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Emerging Infections: Pandemic Influenza

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The report of the Institute of Medicine's Committee on Emerging Microbial Threats to Health in the United States, published in 1992, defines influenza virus as the prototype emerging infection (1). Pandemics of influenza have been recognized since earliest recorded history and, because of the mutability of the virus, still represent a formidable threat to the health of the nation. Although much progress has been made in describing the molecular aspects of the virus, in elucidating the epidemiology and modes of spread, and in developing methods for prevention and treatment, a rational strategy for control has not been established. The trends of modern society, including the increasing availability of rapid human transportation and the urbanization of the rapidly expanding human population, tend to facilitate the spread of influenza and increase morbidity. Modern medicine can reduce the mortality that resulted from complications of infection with influenza virus during earlier epidemics, but the cost of medical interventions has increased to the point that effective methods of epidemic control should be considered. This challenge provides an opportunity to develop, test, and have in place a strategy for control of *interpandemic* influenza before the next *pandemic*.

Pandemics result from the emergence of an influenza A virus that is novel for the human population. Evidence for recycling of subtypes of influenza A after intervals of 60 years or more has been derived by determining antibody prevalence in elderly populations prior to the emergence of subtypes H2N2 in 1957 and H3N2 in 1968 (2, 3). A more ominous threat is the reservoir of 14 influenza A subtypes that persist in avian hosts (4). An avian virus can reassort with a human virus, as occurred in 1957 and 1968, to allow the creation of progeny that possess novel surface antigens with the potential to spread in human populations. Both pandemic viruses, A(H2N2) of 1957 and A(H3N2) of 1968, had evidence of gene reassortment with avian viruses (4). Swine are considered the most likely "mixing vessel" for this event, but viruses with avian genetic characteristics have also been recovered from horses and aquatic mammals.

As pointed out in the Institute of Medicine report (1), many of the essential components for epidemic control are available. Surveillance of influenza activity is maintained by the network of laboratories sponsored by the World Health Organization. The Influenza Branch of the Centers for Disease Control and Prevention (CDC) coordinates surveillance activities in the United States with the worldwide effort. A collaborative arrangement with the Chinese National Influenza Center in Beijing has improved recognition of the emergence of new variants of the currently prevalent influenza viruses (5). In the United States, this has allowed production and distribution of influenza vaccines with antigens that closely match the viruses that are responsible for epidemics. Improved surveillance in the tropics and in the southern hemisphere, especially in India, Africa, and South America, would enhance the ability to recognize new variants of influenza viruses as they arise.

Other components of epidemic control are vaccine production and distribution and the availability of antiviral therapy. The routine use of influenza vaccine for one of the groups with highest priority, persons aged 65 years and older, has improved rapidly during the past 3 years; the proportion of the elderly receiving vaccine has risen from 32.9 to 52 percent between 1989 and 1993 (6). Delivery of vaccine to other priority groups is lagging; only 10–15 percent of high risk patients less than 65 years of age receive vaccine each year. Two antiviral drugs against influenza A viruses, amantadine and rimantadine, are available for prevention. Although the prophylactic effect of these drugs is equivalent to vaccine for interpandemic periods, ranging from 66 to 91 percent (7–9), the protection is less for newly emerged pandemic strains (36–52 percent for A(H3N2) trials performed in 1968–1969 (10)) and the newly reemerged A(H1N1) viruses in 1978–1979 (11, 12). As pointed out in the

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Abbreviations: CDC, Centers for Disease Control and Prevention; ACIP, Immunization Practices Advisory Committee.

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Institute of Medicine monograph on emerging infections, influenza remains an essentially uncontrolled disease (1).

PANDEMIC INFLUENZA

To address the problem of this uncontrolled emerged and emerging infection, the US government has reactivated the Interagency Group for Influenza Pandemic Preparedness. This group consists of experts from the interested government agencies and outside consultants who are charged with the development of a national plan to deal with pandemic influenza. At this juncture, the characteristics of pandemic influenza, particularly as it has occurred during the last century, will be reviewed to provide a framework for strategies for implementation of control measures.

Excess mortality

The hallmark of pandemic influenza has been excess mortality, defined by William Farr in London, England, in 1847 as the number of deaths observed during an epidemic of influenza-like illness in excess of the number expected (13). Originally, most of the deaths were diagnosed as pneumonia or influenza, but over the years an increasing proportion of excess deaths have been attributed to other causes, usually cardiac or pulmonary disease (14). The method of determining the baseline, or the expected number of deaths for the season, also has evolved over the years from simply the number observed the previous season when no influenza epidemic occurred to a forecast of the baseline by various mathematical models cited below. Obviously, the use of excess mortality to define and to measure the impact of influenza epidemics was developed and put in place before the etiology of influenza was known and before virologic surveillance was available.

After a respite of more than 50 years, pandemic influenza struck twice near the end of the nineteenth century, in 1889–1890 and again in 1899–1900 (15). Serologic archeology suggests that the hemagglutinin of the virus of the 1889–1890 pandemic was similar to that of the influenza A(H2N2) virus that caused the 1957–1958 pandemic, and that the hemagglutinin of the virus active in 1899–1900 was similar to that of the influenza A(H3N2) virus that caused the pandemic of 1968–1969 (16). The agents of the pandemics of the eighteenth and nineteenth centuries were thought to have originated in Russia; tracking of outbreaks indicated that they generally spread from east to west through Europe (15). More likely, Russia was the site of the first recognition of the spreading pandemic, but not necessarily the site where the agent originated. The rapidity of spread was remarkable in those days of steamship travel. Both of the pandemics of the late nineteenth century crossed the Atlantic to the United States within 2 months after activity was recognized in Europe. Excess mortality rates by nation were not systematically determined in those years, but cities such as London had rates of pneumonia-influenza mortality that were roughly 10 times that seen currently with a severe influenza A(H3N2) epidemic in the United States, and the curve for age-specific mortality displayed the typical "U"-shape (figure 1) with the highest rates at the two extremes of the age spectrum (17).

The site of origin of the great pandemic of 1918 is unknown, but some choose to think that it was in the United States (18). Scattered outbreaks of disease were detected during the spring and early summer of 1918. Excess pneumonia-influenza deaths were evident from later tabulations by Wade Hampton Frost, who directed most of the epidemiologic investigations of this pandemic for the US Public Health Service (19). Many of the early outbreaks occurred in military installations as recruits poured into training camps to respond to the call for troops in Europe. Outbreaks also occurred on troop ships and among the American Expeditionary Forces in France by April 1918. The disease was soon evident among allied forces. A period of quiescence was noted in the United States during the summer. In some areas it was suspected that a reintroduction from Europe occurred in late summer and early autumn. However, in retrospect, it is evident that "seeding" of many geographic areas of the United States had occurred during the previous spring, that transmission was low during the summer but picked up rapidly as schools reopened in September. The first wave of the pandemic reached a crescendo by the end of October 1918. This was followed by a decline and recrudescence in midwinter 1919. The same pattern of occurrence was observed in the United States in 1957 with the next pandemic caused by influenza A(H2N2) (20).

By 1918, only about three-fourths of the states and territories systematically reported deaths to a national registry (21). From this sample an estimate of over 550,000 excess deaths was calculated from a rate of 598 per 100,000 persons for the biphasic epidemic period spanning September 1918 through April 1919. The third peak occurred in February 1920 and produced over 125,000 excess deaths, for a total of >675,000 excess deaths for the pandemic period. For the 3-year pandemic period, an annual average of 225,000 excess deaths occurred. The designation of a 3-year pandemic period is used for the sake of comparison with similar periods for the 1957 and 1968

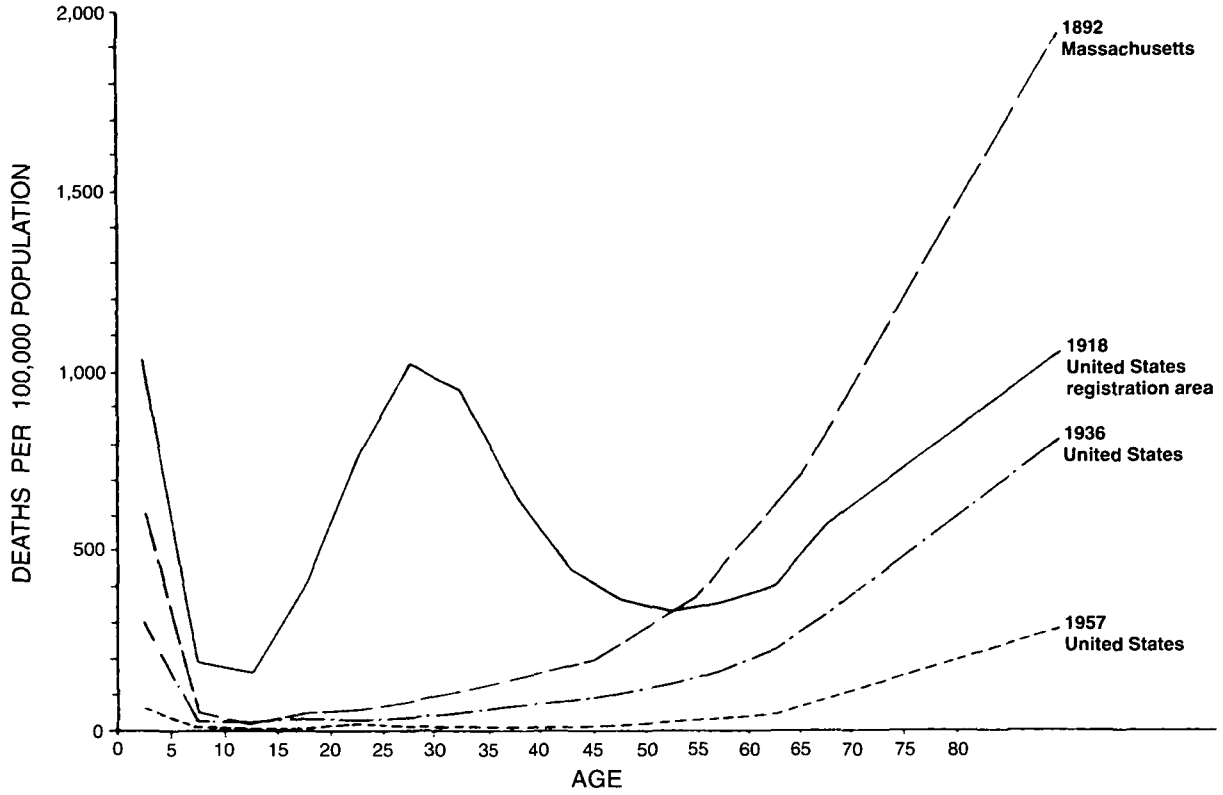

FIGURE 1. Pneumonia and influenza mortality by age in certain epidemic years. (From Dauer and Serfling (17).)

pandemics when virologic surveillance demonstrated that the pandemic virus in each case produced at least three waves before significant antigenic variation was detected (20, 22).

The 1918 mortality numbers alone do not adequately describe the disaster. It was not just the weak and infirm who were taken away but the flower and strength of the land (18). The age-specific mortality curve did not trace the "U" described above, but resembled a "W" with very high mortality rates in healthy young adults aged 20–40 years as well as in those less than 5 years of age and those aged 65 years and older (figure 1). No adequate explanation of this mortality pattern has been presented. It was wartime and young men were crowded together in military camps, but the mortality was highest in men of the same age who remained at home. Pregnancy was a risk factor, and this may provide some explanation for the high mortality in young women (23, 24). The fulminant nature of the clinical course of the fatal pneumonia cases suggests that the virus itself possessed a virulence not seen before nor since.

Many of the young men at military encampments had perioral cyanosis as a presenting sign of their illness along with the usual signs and symptoms of influenza (18). Death ensued rapidly within a few days. Postmortem examination revealed denudation of the respiratory mucosa with the airways full of frothy, blood-tinged fluid. Many of those who survived the first few days developed a secondary bacterial infection, usually with pneumococcus, group A streptococcus, or *Hemophilus influenzae*, and died with typical bacterial pneumonia.

The technology for virus isolation had not been developed in 1918, but some evidence for the identification of the putative agent is available. In 1976, more than 90 percent of persons in the United States aged 52 years and older had antibodies to the influenza A/New Jersey(H1N1) virus (25). This virus was documented to have spread among soldiers at Fort Dix, New Jersey, and was similar to the virus known to have been carried by swine since 1930, the year that the virus was first isolated. A similar virus is thought to be the agent of the great pandemic of 1918. It is very difficult to review the description of the 1918 pandemic and criticize the efforts in 1976 to immunize the population of the United States against this potential threat. Sufficient numbers of intensive care beds do not exist to treat a pandemic of adult respiratory distress syndrome, and if they did exist, we would bankrupt the system with the effort. Over 280,000 pneumonia deaths were reported in young adults, aged 20–39 years, in 1918–1919. The mortality rate was about one per 100 in this young age group (21).

Table 1 compares the excess mortality for the great pandemic of 1918 with those that have followed subsequently, and summarizes the excess mortality for the interpandemic periods (14, 20–22, 26–29, Lone Simonsen, CDC, Atlanta, Georgia, personal communication, 1995). Crude rates were calculated for comparison of the impact at different periods using the average annual number of excess deaths and the estimated population for the midpoint of the period. For some years more than one estimate of excess mortality was available, and for those years the highest number was chosen. Excess mortality remained high for the epidemics that occurred through the 1932–1933 season; eight epidemics were observed during that 13 year interpandemic period (1920–1933). It was estimated that 368,400 excess deaths occurred yielding an average annual rate of 23 per 100,000 persons, or 28,338 excess deaths per year (14). The viruses that caused these epidemics were not identified; it is possible that some were variants of the virus that caused the 1918 pandemic and some were probably influenza B viruses.

Virus identification was available for the next interpandemic period from 1933 until the 1957 pandemic. Nine influenza A(H1N1) epidemics and five influenza B epidemics were recognized during the 24-year period (22). The most severe epidemics were the influenza B epidemic of 1935–1936 and the influenza A(H1N1) epidemics of early 1937 and the winter of 1943–1944 with excess deaths numbering 55,000, 46,000, and 53,000, respectively (14, 22). With these three exceptions, the epidemics were relatively mild and occurred approximately every other year. The average annual excess mortality rate dropped to 7.5 per 100,000 persons during this 24-year period.

The next pandemic began in 1957 when influenza A(H2N2) viruses appeared in the Far East. The precise origin is unknown, but the virus was isolated in Singapore in February and in Hong Kong in April 1957 (20). The prototype strain was designated as A/Japan/305/57(H2N2) and is commonly referred to as the Asian influenza virus. Concurrently, the A(H1N1) viruses known to have been prevalent in human populations for at least 24 years no longer circulated in humans. Detectable antibodies to A(H2N2) viruses were rare in subjects less than 65 years of age, and the virus was observed to spread rapidly in the Far East; therefore, a pandemic was predicted with spread to the Southern Hemisphere in the summer of 1957 to be followed by epidemics in the Northern Hemisphere (30). The predictions were accurate.

The first identifications of Asian influenza were made in coastal cities on both coasts of the United States in June 1957. The virus seeded the population during the summer and became epidemic as soon as schools were back in session. The seasonal pattern of excess mortality was very similar to that observed with the great pandemic of 1918. The first peak of excess deaths occurred in late October 1957, followed by a second peak in February 1958. A small peak of excess mortality caused by influenza A(H2N2) accompanied by influenza B was interspersed before the next substantial wave of Asian influenza in early 1960. Most of the excess deaths were detected in the first biphasic epidemic that covered the period from September 1957 through March 1958; almost 70,000 of the total of 115,700 excess deaths for the pandemic period occurred during that first year. Although some fulminant deaths were reported in healthy young adults, particularly pregnant women, the mortality did not compare with that observed in 1918–1919 (31–33). The age-specific rates returned to the traditional "U"-shaped pattern produced by highest rates in persons at the extremes of the age spectrum. The overall impact was only one-tenth of that observed in 1918–1919.

During the 10-year prevalence period for A(H2N2) viruses, new variants arose to produce major epidemics in early 1963 and in the winter of 1967–1968 (22). Moderate influenza B epidemics were observed in 1961–1962 and in early 1966. The average annual excess mortality rate for the 8-year interpandemic

TABLE 1. Excess deaths estimated for pandemic and interpandemic periods, 1918–1991

Period	Years	No. of excess deaths	Annual average	Crude rate per 100,000 persons
Pandemic	1918–1920	675,000	225,000	218.4
Interpandemic	1920–1933	368,400	28,338	23.0
Interpandemic	1933–1957	242,600	10,108	7.5
Pandemic	1957–1960	115,700	38,567	22.0
Interpandemic	1960–1968	114,900	14,363	7.5
Pandemic	1968–1972	111,927	27,982	13.9
Interpandemic	1972–1981	198,800	22,089	10.3
Interpandemic*	1981–1991	200,000†	20,000	10.0

* Preliminary estimates.
† Approximation.

period (1960–1968) was the same as that seen in the period just before the Asian influenza pandemic.

The next pandemic occurred with the emergence of influenza A(H3N2) viruses in 1968 (34). The prototype virus was influenza A/Aichi/2/68(H3N2) and is usually referred to as A/Hong Kong influenza. This was a "hybrid" pandemic strain because only one of the surface glycoproteins, the hemagglutinin (H3), was unique for the population. The N2 neuraminidase was present also on the preceding H2N2 viruses (35). As mentioned previously, viruses with the H3 hemagglutinin were thought to have caused the pandemic of 1899 (16). Although the Hong Kong influenza virus was detected in the United States as early as September 1968, it did not become epidemic until December. Excess mortality peaked in December 1968 and January 1969 (36). The same virus returned in early 1970 and 1972 to produce epidemics with excess mortality (22). A total of 98,100 excess deaths were noted during the 4-year period yielding an annual excess mortality rate of 12.2 per 100,000 for the pandemic. Most of the excess deaths occurred in persons aged 65 years and older. It should also be noted that influenza A(H2N2) viruses disappeared from human circulation when the influenza A(H3N2) viruses emerged, just as the A(H1N1) viruses had ceased circulation in 1957 with the emergence of A(H2N2).

Several factors may have contributed to the relatively low mortality rate that accompanied the A/Hong Kong(H3N2) pandemic. The excess death rate was about half of that observed with the Asian (H2N2) influenza pandemic in 1957–1958. First, the N2 neuraminidase common to the preceding virus (35) may have produced a cross immunity that modified the severity of illnesses associated with the A(H3N2) virus. Antibodies to the influenza neuraminidase do not prevent infection but may modify the extent of infection by reducing the amount of virus released from each replication (37). Another factor was the timing of the epidemic; the first wave may have been altered by the fact that schools recessed for the Christmas holidays just as the epidemic was gaining momentum (38). Since school children are important for the dissemination of the virus in the community, the recess may have dampened the progress of the first wave of the epidemic. Improved medical care, including more effective antibiotics for secondary bacterial infections, could have resulted in a better outcome.

Although the pandemic produced by influenza A/Hong Kong(H3N2) virus was relatively mild, the subsequent H3N2 variants have continued to amass excess mortality for over 20 years (1972–1991) (29, Lone Simonsen, CDC, Atlanta, Georgia, personal communication, 1995). Most of the excess mortality for the current interpandemic period has occurred during these H3N2 epidemics. The annual average number of excess deaths has remained above 20,000 per year, and the average annual rate has remained above the excess mortality rates observed during the interpandemic periods since 1933. No good explanation exists for the continued toll of H3N2 viruses. Influenza A(H1N1) viruses that reappeared in 1977 have contributed little to the excess mortality (29, Lone Simonsen, CDC, Atlanta, Georgia, personal communication, 1995). It may be relevant that most of the persons now at high risk for the complications of influenza were born and attended school (the period for high risk of infection) during the H1N1 era prior to 1957. This experience has served them well during the recent outbreaks of H1N1 viruses even though the subsequent variants of the 1977 H1N1 prototype virus have been antigenically different compared with the H1N1 viruses that were prevalent before 1957 (39). (The prototype H1N1, A/USSR/77, that appeared in 1977, was identical to a virus that circulated in the United States in 1950.) Influenza B epidemics have resulted in measurable excess mortality on five occasions during the 20-year period compared with nine occasions for influenza A(H3N2).

Critique of excess mortality as a measure of severity

Excess mortality as currently measured is a specific indication of the occurrence of epidemic influenza. When reported pneumonia-influenza deaths exceed the threshold established by the mathematical model used to predict the baseline mortality, an influenza epidemic is in progress. Weekly reporting of deaths to the CDC allows the development of timely information about the course of epidemics. The shortcoming of the system is that it may not be a sensitive measure of the impact of epidemics (40). The models used to predict the baseline have not been validated by determining that the periods used to model the wintertime baseline were free of influenza activity. They have tended to label years with epidemics due to influenza B virus as nonepidemic years, and the epidemic weeks for these years are incorporated into the baseline by circular reasoning. This process assures that excess mortality will not be detected in young people who are susceptible to influenza B viruses (41) and who have high morbidity proven by positive cultures during these epidemics (42, 43). Furthermore, the detection of excess mortality is dependent upon the occurrence of *synchronous* epidemics throughout the country. When epidemics occur at different time periods in different geographic areas, the threshold may not be exceeded for 2 successive weeks; therefore, the pneumonia-

influenza deaths that have occurred over a longer period of time in regional epidemics go undetected as excess mortality. The solution is to validate the models for predicting the baseline mortality with adequate virologic surveillance to document that the baseline accurately represents the occurrence of pneumonia-influenza deaths in the absence of significant influenza virus activity. This would require systematic surveillance of influenza in representative geographic areas throughout the country similar to that maintained in Houston, Texas, for the past 20 years (44). This would also allow for adjusting the detection of excess mortality in each geographic area to the time that influenza is epidemic in that specific region.

Hospitalizations as an alternative measure of severity

Surveys of the occurrence of hospitalizations for acute respiratory conditions in Houston have produced peaks that coincide with the peak of influenza virus activity each winter (44, 46). The peak of hospitalizations lags 1 week after the peak of influenza activity, defined by community surveillance of patients presenting for medically attended acute respiratory illness. Several other investigators have used hospitalization data to measure the impact of influenza epidemics (47) and to determine the effectiveness of interventions (48–50). Hospital discharge records are retrievable by computers and have more complete and accurate information than is available on death certificates. An illness resulting in hospitalization is the most important unit of measure for determining the impact of an epidemic. Furthermore, 10–12 hospitalizations occur for each pneumonia-influenza death, thereby increasing the sensitivity of the measurement for small populations. Analysis of data for persons hospitalized during influenza epidemics provides a more complete description of the persons at risk for serious complications of influenza and will broaden the indications for intervention. Excess mortality can also be determined from hospital data. Deaths of patients with hospital discharge diagnoses of acute respiratory illness during influenza epidemics are about twice as frequent as deaths from pneumonia-influenza, as determined from information collected from death certificates. Data from representative hospitals are currently collected by the National Center for Health Statistics. Timely analysis of hospitalizations during influenza epidemics could provide useful information for planning interventions. In addition to data concerning hospitalizations, the current expansion of managed care groups will allow retrieval of records of ambulatory care and immunization status which should further facilitate the assessment of both impact and interventions (49).

Age-specific attack rates

The morbidity and clinical attack rates produced by pandemic influenza have received much less attention than has excess mortality. In other words, the attention has been focused on the groups of persons who are most vulnerable to complications and death as a result of influenza virus infection. For most pandemics, those at greatest risk are the elderly and the very young. These same persons are, for the most part, at the end of the transmission chain; they are not introducers of influenza into the household (51). Therefore, immunization of these persons may reduce mortality and serious illness but will have little effect on the course of the epidemic. The fires of the epidemic are fed by healthy susceptible school children, college students, and employed persons who have many daily contacts and who are more mobile. If the vaccine administered to high risk persons is less than perfect, and provides only 70 percent protection, allowing the epidemic to proceed unimpeded will result in many vaccine failures. An example of this scenario occurs when personnel of nursing homes are unimmunized, become infected, and are allowed to expose vulnerable elderly persons to infection. Although influenza vaccine reduces the risk of hospitalization for the elderly, the vaccine is far from perfect. A recent study reported by Falsey et al. (52) found that 61 percent of over 200 hospitalized elderly persons with proven influenza A virus infection had been currently vaccinated. Generally, the persons most at risk are the least likely to have generated adequate protection in response to the currently available inactivated vaccines. This, then, is part of the rationale for considering more carefully the role of persons who spread the virus in the community.

Wade Hampton Frost directed and reported large surveys of influenza-like illness that were performed during the 1918–1919 pandemic (53). The sample consisted of 146,203 persons who were representative of the US population, which at that time numbered about 103 million persons. Household representatives were queried about acute respiratory illnesses that had occurred during the first 4 months of the epidemic. The illnesses sought were "influenza", "grippe", and "colds". A cold was significant if the person with the condition was put to bed for at least 1 day. The number of persons who developed pneumonia was also ascertained. A similar survey of 151,193 persons was carried out in 1929 by Selwyn D. Collins following an epidemic in the interpandemic period (21). (The 1928–1929 epidemic was estimated to have caused about 65,000 excess deaths.) The illness rate for the

1918 pandemic (first wave) was 29.4 per 100 persons, compared with 18.9 per 100 persons for the 1928–1929 epidemic (table 2). The age distributions differed, with the highest attack rates in children aged 5–14 years in 1918–1919 and in children aged 1–9 years in 1928–1929. Adult groups aged 55 years and older had consistently higher rates in the later epidemic. Children aged 5–9 years had the highest rate of nearly 40 per 100 in 1918–1919, while the highest rate in 1928–1929 was just less than 25 per 100 for preschool children. The curve for age-specific rates was considerably flatter for the later interpandemic outbreak (figure 2). It is obvious that the mortality curves (figure 1) for these epidemics did not mirror the morbidity curves. The school children and preschool children with the highest attack rates did not have the highest mortality rates.

Subsequent surveys measuring influenza morbidity have all involved households with children; therefore, they have consistently higher attack rates than the earlier community surveys performed by the US Public Health Service. The first community outbreak to be investigated in the 1957 Asian influenza pandemic occurred in the summer in Tangipahoa Parish, Louisiana, where schools opened on July 12 (54). The attack rates were determined by polling the families of children who attended the public schools. The outbreak peaked in early August among families with children in the schools for low income (mostly black) children and almost a month later in the middle income (white) school. The overall attack rate was 41.5 per 100 persons, with the highest rate (58.7) in children 10–14 years of age. Chin et al. (55) surveyed the families of students attending a high school serving an upper middle income area of Kansas City, Missouri. The overall attack rate was 34 per 100 persons, and the highest attack rates occurred in junior and senior high school-aged students at 52 and 54 per 100, respectively (table 2). Jordan et al. (56) looked at the age-specific frequencies of significant antibody rises for persons not receiving influenza vaccine in the Cleveland (Ohio) Family Study (56). Over three-fourths of students aged 10–14 years had an antibody rise to the A(H2N2) virus. Over 70 percent of high school- and college-aged students also were infected. The infection rates for elementary and preschool children and adults were 67 percent, 50 percent, and 24 percent, respectively.

TABLE 2. Age-specific influenza attack rates for pandemic and interpandemic periods 1918–1957

Age (years)	Rates per 100 Persons			
	1918 Pandemic	1928–1929 Interpandemic	Age (years)	1957 Pandemic
<1	20.7	13.8	<5	32
1–4	33.7	24.9		
5–9	39.1	24.8	5–9	33
10–14	38.1	20.0	10–14	52
15–19	34.5	16.3	15–19	54
20–24	32.3	15.7		
25–29	33.7	18.3	20–34	27
30–34	32.6	19.9		
35–39	29.6	19.8	35–39	25
40–44	23.6	18.6	40–44	18
45–49	20.7	17.2	45–49	17
50–54	17.5	16.9	50–54	19
55–59	16.2	16.4	55–59	17
60–64	14.3	16.9		
65–69	13.5	17.5	≥60	10
70–74	11.1	18.1		
≥75	8.8	17.9		
Rate for total	29.4	18.9		24

For the 1968 A/Hong Kong(H3N2) pandemic, another survey was carried out by Chin et al. (57) at the same high school in Kansas City surveyed previously. The influenza A(H3N2) outbreak peaked in Kansas City during the third week of December 1968 just before the Christmas recess. The age-specific attack rates showed a remarkably different pattern than the curve for age-specific attack rates for the first wave of the 1957 Asian pandemic (figure 3). In fact, the contrast is similar to that comparing the age-specific rates for the pandemic of 1918–1919 with the interpandemic outbreak of 1928–1929 (figure 2). The age-specific rates for 1968–1969 were fairly similar for all age groups with a slight excess in students aged 10–14 years and a second peak for adults aged 35–39 years. The factors mentioned above that may have contributed to the relatively low excess mortality associated with the 1968 pandemic may explain the flat attack rate in the first wave. The school holiday may have interrupted the transmission of the virus by dispersing the school children who are important for spreading the infection. Cross protection provided by the N2 surface glycoprotein shared with the A(H2N2) viruses that circulated from 1957 through early 1968 may have reduced the attack rate for influenza-like illness in the school children who were surveyed. A serologic survey showed that many of the students without a history of an influenza-like illness had antibodies to the virus, indicating the frequent occurrence of mild or inapparent infections. Mild illnesses could have been important for spread of the virus, because students with milder illnesses probably did not restrict their activity or contacts thereby increasing the opportunities for spread of the infection. Senior and junior high school students are the group most likely to have the partial protection to infection mediated by antibodies to neuraminidase, N2, because they would have expe-

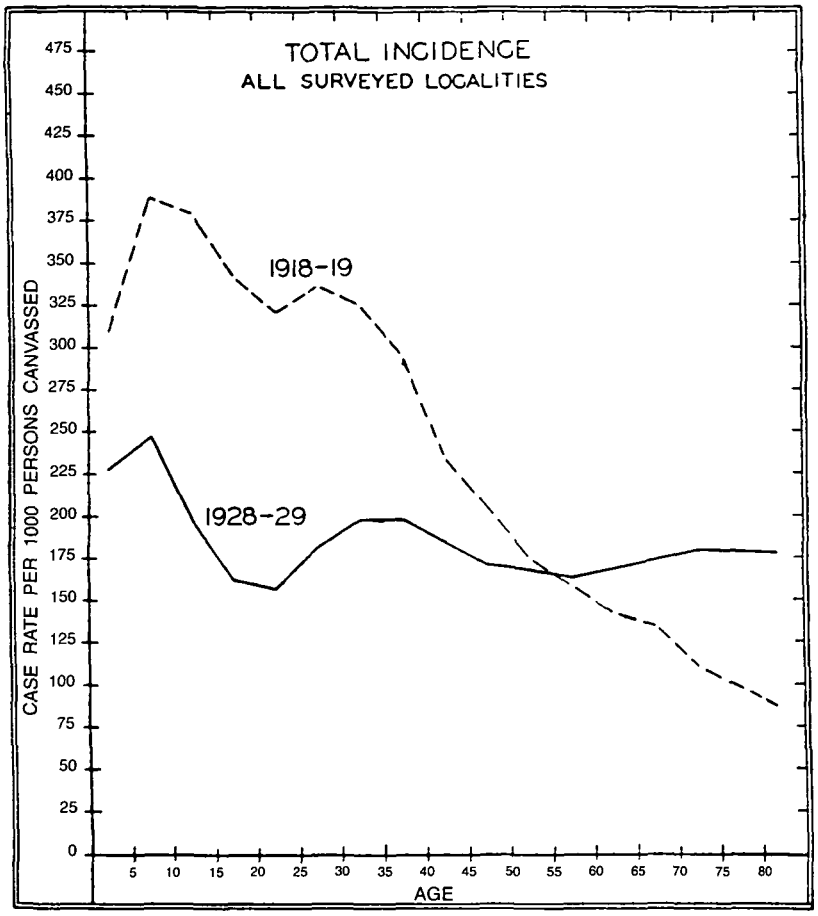

FIGURE 2. Age-incidence of respiratory illnesses in surveyed groups during the epidemics of 1928–1929 and 1918–1919. (From Collins and Lehmann (14).)

rienced the highest attack rates with the influenza A(H2N2) viruses during the previous 8 years.

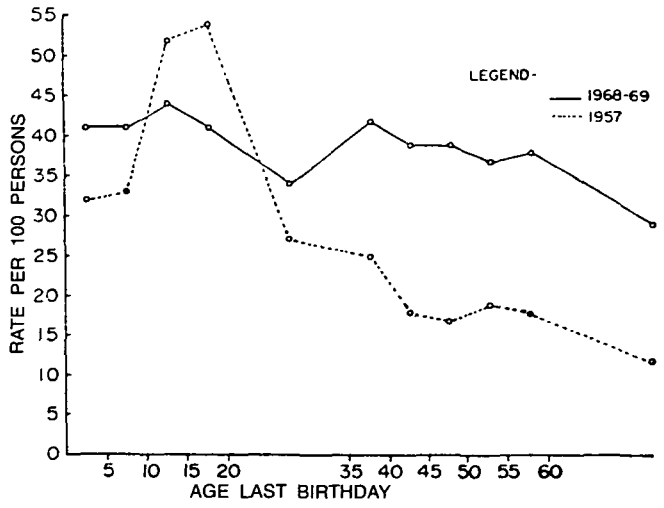

FIGURE 3. Age-specific attack rates of influenza-like illness in families of students who attended a high school serving an upper middle income area of Kansas City, Missouri. (From Chin et al. (55).)

Two family studies have examined influenza virus attack rates in the period since the 1968 A/Hong Kong(H3N2) pandemic (13, 58). The studies differed in structure in that the Seattle, Washington, families were selected for presence of school-aged children while Houston families were selected because of birth of a newborn infant into the family. This difference in age distribution of the children may explain the differences in age-specific attack rates during the interpandemic period (table 3).

Implications of age-specific attack rates

Two features of the age-specific attack rates are evident. The first feature is that only a finite proportion of the population is infected with each annual epidemic (usually between 25 and 50 percent), and this proportion does not vary between pandemic and interpandemic outbreaks (13, 21, 53, 55–58). Even pandemic viruses that are novel for the population do not reduce the pool of susceptibles by more than 50 percent during the first wave. One explanation for this

TABLE 3. Influenza virus infection rates for persons followed in family studies in Seattle, Washington, 1975–1979 and Houston, Texas, 1976–1984

Seattle*				Houston			
Age	No. of Person-years	No. infected	Rate per 100 persons	Age	No. of Person-years	No. infected	Rate per 100 persons
<5	211	52	25	<2	332	118	35.5
				2–5	474	211	44.5
5–9	605	200	33	6–10	300	143	47.7
				11–17	149	60	40.3
10–19	695	269	39	18–24	178	41	23
				25–34	651	140	21.5
≥20	1,222	145	12	>35	257	54	21
Totals	2,733	666	24		2,341	767	32.8

* From Fox et al. (58).

may be that persons naïve for the new virus have more severe illnesses that put them to bed and limit the number of their contacts. On the other hand, during interpandemic outbreaks many persons with partial immunity to the circulating virus have mild illnesses that do not limit activity and reduce contacts. Therefore, the predominance of severe illnesses during pandemics may serve to limit spread, while the mild illnesses observed in interpandemic outbreaks serve to encourage spread even when a portion of persons in the population are immune. This could explain the similarity of attack rates for pandemic and interpandemic periods.

The second important feature evident from the review of age-specific attack rates is that school children invariably have the highest attack rates during both pandemic and interpandemic periods. Epidemiologic studies during pandemics have demonstrated that children are important for spread of virus in the community (59). Observations made during the two major pandemics of this century reinforce the thesis that school children are important in the spread of influenza. Even though the populations were universally susceptible to the new influenza viruses that emerged in 1918 and 1957, and even though both viruses had seeded the population in the preceding spring and summer, the first major wave did not occur until schools were in session. Peak activity of both pandemics occurred in late October after school had been in session for 6–8 weeks.

For interpandemic periods, observations in Houston have demonstrated that school children predominate among persons presenting for health care during the early stage of influenza epidemics (60). The age distribution of culture-positive patients changes during the course of the epidemic, with a shift to preschool children and adults during the latter part of the epidemic (table 4). School absenteeism occurs in the first part of the epidemic and employee absenteeism occurs during the later part (61). Hospitalizations of persons aged 65 years and older tend to occur during the last half of the epidemic, and pneumonia-influenza deaths are lagged at least 2 weeks after the peak of community morbidity (46). All of these observations support the thesis that school children are important disseminators of the virus in the community for both pandemic and interpandemic influenza. A series of family studies also have demonstrated that children are the main introducers of influenza into the household (58, 62, 63). Furthermore, statistical modeling based on longitudinal community and family studies have confirmed the role of children for introducing influenza into the household (51), and have found that immunization of school children would be effective for epidemic control (64).

The high morbidity of children is not without sequelae. Virus infections, particularly influenza, trigger asthma attacks that lead to hospitalization of predis-

TABLE 4. Age distribution of patients with influenza virus infections during epidemics occurring after school holidays compared with those during epidemics interrupted by holidays, Houston, Texas, 1974–1981

Age (years)	% during epidemic stage		
	Early	Peak	Late
	*Epidemic after school holidays**		
	(*n* = 930)	(*n* = 1,695)	(*n* = 750)
<5	16.8	24.2	25.9
5–19	53.4	37.8	31.6
20–24	21.6	26.9	30.0
≥45	8.2	11.1	12.5
	Epidemic interrupted by school holidays†		
	(*n* = 352)	(*n* = 320)	(*n* = 261)
<5	22.7	24.4	20.7
5–19	54.0	31.6	45.6
20–44	18.5	30.3	25.7
≥45	4.8	13.8	8.0

* Early versus late stages, $p < 0.01$.
† Early versus peak stages, $p < 0.01$.

posed children. On average, more than 20 percent of children less than 10 years of age have medically attended illnesses (65). The hospitalization rate (43 per 10,000) for children less than 5 years of age during influenza epidemics is second only to that for persons aged 65 years and older (figure 4). Surveys have shown that less than 15 percent of young children hospitalized have any chronic condition; therefore, most hospitalized children are not in the group given priority for influenza immunization at this time (66). These hospital rates do not include children whose primary diagnoses were not acute respiratory conditions. Almost half of children hospitalized with proven influenza virus infections have major involvement with another organ system (67, 68). Febrile convulsions and encephalopathy were prominent (69–70); pericarditis and gastrointestinal problems also occur.

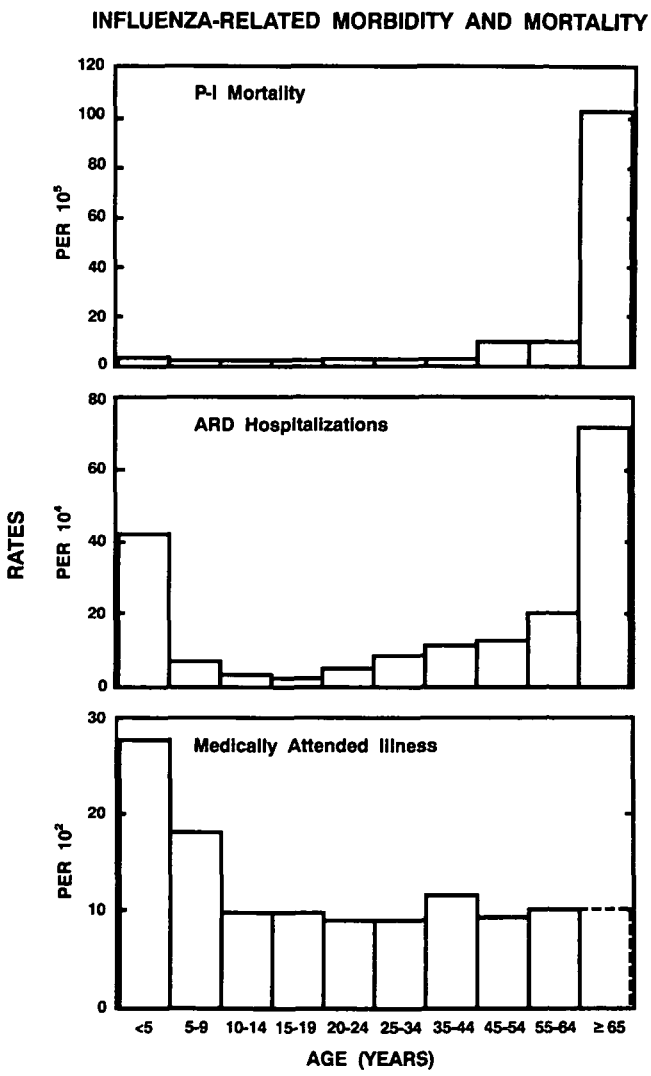

FIGURE 4. Age-specific rates for medically attended illness and mortality during influenza epidemics, Houston, Texas. (From Glezen (65).) P-I, pneumonia-influenza; ARD, acute respiratory disease.

Severe myositis is common with influenza B infections (72). Suspected bacterial sepsis is a frequent diagnosis for febrile infants under 3 months of age (67, 73). Limiting consideration of serious morbidity to only pulmonary conditions underestimates the role of influenza virus infections as causes of hospitalization of children. Therefore, children have serious morbidity that justifies universal influenza immunization.

CONTROL OF EPIDEMICS

The use of licensed inactivated trivalent influenza vaccine is increasing, but even if all high risk persons currently given priority for this vaccine should be vaccinated each year, influenza epidemics would continue to occur. Healthy school children, preschool children in day care, college students, and working adults would continue to have high morbidity and would continue to spread the virus in the community. Vulnerable high risk patients would be at risk because of repeated challenge to their immunity by contact with infected persons.

Recent pandemics illustrate another problem that must be faced with an impending pandemic. The time between recognition of the emergence of a new pandemic virus and the occurrence of the first wave may be short. The lead time for the production and distribution of the currently licensed influenza vaccine, trivalent influenza vaccine, is 6 months. It is highly unlikely that sufficient vaccine can be produced, distributed, and administered to the entire population before the first wave of the pandemic. In 1918 and 1957, the first wave of the pandemic peaked in late October allowing less time than usually occurs before the onset of interpandemic outbreaks, in the usual sequence of vaccine production starting in January.

Priorities for vaccine use have been established by the Immunization Practices Advisory Committee (ACIP) of the US Public Health Service (74). Unfortunately, high risk patients are not easily accessible for administration of vaccine within a short period of time. Some alternatives for use of vaccine have been suggested by mathematical models developed by Longini (75). Two models were presented, one based on the first wave of the 1957 pandemic and the other on the 1968 pandemic. The first model suggested that if vaccine were available for only 30 percent of the population, the most effective use would be for school children and 44 percent of preschool children (those in day care). The second model distributed the vaccine to preschool and school-aged children, and to young adults. These models suggest rapid deployment of the first available vaccine to groups that will experience the highest attack rates. These are accessible groups, particularly if vaccine can be administered at school

and at the workplace. Prevention of the spread of virus in these groups would allow time to produce additional inactivated vaccine and to distribute it to high risk patients. Even if the vaccine is produced too late for distribution before the first wave, it can be used to abort the second and third waves.

Priorities for the use of first available vaccine have been discussed, and cogent arguments can be made for immunizing several different segments of the population. The resulting tension can be relieved by inserting the use of a vaccine preparation other than inactivated influenza vaccine. The live attenuated cold-adapted influenza vaccine of Maassab (76), that is administered by nose drops or spray, could prove to be a more effective tool for epidemic control. The cold-adapted vaccine has been studied for over 20 years and given to more than 7,000 persons of all ages (77, 78), but it is not yet licensed. Investigations have shown this vaccine to be better than inactivated influenza vaccine for young children, aged 3–9 years, and equivalent to inactivated influenza vaccine for older students and young adults (79–81). The cold-adapted vaccine has not been tested sufficiently in high-risk patients to allow its use in such patients, thereby reducing any tension that might accompany a directive to limit its use to certain groups specifically for epidemic control. The available inactivated influenza vaccine could be distributed to high-risk patients and the priorities for its use would not be altered.

The cold-adapted vaccine has several advantages for use in epidemic control. Not only does it provide better protection for children aged 3–9 years who usually have the highest attack rates, but studies also have suggested that cold-adapted vaccine provides broader and longer-lasting immunity against variants of influenza A (79, 80). The cold-adapted vaccine is easier to administer and is much more acceptable by young children.

The important putative advantage of cold-adapted vaccine has yet to be demonstrated, i.e., its use for epidemic control. The concept of immunization of school children to reduce community morbidity is not new. Monto et al. (82) immunized school children in Tecumseh, Michigan, with inactivated influenza vaccine in 1968 and found lower total morbidity than that experienced by a matching community during the first wave of the influenza A(H3N2) pandemic (82). Monto suggested at that time that the use of an intranasal vaccine (cold-adapted) might be accomplished readily and at a lower cost. In addition to the Tecumseh study, Warburton et al. (84) used a subunit vaccine to A(H3N2) in communities of the Northern Territory of Australia in 1968 to demonstrate "herd" immunity. The people in the "vaccinated" communities had immunization rates ranging from 5 to 50 percent (mean 29 percent) and had significantly lower attack rates (5–28 per 100, mean 15 per 100) compared with the people in the "unvaccinated" communities who had higher attack rates (6–100 per 100, mean 65 per 100).

Several resources now available should facilitate the evaluation of the cold-adapted vaccine for epidemic control. The advantages of the vaccine are listed above. The ready availability of clinical information from computerized sources, such as hospitalizations, clinic visits, and school attendance, will allow an assessment of the effect of the vaccine. The epidemics can be defined for the community by virologic surveillance, and the coincident effect on the rates for health care visits and hospitalizations can be used to measure the effect. Similar surveillance systems can be established in matching communities to determine the net benefit of the immunization program. If these investigations can document a significant benefit, this approach to epidemic control could be used currently to control interpandemic influenza and could provide an effective method for confronting the next pandemic. Even if vaccine should not be available for the first wave of the next pandemic, immunization of school children could dampen the second and third waves.

Epidemic influenza has been shown to significantly disrupt and adversely effect the delivery of health care. Control of yearly epidemics would not only reduce pain, suffering, and death, but would facilitate planning for efficient delivery of care by reducing the annual stress imposed by the influx of patients during annual influenza epidemics and provide an effective means of combating the threat of the next pandemic.

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