials until we find out what the right dose is."[5] Only further testing will yield that answer. There is also the logistical question of getting the millions of eggs required. Creating an effective treatment on a worldwide scale is an incredibly complex undertaking, and time is not on humanity's side.

The great imponderable, of course, is how governments, particularly in developing nations, will react. As China's initial recent response to the SARS experience makes clear, the inclination of many governments is to conceal, rather than acknowledge, an outbreak that holds pandemic potential. The *Science* and *Nature* studies both make clear this could prove disastrous.

In contrast to this dire future, the models also show that, if the world response is in place and appropriate and taken within a critical three-week window, the outbreak could be reduced to affecting fewer than 100 people within two months.[3,4]

While governments are deciding how seriously to take all this, avian flu is sweeping through poultry stocks in Southeast Asia. Between those that have died of flu and those culled to stop outbreaks, avian flu has led to the death of 140 million birds at a cost running to billions of dollars. And it is on the move. In Siberia in the Altai and Tyumen regions and in Novosibirsk, hundreds of dead birds have been identified as having died of the same strain of flu that has killed chickens, ducks, and geese in China as well as 57 humans in Vietnam, Thailand, Cambodia, and Indonesia, which announced its first three human deaths in August.

The presence of the flu has also been confirmed by the Russian Ministry of Agriculture in wildfowl in two regions, Kur-

gan and Omsk.[6] To stop the spread of bird flu, Russia has culled and killed over 10,000 birds in the few days prior to my writing this article.[6] The number will probably be far greater by the time of reading.

Meanwhile, officials in neighboring Kazakhstan have come forward with confirmations of bird flu in the Pavlodar region, which borders Novosibirsk. So far no human cases have been reported in the Russian and Kazakhstan outbreaks, but officials fear it is only a matter of time.

The Russian Agriculture Ministry in the brief statement identified the virus as avian flu type H5N1 and said, "That raises the need for undertaking quarantine measures of the widest scope."[7]

As this goes to press the spread has reached Turkey and Great Britain. Mercifully, it has not achieved human-to-human transmission. But it has demonstrated how fast a pandemic could spread. H5N1 has taken no longer than from July to September to move from Asia, across Russia, and into Europe–death on the wing.

All too slowly, the US Department of Health and Human Services (HHS) began to engage the implications of H5N1. The Senate has just voted $4 billion to the Centers for Disease Control and Prevention to underwrite the cost of stockpiling anti-flu medicine to protect people against H5N1 and prepare for a potential outbreak. Most of this money, $3 billion, would be used to buy the anti-flu drug Tamiflu. By comparison, according to the Congressional Budget Office, the Iraq War is running a tab of six to nine billion dollars a month.[8]

"If we have learned anything from the recent disasters on the Gulf Coast, it is that we must confidently prepare for disasters before they strike so that we are not left picking up the pieces," said Sen. Tom Harkin, (D-Iowa) who sponsored the measure. It was also Harkin who was responsible for creating the complementary and alternative medical program at the National Institutes of Health.

"The secretary or the chief of staff–we have a discussion about flu almost every day," said Bruce Gellin, head of HHS's National Vaccine Program Office. As I write this article, the HHS committee is scheduled to deliver to its secretary, Mike Leavitt, a revised plan for confronting a pandemic.[9] The White House has just announced it will stockpile $100 million of the still experimental vaccine as part of this new plan.

In spite of these increases, however, America's and the world's ability to truly respond if H5N1 mutates or merges with an extant human virus is very much in question. Not least, would it be politically possible for a democracy to sacrifice its own stock to treat some developing nation, particularly if it is a state with which it is in conflict? Would the United States turn over its vaccine stocks to North Korea if the virus crossed over and achieved human-to-human transmission there? Could the world watch the population of another country die by the millions? Rowanda, while obviously not the result of a disease process, is not an encouraging example.

"The only reason nobody's concerned the emperor has no clothes is that he hasn't shown up yet," Harvey V. Fineberg, president of the National Academy of Sciences' Institute of Medicine, said recently of the world's efforts to prepare for pandemic flu. "When he appears, people will see he's naked."

If the Spanish flu was so traumatic that people stopped talking about it, one can only wonder what something that has the potential to kill a billion men, women, and children within a year would do. The Black Death killed approximately a third of Europe. H5N1 has the power to do this just as capriciously. The medieval plague changed the course of every nation it touched and depopulated large swaths in the lands that now make up the European Union. Midway through the first decade of the 21st century, H5N1 is believed by the scientists and physicians who have studied it to hold the same potential for death.

Dr. Irwin Redlener director of the National Center for Disaster Preparedness at Columbia University's Mailman School of Public Health, echoes these sentiments saying, "If we had a significant worldwide epidemic of this particular avian flu, the H5N1 virus, and it hit the United States and the world, because it would be everywhere at once, I think we would see outcomes that would be virtually impossible to imagine."[10]

Meanwhile, in Britain, the Blair government is trying to stockpile enough oseltamivir (Tamiflu) to protect "a quarter of the population," with special priority being given to senior government officials so that they will survive to maintain government stability. An order has been placed for nearly 15 million doses to be completed by April 2007. At the same time, ABC News reports that the government is also quietly making plans for extra morgue space to handle the massive death numbers the British medical research community anticipates.[11]

Even as these measures are being taken, however, H5N1 may be outflanking human efforts. Two papers in The Lancet report resistance to anti-flu drugs is growing worldwide.[12] Experts in Hong Kong say the H5N1 strain which surfaced in northern Vietnam this year was resistant to Tamiflu.

"There are now resistant H5N1 strains appearing, and we can't totally rely on one drug (Tamiflu)," William Chui, honorary associate professor with the department of pharmacology at the Queen Mary Hospital in Hong Kong, told Reuters.[13] And in China, drug resistance reportedly exceeded 70 percent, suggesting that not only may Tamiflu be compromised but drugs like amantadine and rimantadine will no longer be useful.[14] Asian medical researchers are urging drug companies to also focus on Relenza, another antiviral shown to be effective in battleing H5N1.[13]

And, if it is not H5N1, it will be something else. Pandemics are part of our history, and one of the unintended consequences of globalization is the vast increase of vectors by which disease can spread globally. This is not a happy conjoining. After 1918, pandemics occurred again in 1957 and 1968, albeit not with the same dire consequences. If we have billions of dollars to spend on a war against terrorism, which has killed in the thousands, how can we do less on a threat like this that can kill billions of people?

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