

White Paper On Novel H1N1, Prepared for the MIT Center for Engineering Systems Fundamentals

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Note: This paper's purpose is to provide a relatively in-depth understanding of the problem and the issues, now and as they change. Therefore, it omits an executive summary.

Contents:

1. Background on the Influenza Virus
2. The Epidemiological Picture and Cross-Protection as of Late June 2009
3. Antivirals and Vaccines
4. Recent Non-Pharmaceutical Interventions and International Actions
5. Communication
6. The Past as Prologue: Waves and Patterns from Past Pandemics
7. The Future of Novel H1N1

1. Background on the Influenza Virus:

Influenza is an RNA virus with eight genes on a segmented genome. There are three types of influenza viruses: A, B, and C. Although B can cause human disease, only influenza A viruses threaten pandemics. The virus is identified by its most visible antigens, hemagglutinin – H1 to H16 – and neuraminidase-N1 to N9, which are outside the viral envelope and allow the virus to bind to and then escape a cell.

Birds are the natural reservoir for all influenza viruses, and in birds the virus is generally a stable and benign intestinal virus. On occasion, highly pathogenic influenza viruses such as A/H5N1 or just H5N1, emerge in birds. (The “A/” will be dropped in further references to the virus; all subsequent viruses mentioned are influenza A.)

Influenza can jump species in two ways. One is a function of its extraordinarily rapid mutation rate. About 8 hours after a single influenza virus infects a single cell, that single cell will produce between 100,000 and 1,000,000 new virus particles, but it mutates so rapidly that all of these particles are different and only 1 percent of these particles can function as actual viruses, able to infect a cell and replicate. That still translates into between 1,000 and 10,000 functioning viruses, each of which is different, produced by a single cell. All possible permutations of the virus are produced, and that mutation rate allows an entire virus to jump from one species to another. ***At some point in history, at least one avian virus (and possibly many) committed the original pandemic sin by jumping from birds to humans, either directly or indirectly by going through another mammal. H5N1 now threatens to jump directly to humans.***

Influenza can also jump species because of its “segmented genome” – that is, its genes stand alone, individually. Genes of nearly all other organisms run continuously along a strand of nucleic acid. This attribute allows influenza to jump species by “reassorting” its genes, which occurs when different influenza viruses infect the same cell and all the genes become shuffled together, much like a deck of cards, and a new virus is dealt out of the cell with genes from each virus. The 1957 (H2N2) and 1968 (H3N2) pandemics were caused by “reassortant” viruses; in both cases, the new viruses joined new genes to those of the human virus that was already circulating.

Both seasonal and pandemic influenza usually burn through a community in 6-8 weeks. The chief differences are morbidity and mortality. Seasonal flu infects about 10 percent of the population. Pandemic flu, in contrast, can be expected to infect from 15 to 40 percent – and occasionally even more – because it presents the human population with new antigens that the human immune system does not recognize. There have been at least 10 pandemics in the last 300 years, and probably many more going much further back in history. All pandemics about which we know in any detail – 1889, 1918, 1957, and 1968 – have been caused by H1, H2, or H3 viruses. (Some virologists speculate that only viruses with these three hemagglutinin can cause human pandemics; others dismiss this speculation since it is based on so few samples.)

Influenza is spread by virus in large droplets and, possibly, aerosolized form. The influenza virus survives outside the body on hard surfaces, such as a doorknob, for many hours at least, and sometimes for a day or longer-- in some circumstances, much longer. It also survives best in low humidity and low temperatures; this fact, coupled with human social behavior, helps account for the tendency of influenza to be more common in cold weather. Compared to warmer times of the year, winter is when people are more likely to crowd together indoors, in spaces where there is less circulating air (e.g., at a basketball game rather than a baseball game). Nevertheless, influenza also can achieve high morbidity in tropical countries with consistently higher temperatures.

Influenza infects a wide range of mammals, including dogs, cats, tigers, horses, seals, and so on. In 1918, the original H1N1 virus – after first infecting humans – jumped to pigs, and subsequently was reported in many wild animals, including moose. H1N1 has survived in pigs ever since. Pigs have receptors for both avian and human influenza viruses – they have long been referred to as “mixing bowls” – and therefore are considered a likely path for avian and other influenza viruses to enter the human population. Since 1998, triple reassortant viruses with genes derived from birds, humans, and swine have caused illness in pigs, along with viruses descended from the 1918 H1N1 virus.

A 2007 survey found 37 additional reports in medical literature of swine influenza in humans between 1958 and 2007. Between December 2005 and February 2009, 11 human clinical cases caused by triple reassortant swine viruses were reported to CDC, 10 of them being H1N1 viruses.

In 1976, an outbreak of so-called “swine flu” was completely contained within Fort Dix, a U.S. Army base in New Jersey. It infected numerous soldiers, killed one, and resulted in 13 clinical cases. Antibodies in blood showed that several hundred more soldiers were exposed.

Since 1968, the dominant circulating influenza A virus has been H3N2, but for approximately 30 years an H1N1 virus has co-circulated; existing vaccines against seasonal influenza are designed to protect against H3N2, this older H1N1, and influenza B. The novel H1N1 virus bears little resemblance beyond its name to the currently circulating H1N1. The novel H1N1 which now threatens is a triple reassortant of bird, human, and several different swine viruses with predecessors traced back to 1998. While the individual genes have all been seen before in other influenza viruses, the present combination has not been seen.

In humans, the influenza virus generally binds to cells in the upper respiratory tract, although in 1918 symptoms suggest it may have bound to cells in the lung itself as well as organs outside the respiratory system. H5N1 binds only to cells in the lung; this accounts both for its inability to spread from human to human and for its high case mortality rate. Symptoms also suggest it may infect other organs.. Symptoms of novel H1N1 also suggest occasional abdominal infection; symptoms are those common to influenza, plus diarrhea and vomiting in some cases. These abdominal symptoms have occasioned concern that oral-fecal spread may be possible with novel H1N1, which brings transmission through water into the picture – a potential problem for the developing world. In birds, this transmission clearly occurs. In addition, novel H1N1 seems capable of binding to cells in both the upper respiratory tract and the lung¹.

2. The Epidemiological Picture and Cross-Protection as of Late June 2009

Epidemiologists believe they have identified an index human case in Mexico dated March 17, 2009, although other analysis (based on mutation rates) suggests the virus may have begun to circulate in January 2009 and possibly as early as September 2008.

As of this writing, we do not have a good sense of R0 (the reproductive number, i.e., the number of cases caused by one case). An R0 less than 1 means an outbreak will die out. R0 for seasonal influenza ranges widely, with a mean of 1.3, although in 1951 – which was not a pandemic virus, just a particularly bad seasonal one – R0 approached 2.0. As R0 rises past 2.0, models that suggest non-pharmaceutical interventions (NPIs) could mitigate morbidity or mortality become less useful, and an R0 over 3.0 makes them

¹ Itoh, Y. et al. *In vitro and in vivo characterization of new swine-origin H1N1 influenza viruses.* *Nature*, July 13, 2009 DOI: 10.1038/news.2009.680

useless. New work suggests the R0 in 1918 was well in excess of 2.0, and may have approached 4.0.²

Estimates of R0 for novel H1N1 vary widely. On May 11, the World Health Organization (WHO) announced that the disease seemed more infectious than seasonal influenza, noting that while the secondary attack rate in households of seasonal flu is 5 to 15 percent, that rate for novel H1N1 was 22 to 33 percent. On May 20, the U.S. Centers for Disease Control (CDC) contradicted this statement, asserting that attack rates approximated seasonal influenza. A third study put the R0 slightly higher than most seasonal flu, at 1.4 to 1.6.³ A fourth study suggested an R0 range from 2.2 to 3.1,⁴ while a fifth estimated R0 at 1.2.⁵ *In July a study in New Zealand also estimated an R0 of 2⁶.*

One problem is the case count, which is unknown. But we also do not know, for example, the incubation period, which is a significant factor in an outbreak's explosiveness and in calculating the R0. Reasonable assumptions have been made that incubation is comparable to seasonal influenza, but data from Spain suggests incubation is longer.⁷

Case mortality has been estimated from 0.1 percent – approximately the same as seasonal influenza – to as high as 0.4 percent. However, a case fatality of even 0.1 percent for those younger than age 65 represents a substantial increase in lethality in the non-elderly population.

The number of cases worldwide is impossible to ascertain. In mid-May, when the official count of confirmed U.S. cases was less than 5,000, CDC estimated 100,000 cases in the United States. (On June 1, confirmed U.S. cases exceeded 10,000.) It was not surprising when Dr. *David* Fleming, the public health director in Seattle and King County, said, "We had widespread community illness before CDC posted a single confirmed case in Seattle."⁸ More recently, the New York City Health department estimated that cases reached several hundred thousand in its jurisdiction.

² Andreasen, V, Viboud, C and Simonsen, L (2008), Epidemiologic characterization of the 1918 influenza pandemic summer wave in Copenhagen: implications for pandemic control strategies, *Journal of Infectious Diseases* 197(2), 270-8.

³ Fraser C, Donnelly CA, Cauchelme S, Hanage WP, Van Kerkhove MD, Hollingsworth TD, et al. Pandemic potential of a strain of influenza A (H1N1): early findings. Published 11 May 2009 on Science Express. DOI:

10.1126/science.1176062.<http://www.sciencemag.org/cgi/content/abstract/1176062>

⁴ P Y Boëlle, P Bernillon, J C Desenclos: "A preliminary estimation of the reproduction ratio for new influenza A(H1N1) from the outbreak in Mexico, March-April 2009," *Eurosurveillance*, Volume 14, Issue 19, 14 May 2009

⁵ personal communication, Richard Larson, May 2009

⁶ Nishiura, H, et al, "Estimating the Reproduction Number. of the novel influenza A virus (H1N1) in a Southern Hemisphere setting: preliminary estimate in New Zealand, *New Zealand Medical Journal*, 24 July 2009, 122:1299

⁷ Surveillance Group for New Influenza A(H1N1) Virus Investigation and Control in Spain. New influenza A(H1N1) virus infections in Spain, April-May 2009. *Euro Surveill* . 2009; 14(19): p11=19209. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19209>

⁸Trust for America's health report on early lessons, <http://healthyamericans.org/assets/files/pandemic-flu-lesson.pdf>

Initial worldwide surveillance suggests that the virus has not spread nearly so widely in other parts of the world as it has in the United States and Mexico. Although more than 70 countries had reported cases as of mid-June 2009, the confirmed case counts remain less than 100 in roughly 80 percent of these countries. While there is significant under-reporting – Britain has been accused of under-reporting by a factor of 200-300 –there has, nevertheless, been little sign around the world of truly explosive spread as of late June, in what appears to be a first wave.

Two possibilities explain these figures: 1) R_0 varies from country to country and from setting to setting, probably due to many biological, social, and environmental factors; 2) the virus is still adapting to humans and has not yet reached maximum efficiency in infecting people.

Despite WHO's delay in declaring "Stage 6," a full-fledged pandemic, the technical threshold for such a declaration was clearly passed by mid-May. Lack of flexibility in the pandemic planning process, and the fact that plans failed to account either for a mild pandemic or a mild first wave of a dangerous pandemic, explains WHO's reluctance, since Stage 6 would trigger certain responses – including shifting resources from preparing vaccine for seasonal influenza to a vaccine for the pandemic strain – that may not be appropriate for the current situation. Despite continued opposition to declaring Stage 6, especially from Britain, WHO finally did so on June 11.

Based on ages of confirmed cases, it does seem that some cross-protection in older adults exists. On May 22, CDC concluded that 64 percent of U.S. cases (and the United States had more than half of all the world's confirmed cases on that date) are ages 5 to 24.⁹ Only 1 percent of cases have occurred in people older than 65. These numbers reflect several factors, such as that those over 65 are less likely to be exposed because of social habits. But cross-protection is also a probable factor. Some 6 to 9 percent of unvaccinated adults ages 18 to 64 showed antibody reactive against novel H1N1, while 33 percent of those over 60 had antibody. (We recognize these numbers represent a shifting base; however, that is the way CDC released the data.) It has not been established that the measured antibody is sufficient to protect, but the epidemiology suggests that it is sufficient.

After vaccination with the trivalent seasonal flu, which includes a component of the already-circulating H1N1 virus, 7 percent of adults ages 18 to 40, 25 percent of adults ages 40 to 64, and 43 percent of those under age 60 had protective antibody against novel H1N1.

There is also evidence that exposure to any influenza virus provides some cross-protection, at least compared to a completely virgin population; children are much more likely than adults not to have had any exposure to influenza.

⁹ MMWR, May 22, 2009 / 58(19);521-524

3. Antivirals and Vaccines

As of this writing, H3N2 has shown some resistance to the neuraminidase inhibitors oseltamivir and zanamivir (tamiflu and relenza), while previously circulating H1N1 *in some parts of the world (including the U.S.)* has demonstrated nearly universal resistance to those drugs, *while in other parts of the world it remains sensitive to the drugs*. Novel H1N1, however, has not shown any resistance to them. While the novel virus will likely share that resistance eventually, it is impossible to predict when that resistance will develop. In the meanwhile, antivirals will be useful.

In the United States, the Department of Health and Human Services (HHS) had stockpiled 50 million courses of treatment of neuraminidase inhibitors, and states had stockpiled another 23 million courses – enough to cover 25 percent of the U.S. population. Early in this outbreak, when there was widespread fear that this virus might be virulent, HHS released 25 percent of its stockpile to states and contracted for replacement. European states have stockpiles for larger proportions of their populations.

The United States also shipped antivirals to Mexico, which was an important diplomatic statement and precedent. (Japan and China also quickly donated masks, gloves, and gowns; in the latter case, this may have been to make amends for aggressive actions against Mexican nationals in China.)

Britain has used Tamiflu not only on cases but on those exposed to cases, in an effort to snuff out the outbreak. This action is absurd, because the virus is too well established for the strategy to succeed – and even in the extraordinarily unlikely event that Britain could snuff out the initial outbreak, the virus would only reenter later. It is also dangerous, because it increases the possibility of the virus developing resistance without any benefit.

As of mid-June, no resistance to neuraminidase inhibitors has been reported for novel H1N1. But more than 90 percent of samples of both H3N2 and previously circulating H1N1 have developed resistance.

HHS, WHO, and European governments have signed contracts with several vaccine manufacturers using different technologies to produce vaccine against novel H1N1, and seed virus has been provided. Traditional egg-based production will supply the overwhelming bulk of the vaccine, cell-based production will supply some, and contracts for “virus-like particles,” monoclonal antibodies, and other technologies have also been signed.

In a best-case scenario, the virus will require no more antigen than a seasonal influenza vaccine, only a single dose will be needed to provide protection, and adjuvant will cut in half the amount of antigen needed. If all that occurs, sufficient vaccine could be available to protect the entire U.S. population by October 2009. In a worst-case scenario, the virus will grow more slowly than anticipated, more antigen will be required to generate an immune response than for seasonal influenza, and – since this is a new virus – two doses will be required as well. In that case, it could take a year or more to produce enough

vaccine for the entire population. *As of this writing, the best case scenario is already collapsing. Most vaccine production requires viruses to be grown in eggs, and then harvested; the seed virus is not producing nearly as much antigen as anticipated, and a more productive seed virus is being sought.*

Only 31 percent of the vaccine needed is produced in the United States. This raises the question of whether foreign governments would block the export of vaccine until their own populations are fully protected. The more virulent the virus, the more likely it is that foreign governments will intervene.

The same supply question applies to the developing world: how soon will advanced countries export vaccine?

The final point on vaccine is that for most diseases, vaccines approach 100 percent effectiveness. For influenza, however, a good vaccine is 70-percent effective and a great vaccine is 90-percent effective. In the 2007-2008 flu season, the vaccine was only 44 percent effective. Producing a highly effective vaccine for a new virus, which may be less stable than seasonal influenza, should be more difficult than for ordinary influenza.

4. Recent Non-Pharmaceutical Interventions and International Actions

Several countries have undertaken various non-pharmaceutical interventions. These include, but are not limited to school closings, airport screening of passengers, quarantine of Mexicans visiting foreign countries, and quarantine of people returning from Mexico. In the United States, there was initial pressure to close the border with Mexico from people who with understanding of either the impact of such closing or its ineffectiveness.

In the United States, the decision to close schools is one of the most difficult for policy makers, given the burden it imposes on working parents, employers, and children who get their best meals in schools. Prior to this outbreak, CDC had determined that in a serious pandemic it would recommend school closings. On Friday, May 1, CDC pushed far past its own guidelines for a pandemic of the mildness that novel H1N1 had by then demonstrated, and took the extreme position that a school with a single case should close for 14 days, and that local officials should consider closing all neighboring and feeder schools. This guidance was apparently designed to snuff out the outbreak entirely. Recognizing the impossibility of this task, CDC reversed itself a few days later and simultaneously declared that closing schools was not effective in stopping spread.

Since then, local officials have occasionally closed schools. In New York City, and probably elsewhere, there has been political pressure to do so more aggressively. Mayor Bloomberg finally responded by saying it might make sense to become exposed to this virus because the attack was mild and it likely provided immunity against later attacks. (The widow of an assistant principal who died from novel H1N1 attacked the mayor for this statement.)

The question of whether school closing is worthwhile remains open. Models suggest that it is, but for closing to be most effective it must be sustained for at least several weeks and children cannot congregate in other venues. Both of these requirements are problematic, and the press has reported on the difficulties of keeping children away from each other during closures. It is unclear how much these problems undermine whatever benefits may accrue from closure.

Seasonal influenza outbreaks, the 1957 pandemic, and experience this spring do seem to demonstrate that schools are a major vehicle of spread. But there is solid contradictory evidence from 1889, 1918, and 1920 that schools did not play a significant role in transmitting infection. *One speculative explanation for this contradictory data is that if the 1918 virus was radically different from any circulating seasonal virus, then in 1918 and 1920, immune systems of adults and children may have been equal (we do not know enough about 1889 to make any assertions). In 1918, no one (except possibly the elderly; over 95% of excess deaths occurred in people <65) had been previously exposed to it, and by 1920 everyone old enough for school had been exposed. In seasonal flu, 1957, 1968, and today's H1N1, a reassortant virus caused illness. Adults therefore had some protection, while children had little or none, making school transmission much more important.*

Whether this is the explanation, these data do support the conclusion that in some outbreaks schools play an important role in transmission, while in others they do not. This obviously makes contemporaneous analysis of data important. At any rate, data from recent school closings are now being evaluated for their effectiveness and may yet yield an answer at least for novel H1N1.

As far as other NPIs in the United States, advice to wash hands came seemingly every five minutes on television. Messages regarding cough etiquette and for the ill to stay at home did not come through nearly as well.

In Mexico City and in the neighboring state, all schools were closed on April 24. Two days later, on April 26, the president of Mexico advised people to wear masks on public transport, exercise cough etiquette, avoid crowded places, and wash their hands. Soldiers handed out 6 million masks to the general public. In Mexico City, taxi and bus drivers were required to wear masks and gloves (the latter order being nonsensical, since the gloves would require constant changing).

One study concluded that mask usage on public transportation peaked at 65 percent for a three-day period (the peak was April 29) and then declined to below 27 percent by May 4.¹⁰ This decline occurred even while the government was taking the extreme measure, from May 1 to May 5, of closing all non-essential business and services in Mexico City. Whether masks do any good, the decline in compliance does not portend well for sustaining an NPI.

¹⁰ Condon, Bradley and Sinha Tapen, "The Use of Face Masks on Mexico City Public Transportation During the 2009 Influenza A (H1N1) Outbreak, draft, personal communication from Tapen Sinha.

It is not clear whether these measures had any effect. Every model, including those which conclude that social distancing measures could mitigate an outbreak, has also concluded an intervention has to come very early if it is to succeed. By the time Mexico City closed businesses (May 1 to May 5), the virus had already become widely distributed – in fact, the epidemic had just peaked and was already waning. In addition, five days is not long enough to interrupt spread. The fact that the outbreak in Mexico City did not flare up again after the closing order was lifted is further evidence that the outbreak was already in rapid decline.

Politics no doubt played a role in the Mexican reaction. Competing parties run Mexico City (PRD) and the national government (PAN). Each ran competing news conferences to release information about their jurisdictions, and each wanted to be seen as most effective. Congressional elections are scheduled for July 2009.

International restrictions were significant, especially given that the WHO explicitly recommended against trade or travel restrictions. The irrationality of many of these responses is disturbing, and they do not portend well for a more serious outbreak.

Between April 24, when news first surfaced of the H1N1 outbreak in Mexico, and May 5, 25 nations took some action on trade with or travel from Mexico, not including suggestions by governments, including the United States and the European Union (EU), that non-essential travel be canceled. China was probably most aggressive, not only imposing travel restrictions and quarantine of arriving passengers, but also quarantining all Mexicans in the country. Argentina, Ecuador, and Peru suspended flights to Mexico. France urged the EU to also suspend all flights to Mexico; the EU declined.¹¹

On a related note, some countries imposed some form of quarantine. Historical data clearly demonstrate that quarantine does not work unless it is absolutely rigid and complete. In World War I, there was no statistical difference between the 83 percent of U.S. Army training camps (N=99) that imposed quarantine and the 17 percent that did not (N=21). While quarantine regulations varied from camp to camp, in most camps they involved isolating companies when a soldier became sick, and also sealing off larger organizations as disease spread beyond the individual company. If a military camp cannot be successfully quarantined in wartime, it is highly unlikely a civilian community can be quarantined during peacetime.¹² (An investigator did see some success, at least in slowing transmission, in a few camps where quarantine had no leakage.)

Some 20 countries also banned pork imports from Mexico, Canada, and/or several U.S. states, and Russia also banned pork imports from Spain.

5. Communication

¹¹Condon, Bradley, and Sinha, Tapen, Chronicle of a Pandemic Foretold: Lessons from the 2009 Influenza Pandemic, available at SSRN: <http://ssrn.com/abstract=1398445>

¹², Soper, G, "The influenza Pandemic in the Camps," undated draft report, US National Archives, Record Group 112; BOX 394

Candid communication is crucial in most crises, and this certainly includes a pandemic.¹³ In general, Mexico, the United States, and the WHO were extremely candid. Mexico even overstated the threat, chiefly because it initially reported “suspect” cases, which peaked at 2,498 on April 28. On April 29, when Mexico began reporting only confirmed cases, the number dropped to 97. The same day, there were 109 confirmed U.S. cases.

Mexico clearly paid a price for candor. On April 30, Mexico’s secretary of finance declared that the impact of the virus on the Mexican economy would be on the order of magnitude of 0.3 to 0.5 percent of the Gross Domestic Product (GDP). In mid-June, the World Bank estimated the impact would be 0.7 percent of GDP.

It is less clear that other countries have been candid, either in reporting or in communicating to their publics. In fact, several either lied or failed utterly to understand the threat. Indonesia’s health minister told his citizens they had no need to worry about H1N1 because they lived in a tropical climate. Chinese Health Minister Chen Zhu declared, “We are confident and capable of preventing and containing an H1N1 influenza epidemic.”¹⁴ Some British epidemiologists have wondered aloud whether Britain’s under-reporting was purposeful and have complained that Britain failed to release information that later emerged only in a European report.

Although the United States generally did very well communicating, even it came close to a blunder when the president spoke of “concern, but not a cause for alarm.”¹⁵ At the time, no one knew what direction the virus might go, and he ran the risk of putting himself behind the curve and having to reverse himself overnight.

6. The Past as Prologue: Waves and Patterns from Past Pandemics

More Distant Past

Influenza proved itself capable of spreading in pandemic fashion long before air travel-- or even steam travel. In the 1600s, for example, it passed from Europe to North America when it took seven to twelve weeks to cross the ocean. It seems remarkable that on a small ship, with passengers in close quarters, the virus did not burn itself out in that time. That it did not is provocative, with several explanations, all of them highly speculative. Also, in Europe its rapid spread—so rapid that travel did not seem capable of explaining it-- accounted for theories that influenza was both contagious and spread by an atmospheric force. One physician said of the 1789 pandemic that it was “incontestable” that it is “propagated from one person to another by emans of contagion.” But he also insisted that the rapidness of spread meant that “the disease

¹³ See my commentary “Avoiding Mistakes of 1918” in May 21 *Nature*.

¹⁴ Peter Brown, “Swine Flu Tests Confidence in China, Japan,” *Asia Times*, May 8, 2009,

¹⁵ Obama speech, National Academies of Science, April 27, 2009

*also must arise from some vicious quality of the air... as well as from the body of a man laboring under disease*¹⁶.”

1889

The 1889-1892 pandemic, an H2N2 virus, came in three extended waves. It first surfaced in Turkestan in May 1889, took several months to reach Berlin and Paris, and then took only a few more weeks to cross the ocean to the United States. By January 1890, what was still considered the first wave had reached Hong Kong and Japan. Although this wave spread worldwide, an observer noted, “In 1890 the influenza outbreaks were as a rule single or isolated and occurred in only a few places in Europe, particularly in Lisbon, Nuremberg, Paris, Copenhagen, London, etc.”¹⁷

By the time the second wave emerged, the virus had already seeded itself around the world. A second observer noted, “The transfer of the disease by ships which played such an important role in the first [wave] appeared to be insignificant in 1891.”¹⁸ This second wave caused more widespread illness than the first, but it still did not achieve full pandemic status. This did not occur until later that year, in a third wave. A contemporary epidemiologist wrote, “The third real epidemic spread of influenza was a true pandemic which began in October 1891 and lasted through the whole winter until the spring of 1892.”¹⁹

While transportation time and the fact that parts of the world were more isolated in 1889 than even in 1918 – and far, far more than today – may account for some of this stretched-out pandemic progress, the behavior of the virus also suggests that it required several years before it became fully efficient in infecting humans. The third wave also was considered by contemporaries to be the most lethal, even in those places, such as London, that experienced the first two waves.

Although good statistics for the 1889 pandemic are unavailable, extrapolating from available statistics suggests it ranks second in severity, and was incrementally more severe than 1957. Comparison is difficult, though, because in 1957 antibiotics were available to treat secondary bacterial infections.

1918

In 1918, the virus seems to have emerged in January in Kansas (another hypothesis suggests the virus jumped species as much as two years earlier), and the first wave began to spread rapidly in U.S. Army camps, with intermittent spread in civilian communities in March. By April, it was spreading through Europe. By late May, this first wave had disappeared from the United States but was reaching Asian cities, and the first wave continued through the summer in Europe. This wave was more mild even than seasonal influenza, and articles in medical journals suggested it was so mild that it might be

¹⁶ Shope, R., “Influenza: History, Epidemiology, and Speculation, *Public Health Reports*,. 73:2, February 1958..

¹⁷ Vaughan, WT, Influenza: An epidemiologic study, *American Journal of Hygiene*, Baltimore, 1921, 45

¹⁸ *Ibid*, 46¹⁸

¹⁹ *Ibid*, 45-46.

another disease. A thorough 1927 study of epidemiological data also concluded that “a striking feature of the first wave was that ... it lacked the extreme diffusive vigor” of the second wave and had “a tendency to die out.”²⁰

The first widespread outbreak of the lethal second wave occurred in late July in Switzerland. By mid-October, most of the world’s cities had experienced this deadly wave, and it did not die out. R_0 almost certainly exceeded 2.0 and may have approached 4.0.

A third wave struck intermittently around the world from January-April 1919, and caused about one-third of the total deaths. Exposure to the first wave did generate immune protection to the second wave, but strangely evidence suggests neither first nor second wave exposure protected against the third wave.²¹

Although case mortality in the developed world was 2 to 2.5 percent, even in the West, certain subgroups suffered much higher numbers. Metropolitan Life found that 3.26 percent of U.S. industrial workers it insured ages 20-45 died, so case mortality in that population had to be in the neighborhood of 10 percent. In total, the 1918 virus killed between 1.9 and 5.5 percent of the total world population. As more than half the dead were young adults, the percentage of that population killed was significantly higher.

Symptoms could be horrific, including bleeding from the eyes and ears. In some countries, including the United States, society nearly broke down. My hypothesis is that the government’s effort to reassure people became counterproductive, destroying trust and alienating the public from those in authority and from each other. National public health leaders had said, “This is ordinary influenza by another name,” and, “You have nothing to worry about if proper precautions are taken.”²²

In 1920, influenza returned. While not as severe as either the fall 1918 or winter 1918-1919 waves, it was one of the most severe seasonal outbreaks of the century.

Before discussing other pandemics, the point should be made that seasonal flu can turn virulent at any time; in 1951, seasonal flu was more deadly, with a higher R_0 , than either the 1957 or 1968 pandemics.

1957

The 1957 “Asian Flu” virus, H2N2, was first identified in late February in China, and by April 12 was epidemic in Hong Kong. On April 25, it reached Japan and by June 1 it was “all over the country.”²³ An epidemic peaked by mid-June and disappeared by July;

²⁰ Jordan, EO, Epidemic Influenza, American Medical Association, Chicago, 1927.

²¹ Barry, JM, Viboud, C, Simonsen, L., Cross Protection Between Successive Waves of the 1918-19 Influenza Pandemic: Epidemiological Evidence from US Army Camps and Britain, [J Infect Dis.](#) 2008 Nov 15;198(10):1427-34.

²² For more on this, see my essay in May 21 *Nature*, *op. cit.*

²³ Dunn, FL, Pandemic Influenza in 1957. Review of International Spread of new Asian strain, *JAMA*, 1958, 166:1140-1148

disease was mild, affecting primarily children, with low mortality. By late June, the first wave in Indonesia had caused approximately 10 percent morbidity.

The virus behaved differently in different countries. It reached England with some sailors in early June, but few secondary cases developed. In Holland, several schools had attack rates above 50 percent but, again, there were only sporadic adult cases and no community spread. In Iran, though it was first reported June 24 and one month later the country had an attack rate of 30 to 35 percent. Through July in most northern hemisphere countries, only sporadic cases occurred in community settings, despite intense outbreaks in closed populations (some schools and military bases). In August, however, widespread outbreaks began.

The United States was typical. In 10 days in June, 10,000 cases occurred on military bases in California alone. Few civilian outbreaks occurred, however, except in special situations of close contact. For example, there was an 80-percent attack rate at a conference attended by 300 schoolgirls. Several similar eruptions occurred over the summer, but no community-wide outbreaks developed. Of 2,000 college students attending a national conference in Iowa on June 26, 10 percent fell ill. State health officials in numerous states tracked them upon their return home, but no community outbreaks developed. A similar, but more limited, H2N2 spread occurred at a Boy Scout jamboree of 53,000 young boys July 10-24, but again no community spread was seen after the boys returned home. Additional outbreaks occurred through August, but “the influenza-related mortality rate was extremely low.”²⁴

These first exposures are not generally considered the first wave of the 1957 pandemic, but that is largely a question of definition. Obviously, Iran and a few other countries suffered significant epidemics in this period. But this early spread did seed the virus around the country as it was seeded around the world.

The first U.S. and European wave is generally considered to have commenced in August in Louisiana, when children returned to school, got sick, and quickly spread disease to the community. Schools are also suggested as involved in transmission by the fact that in 11 of 14 U.S. cities studied, peak school absenteeism preceded peak industrial absenteeism by from 1 to 4 weeks; in 2 cities, school and industrial absenteeism peaked the same week; and in 1 city, industrial absenteeism peaked 1 week before schools.

By September 28, 50 percent or more counties reported at least 20 cases in Louisiana, California, Arizona, New Mexico, Mississippi, the Gulf Coast of Alabama, and Florida. By October 26, 45 states reported the same. This wave peaked the preceding week, and decline continued into December. Excess U.S. deaths were about 40,000.²⁵ Morbidity was estimated at 30 percent of the population in October and November alone.

²⁴ Trotter, Yates, et al, Asian Influenza in the United States, 1957-58, *Am. Jour. Hygiene*, 1959, vol 70, 34-50.

²⁵ Eickhoff TC, et al, Observations on Excess Mortality Associated with Epidemic Influenza, *JAMA*, June 3, 1961,

First wave activity never declined to near zero, but contemporary observers still defined increased activity from January to March 1958 as a second wave. This second wave had a much flatter peak and lower intensity, and during it excess U.S. deaths were about 20,000. This second wave is particularly interesting because deaths occurred without significant widespread illness. One study observed “an absence of community-wide outbreaks of influenza, but ... continued sporadic occurrence of small outbreaks. These were not considered sufficient to cause the high level of mortality unless the disease had increased in virulence. Several large influenza diagnostic laboratories reported a marked decrease in the number of influenza specimens submitted, and a lower yield of positives.”²⁶

The third wave from January to March 1960 actually had a much sharper peak – higher than either the first or second wave – but a quick falloff, causing 26,000 excess U.S. deaths. Approximately 20 to 25 percent of the deaths were attributed directly to viral pneumonia; secondary bacterial pneumonias accounted for most of the remaining deaths, but other factors also are reflected in these excess mortality numbers.

There were almost no net excess deaths in those younger than age 14; 2,000 excess deaths among those ages 15-24; 6,000 among those ages 25-44; 22,900 among those ages 45-64; and 57,000 among those 65 and older. It should be pointed out that mortality among those <65 is substantially higher than in seasonal flu. Today, in a population almost double that of 1957, annual influenza-associated deaths in those younger than 65 is only 7,000.

Exposure did generate immune protection. Mountain and Pacific regions had little excess mortality in the fall wave and virtually no second wave, but the third wave in early 1960 was most severe there, while the Mid-Atlantic region, hit hard in 1957-58, largely escaped the third wave.²⁷ (The mortality expressed here, a total of 86,000, comes from a 1961 study in *JAMA*²⁸; today, the death toll is usually reported as 70,000, but I have been unable to locate the source for this number or an explanation for the discrepancy.)

1968

The 1968 virus, H3N2, was first isolated in Hong Kong in July 1968, and reached the United States and Japan in August and England and Wales in September. In all these countries, there was sporadic influenza activity for 2.5 to 4 months before the disease erupted in November. In Canada, the virus was not isolated until immediately before it reached epidemic status, also in November.

No civilian outbreaks in the continental United States occurred until the third week of October, with no outbreaks on the East Coast until the week of November 16. One week

²⁶ Ibid.

²⁷ Eickhoof, TC, Sherman, IL, Serfling, RE, “Observations on Excess Mortality Associated with Epidemic Influenza,” *JAMA*, June 3, 1961, 776-782.

²⁸ Ibid

later, 21 states showed epidemic activity, and by December 28 all 50 states had epidemic activity.

In all the countries above, a first wave peaked in January 1969. U.S. morbidity was around 20 percent overall and much higher in schoolchildren. A second wave peaked a year later, in January 1970, in Canada, Japan, and England and Wales, and in February in the United States.

Yet, there are significant unexplained differences. In the United States, 70 percent and in Canada 54 percent of all mortality occurred in the first wave, with the rest of the deaths coming a year later. Japan, however, suffered only 32 percent mortality. In England and Wales, 23 percent of total deaths came in the first wave; the second wave was more deadly. In those countries, the second wave was 2 to 3 times more severe than the first.²⁹

Mortality in the United States was an estimated 34,000 people, compared to a then annual influenza-attributed mortality of 20,000. There were few cases of viral pneumonia, in contrast to 1957. This was by far the mildest of the four pandemics discussed.

7. The Future of Novel H1N1

Three of the preceding four pandemics, 1889, 1918, and 1957, show clear evidence of some fairly intense but sporadic initial local outbreaks, often with significant morbidity locally, scattered around the world. The 1968 pandemic also demonstrated sporadic activity for several months before generating widespread morbidity.

The novel H1N1 virus seems thus far to be following the pattern of the first three pandemics, and it seems highly likely that it will return in full flower. If the virus is fully adapted to and efficient at infecting humans, this would occur soon, possibly during the influenza season in the southern hemisphere or possibly a few months later in the northern hemisphere. The 1918 and 1957 viruses both exploded in September and October in the northern hemisphere, even though this is not the influenza season.

If the virus needs further adaptation to become fully efficient in infecting humans, that could be delayed, quite possibly a year or two later. It seems very unlikely that this virus will peter out.

The most disturbing pieces of information are two:

First, unlike seasonal influenza viruses, novel H1N1 seems to have the ability to bind to cells deep in the lung, which H5N1 does and which the 1918 virus could do³⁰.

²⁹ Viboud, et al, Multinational Impact of the 1968 Influenza Pandemic: Evidence for a Smoldering Pandemic, *Jour. Inf. Dis.*, 2005:192 (15 July), 233-248

³⁰ Itoh, Y. et al. In vitro and in vivo characterization of new swine-origin H1N1 influenza viruses. *Nature*, July 13, 2009 DOI: 10.1038/news.2009.680

Second, molecular biology has provided is that, according to scientists at CDC and elsewhere, “genetic markers predictive of adaptation to humans are not currently present in the [H1N1] viruses, suggesting previously unrecognized determinants could be responsible for transmission.”³¹ This suggests two things: first, this virus may have other things to teach us; second, we do not know the whole story of how influenza becomes transmissible from human to human, so our monitoring of H5N1 for these markers is incomplete.

Novel H1N1 also lacks genetic markers for virulence identified in the 1918 virus and is expected to remain a mild virus, but this information about transmissibility has unsettling implications.

H5N1 continues to infect and kill people, and Robert Webster, one of the most respected virologists in the world, has expressed concern about a further reassortment of novel H1N1 with H5N1³². This is not so far-fetched. A recent laboratory study in which ferrets (the usual animal model for influenza studies) were coinfecting with H5N1 and the seasonal H3N2 virus found that a new reassortant virus with genes from both was produced 9 percent of the time.³³ This reassortant was likely much milder than H5N1 itself. (H5N1 is virulent because it binds only to receptors deep inside the lung; other influenza viruses bind to receptors, usually in the upper respiratory tract; the reassortants all were found in the upper respiratory tract.) But given the lethality of H5N1, a reassortant that includes it is frightening. Assuming H1N1 matures to full pandemic status and begins to infect 20 to 40 percent of the population, reassortment with H5N1 is a threat.

There are no certainties about influenza, but the most likely scenario and also the consensus view at the moment is that novel H1N1 will surge in the next influenza season in the northern hemisphere. Like the 1918 and 1957 pandemics, it will infect **20** to 40 percent of the population. ***However, it could take considerable longer—as it did in the pandemic beginning in 1889—for novel H1N1 to attain maximum efficiency in infecting humans and blanket the world with high morbidity.***

The key question is how much immune protection the middle-aged and elderly will have, that is, how vulnerable they will be. This is a major variable. Another is how many people will have been exposed to the wave currently moving through the country; this will probably be an insignificant percentage of the population, but these people will likely have considerable protection against a second wave.

³¹ Garten, RJ, et al, Antigenic and Genetic Characteristics of Swine-Origin 2009 A (H1N1) Viruses Circulating in Humans, *Science* DOI: 10.1126/science.1176225

³² Associated Press, May 8, 2009

³³ Jackson, Van Hoeven, Chen, Maines, Cox, Katz, and Donis, “Reassortment between avian H5N1 and human H3N2 influenza viruses in ferrets: a public health risk assessment,” *Journal of Virology*, online 6/5/09

The key questions relating to drugs are the obvious. Will the virus develop resistance to anti-virals and will drugs be available? More important, how long will it take to produce and distribute a vaccine?

In 1999, CDC modeled a moderate pandemic, factored in vaccine availability, and concluded that deaths would most likely range between 89,000 and 207,000.³⁴ But CDC assumed deaths would occur primarily in the elderly, as happened in 1957 and 1968 (although in both pandemics, a higher number of young adults also died than in seasonal flu). H1N1 is hitting a different target. If the young are the chief susceptibles and the virus does not increase in virulence, deaths would probably be less than CDC's projected best case.

The world could also benefit from its experience this spring. Numerous studies have examined the economic impact of a pandemic, with most estimating a 1918-like outbreak would cut world GDP by about 4 to 6 percent, while a mild pandemic would cut GDP by 1 percent.³⁵ Some experts think these estimates, especially for a mild pandemic, understate economic impact because of supply chain vulnerabilities, which have greatly increased with just-in-time inventory systems. Just-in-time, of course, discourages stockpiling supplies, not only for health care – and not just antibiotics but also syringes, gowns, gloves, and so on – but also for businesses. A mild pandemic could well infect the same proportion of the population as a severe one, and some workers would stay home to care for sick family members; this could easily cause peak absenteeism in the 20 percent or higher range for a week or more. This could ripple through the economy and create major bottlenecks. However, the current H1N1 wave could cause businesses to anticipate supply chain problems in the next 6-10 months and adjust stockpiles accordingly, which could improve resilience and lessen economic impact, assuming a full-bore pandemic does strike.

If the current outbreak intensifies or another wave builds, it will be interesting to watch international reaction. Will nations again try to screen airport passengers, close borders, and so on? The problem is that almost any leakage completely destroys the entire edifice. And, for example, models predicting that airport screening could delay the arrival of a pandemic by several weeks focus only on passengers. Even in the extraordinarily unlikely event that screening caught all infected passengers, keeping influenza out also requires keeping freight, mail, express packages, and so on out, as well as quarantining baggage handlers, workers who clean planes, and others. Shutting down all air travel – and not just with infected nations – has a theoretical chance of success, but a virus would have to be extraordinarily dangerous to take such steps simply to delay its arrival by a few weeks. However, 90 years ago Australia did delay the arrival of the second lethal wave until January 1919 by instituting a stringent quarantine of all vessels. By then the virus had weakened, and Australia's per-capita mortality was only half that of most other developed countries.

³⁴ Meltzer, M, Cox, N, Fukuda, K, "The Economic Impact of Pandemic Influenza in the United States," <http://www.cdc.gov/ncidod/eid/vol5no5/meltzer.htm>

³⁵ See Warwick McKibbin and Alexandra Sidorenko, *Global Consequences of Pandemic Influenza*, (Washington, D.C.: Brookings Institution, Lowy Institute for International Policy, February 2006

This author supports most proposed NPIs except for quarantine, which historical evidence strongly suggests is ineffective, and possibly school closing, pending analysis of recent events. But some things clearly do work. Having the ill stay home, and once at home minimizing contact with other family members, should have an impact. Data strongly suggest an important role for hand transmission, hence handwashing matters. Isolating the sick as much as possible is protective, and historical data clearly correlate the amount of space per person and morbidity. Masks on the sick protect the healthy, although only in very narrow circumstances does it make sense for healthy people to wear them – and they can be dangerous when removed. (Evidence from the SARS outbreak suggests that most health care workers infected themselves while removing protective equipment.) Social distancing is useful, but telecommuting will collide with capacity limits.

NPI strategy does involve “layering” interventions, with the idea that reasonable compliance with a number of interventions would have a cumulative effect. Nonetheless, although this layering could improve upon the impact of individual NPI measures to mitigate outbreaks, this author is less optimistic than most who recommend them. This is partly because some assessments are based on models that use deficient 1918 data and partly because in 1918 most U.S. cities took dramatic actions and their statistics already reflect the impact of these measures. Improving upon that may be possible, but advocates underappreciate the difficulties in changing behavior and sustaining compliance. Even in 1918, under horrific circumstances, compliance with essentially the same measures as proposed today quickly declined, and public health leaders expressed disappointment with their “education” efforts. The rapid decline in mask usage in Mexico during the current outbreak suggests that such dynamics remain true today, and is not conducive to optimism.

The long-term answer to influenza is a vaccine that works against all influenza viruses, which does seem to be possible. Meantime, sustained investment in vaccine production technologies is essential. Cell-based production, while faster than current egg-based methods, still take many months. Only newer technologies, such as but not limited to “virus-like-particles,” have the potential to produce tens of millions of dosages rapidly.

The second most important resource is communication. Getting and sustaining compliance – changing behavior and keeping it changed – requires winning public trust. Gaining trust requires explaining in detail why each recommendation was made and why others were not. It also requires, when decisions are made, taking the offense through a massive campaign to dominate all media, including the internet. And if the situation becomes severe, experience from 1918 to SARS demonstrates that only full and candid disclosure of the truth will contain panic. This author is wary of the term “risk communication.” It implies management of information. You do not manage the truth. You tell the truth.