Historical

Observations on Past Influenza Pandemics

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Influenza is an RNA virus with 8 genes on a segmented genome. There are 3 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–H16) and neuraminidase (N1–N9), which are outside the viral envelope and allow the virus to bind to and then escape a cell.

Seasonal flu infects about 10% of the population. Pandemic flu, in contrast, can be expected to infect from 15% to 40%, 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 of the 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 3 hemagglutinins can cause human pandemics; others dismiss this speculation because it is based on so few samples.)

THE PAST IS PROLOGUE: WAVES AND PATTERNS FROM PAST PANDEMICS

1889

The 1889–1892 pandemic, caused by an H2 or H3 virus, came in 3 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."[1]

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."[1] 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."[1]

Although transportation time and the fact that parts of the world were more isolated in 1889 than even in 1918, and far more than today, may account for some of this protracted 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 places such as London that experienced the first 2 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, however, for the obvious reason that antibiotics were unavailable in 1889 to treat secondary bacterial infections.

1918

In 1918, the virus seemed to have jumped species in January in Kansas (other hypotheses suggest the virus jumped species more than 1 year earlier), and the first wave began to spread rapidly in US Army camps, with intermittent spread in civilian communities in March. By April, it was spreading through Europe. By late May, the 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 generally more mild than seasonal influenza, and articles in medical journals suggested it was so mild that it could be 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."[2]

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. R0 certainly exceeded 2.0 and may have approached 4.0.

A third wave struck intermittently around the world from January to April 1919, and caused about one third of the total deaths attributed to this pandemic.

The difference in case mortality between the first 2 waves has led to a hypothesis that they were caused by different viruses. That hypothesis, however, does

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not account for several facts, including that exposure to the first wave generated significant immune protection to the second wave—exposure was as much as 94% effective, considerably higher than could be expected by cross-protection between different strains.[3]

Although case mortality in the developed world was 2% to 2.5%, even there certain subgroups experienced much higher mortality rates. Metropolitan Life found that 3.26% of US industrial workers ages 20 to 45 years that it insured died, so case mortality in this population had to be in the neighborhood of 10%. In total, the 1918 virus killed between 1.9% and 5.5% of the total world population. Because more than half the dead were aged 15 to 40 years, the percentage of the 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. 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."[4] These government efforts to reassure people seemed to be counterproductive, however, destroying trust and alienating the public from those in authority and from each other. As a result, in some countries, including the United States, society nearly broke down.

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 R0 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.[5] An epidemic peaked by mid-June and disappeared by July; disease was mild, affecting primarily children, with low mortality. By late June, the first wave in Indonesia had caused approximately 10% morbidity.

The virus behaved differently in different countries. It reached England with some sailors in early June, but few secondary cases developed. In the Netherlands, several schools had attack rates above 50%, but, again, there were only sporadic adult cases and no community spread. In Iran, it was first reported on June 24 and 1 month later the country had an attack rate of 30% to 35%. 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 outbreak in 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% attack rate at a conference attended by 300 schoolgirls. Several similar eruptions occurred during the summer, but no community-wide outbreaks developed. Of 2000 college students attending a national conference in Iowa on June 26, 10% 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 from July 10 to 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.[6]

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 experienced significant epidemics in this period, but this early spread seeded the virus around the United States, just as it was seeded around the world.

The first US and European wave is generally considered to have commenced in August in Louisiana, when children returned to school, became sick, and quickly spread disease to the community. The fact that in 11 of 14 US cities studied peak school absenteeism preceded peak industrial absenteeism by from 1 to 4 weeks also suggests that schools were avenues of transmission. 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% 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 figures. This wave peaked the preceding week, and decline continued into December. Excess US deaths were about 40,000.[7] Morbidity was estimated at 30% of the population in October and November alone.

First-wave activity never declined to near zero, but contemporary observers 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 US deaths were about 20,000. This second wave is particularly interesting because deaths occurred apparently 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."[7]

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 US deaths. Approximately 20% to 25% 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 years; 2000 excess deaths ages 15 to 24; 6000 among those ages 25 to 44; 22,900 ages 45 to 64; 57,000 people older than 64 years. It should be pointed out that mortality among those younger than age 65 was substantially higher than in seasonal flu. Today, in a US population that is almost double that of 1957, the number of annual influenza-associated deaths in people younger than 65 years is only 7000.

Exposure did seem to 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, whereas the mid-Atlantic region, hit hard in 1957–1958, largely escaped the third wave.[7] (The mortality expressed here, a total of 86,000, comes from a 1961 study in *JAMA*[7]; 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 of 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 later, 21 states showed epidemic activity, and by December 28 all 50 states had epidemic activity.

In all of the countries above, a first wave peaked in January 1969. US morbidity was around 20% overall and much higher in schoolchildren. A second wave peaked 1 year later, in January 1970, in Canada, Japan, and England and Wales, and in February in the United States.

There are significant unexplained differences. In the United States 70% and in Canada 54% of all mortality occurred in the first wave, with the rest of the deaths coming 1 year later. Japan, however, experienced only 32% mortality in the first wave. In England and Wales, 23% of total deaths came in the first wave. In those countries, the second wave accounted for 2 to 3 times more mortality than the first.[8]

Total 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 4 pandemics discussed, but although a majority of the dead were elderly people, mortality among young adults was much higher than in seasonal influenza.

THE FUTURE OF NOVEL H1N1

Three of the preceding 4 pandemics, 1889, 1918, and 1957, show clear evidence of some fairly intense but sporadic initial local outbreaks scattered around the world. The novel H1N1 virus seems thus far to be following the pattern of those 3 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, then 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, however, the virus needs further adaptation to become fully efficient in infecting humans, spread could be delayed, possibly for 1 or 2 years, as seems to have occurred in the 1889–1892 pandemic.

The most disturbing information molecular biology has provided is that, according to scientists at the Centers for Disease Control and Prevention (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."[9] This, in turn, suggests 3 things: this virus may have other things to teach us; 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; and this virus may spread far more explosively than it has thus far. Novel H1N1 also lacks genetic markers for virulence identified in the 1918 virus and is expected to remain a mild virus generally, even though it can bind to cells in the lower respiratory tract and cause severe disease, but this information about transmissibility has unsettling implications.

H5N1 continues to infect and kill people, and Webster and others have expressed concern about a further reassortment of novel H1N1 with H5N1. This is not so far-fetched. A recent laboratory study in which ferrets (the usual animal model for influenza studies) were co-infected with H5N1 and the seasonal H3N2 virus found that a new reassortant virus with genes from both was produced 9% of the time.[10] A reassortant would likely be much less virulent than H5N1 itself because the location of the cells to which it binds would likely change. 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 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% of the population, reassortment with H5N1 is a threat. The fact that turkeys have been found to be infected with novel H1N1 also suggests a reassortant of H1N1, and H5N1 could occur in birds.

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

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northern hemisphere. Like the 1918 and 1957 pandemics, it will infect 20% to 40% of the population. The key question is how much immune protection middle-aged and elderly people will have—that is, how vulnerable they will be. Data from Brazil suggest considerable protection: 69% of the deaths have been in people aged 15 to 49 years, 9% among people 50 to 59 years, and 2% in people older than 60.[11] Age-based protection is a major variable. Another variable is how many people will have been exposed to the spring and summer waves in the northern hemisphere; this will probably be an insignificant percentage of the population, but these people may have considerable protection against a second wave.

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

In 1999, the CDC modeled a moderate pandemic, factored in vaccine availability, and concluded deaths would most likely range between 89,000 and 207,000[12]; however, the CDC assumed deaths would occur primarily in elderly people, 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, then deaths probably would be less than the 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 gross domestic product by about 4% to 6%, whereas a mild pandemic would cut gross domestic product by 1 percent.[13] 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 in antibiotics, 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% or higher range for 1 week or more. This effect could ripple through the economy and create major bottlenecks. The current H1N1 wave could cause businesses to anticipate supply chain problems in the next 6 to 10 months and adjust stockpiles accordingly, which could improve resilience and lessen economic impact, assuming a full-bore pandemic does strike.

Should the present outbreak intensify 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. 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 the like out, as well as quarantining baggage handlers, workers who clean planes, and others. Shutting down all air travel, and not just in infected nations, has a theoretical chance of success, but a virus would have to be extraordinarily dangerous to justify taking such steps simply to delay its arrival by a few weeks. In the 1918 pandemic, 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.

I support most proposed nonpharmaceutical interventions (NPIs) except for quarantine, which historical evidence strongly suggests is ineffective, and possibly school closing. Analysis of recent events does demonstrate closings can flatten a wave, but the societal costs of doing so are significant. If lethality increases, however, then school closings would make sense. Some things clearly do work. Having sick people stay home, and once at home minimize contact with other family members, should have an impact. Data strongly suggest an important role for hand transmission, hence handwashing matters. Isolating sick individuals as much as possible is protective, and historical data clearly correlate the amount of space per person and morbidity. Masks on sick people protect healthy people, although only in narrow circumstances does it make sense for healthy people to wear them, and they can be dangerous when removed. (Evidence from the severe acute respiratory syndrome 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. I am less optimistic than most of the people who recommend NPIs. This is partly because some assessments are based on models that use deficient 1918 data and partly because in 1918 most US cities took dramatic actions and their statistics already reflect the impact of comparable layering. 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 spring 2009 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. In the meantime, sustained investment in vaccine production technologies is essential. Cell-based production, al-

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though faster than egg-based methods, still takes 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. Obtaining 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 offensive through a massive campaign to dominate all media, including the Internet. If the situation becomes severe, experience from 1918 to the severe acute respiratory syndrome outbreak demonstrates that only full and candid disclosure of the truth will contain panic. I am wary of the term "risk communication." It implies management of information. You do not manage the truth. You tell the truth.

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