

Epidemiology and Virology of Influenza Illness

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Presentation Summary

Although researchers have demonstrated that influenza illness has affected societies for many centuries, in more recent decades, the World Health Organization and the Centers for Disease Control and Prevention have developed sophisticated means of tracking the virus' activity around the globe. The importance of tracking influenza activity lies not only in detecting what is circulating in other countries, but also in enabling global manufacturers of vaccine to prepare the appropriate A and B compositions for the impending epidemic. Tracking influenza also allows quantification of its great toll in terms of morbidity and mortality. Influenza has broad societal and financial impact, with as much as \$12 to \$14 billion in indirect economic impact in the United States annually and a significant increase in physician vis-

its for febrile respiratory illness. For example, during many influenza outbreaks visits to family care physicians and internal medicine specialists can increase by 150% to 450%.

Influenza presents an ongoing public health issue because of the virus' ability to continually reinvent itself. Antigenic *drift*, caused by subtle changes in influenza's surface proteins, partially accounts for annual epidemic outbreaks of the illness. Antigenic *shift* that occurs because of major changes in the viral hemagglutinin and sometimes in the neuraminidase, the other surface protein, results in the more widespread and lethal pandemic forms of influenza. Moreover, type A influenza is not an exclusively human infection. By understanding how both of these types of changes occur in waterfowl, the virus' primary nonhuman hosts, scientists can develop both drugs and epidemiological strategies to avert or minimize the most severe effects of influenza.

Among acute respiratory infections, influenza is the only one that causes regular, large-scale morbidity and mortality every year, although the exact magnitude of outbreaks and their lethal consequences varies. A system developed by the Centers for Disease Control and Prevention (CDC) to rank different outbreaks quantifies the mortality fig-

ures associated with influenza. Traditionally, the extent of mortality has been tracked by counting deaths coded as being caused by pneumonia and influenza (P&I). These death rates are specific measures that rank outbreaks conservatively (Table 1); however, they offer less sensitive data than those of all-cause mortality in determining the full impact of

influenza. Pneumonia and influenza statistics, although useful in timing outbreaks, underestimate the total impact of an outbreak by a factor of 3.8.¹

Because of influenza's ability to cause death, researchers are able to

track the occurrence of the illness back over the centuries. As a result, scientists know that influenza is not a new disease but one that has been with humanity for hundreds of years and that will continue to present problems unless clinicians and epidemiologists

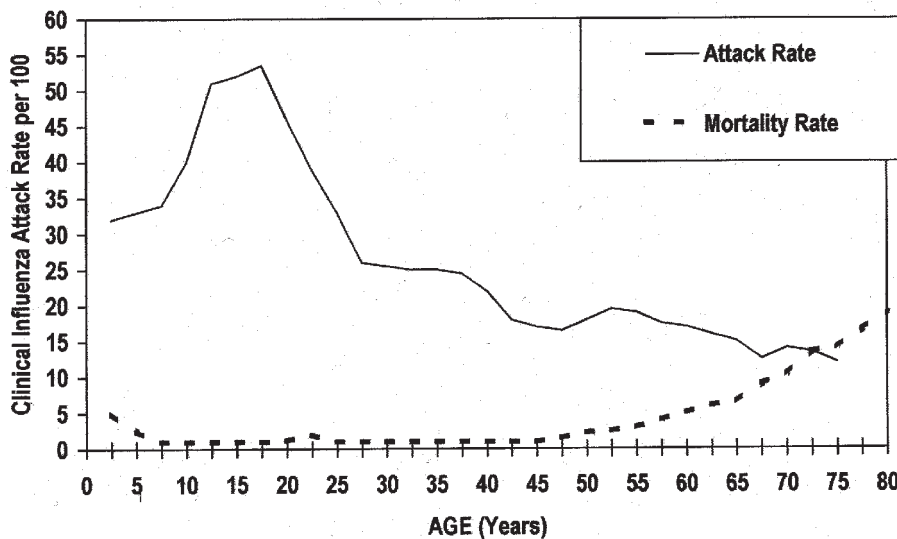
are able to institute better control measures.² Researchers have been able to demonstrate clearly the exact subpopulations, or high-risk groups, in which death is most likely to occur in many different influenza pandemics and major pandemics. The normal influenza mortality curve resembles the letter U, with a moderate impact at young ages, mainly in children younger than 1 year of age, then leveling until middle age. However, most deaths occur in the older age groups (Figure 1). Mortality begins to increase at age 45, with an even greater increase at age 65 years.³ The increase among the population aged 45 to 64 years relates to the proportion of individuals in that age group who have any of various chronic or high-risk conditions. The previous US policy of recommending vaccination for Americans older than age 65 to prevent deaths and complications from influenza illness is now being lowered from age 65 to age 50, in recognition of the unmet need to vaccinate this population.

Table 1. The Influenza Epidemic Severity Index

Category	Range of P&I Excess Deaths	Range of Total Influenza-Associated Deaths	Influenza Seasons 1972 to 1997 and 2 Most Recent Pandemics
1 (Mild)	0-2000	0-8000	5 years
2	2000-4000	8000-15,000	1981/82, 1983/84
3	4000-6000	15,000-23,000	6 years
4	6000-8000	23,000-30,000	6 years
5	8000-10,000	30,000-38,000	1977/78, 1984/85, 1993/94
6	10,000-12,000	38,000-45,000	1975/76, 1980/81, 1989/90
7	12,000-14,000	45,000-53,000	1968/69 pandemic
8	14,000-16,000	53,000-60,000	
9	16,000-18,000	60,000-68,000	
10 (Severe)	18,000-20,000	68,000-76,000	1957/58 pandemic

P&I = Pneumonia and influenza.

Figure 1. Clinical Influenza Attack Rates (Kansas City, 1957) and Annual Mortality Rate of Pneumonia and Influenza (United States, 1957)



The 1918 influenza outbreak stands out as an exception to the U-shaped pattern (Figure 2); in that instance, mortality among young adults was also very high. Although influenza-associated deaths often occur from bacterial complications, that factor cannot fully explain the 1918 situation, because mortality sometimes occurred very rapidly—an unlikely outcome with bacterial superinfection. Moreover, the influenza pattern of 1892, which was also a period when no antibiotics were available, followed the usual U-shaped curve. In 1918, more than 500,000 deaths occurred in the United States alone, with between 20 million and 40 million occurring worldwide.² Other figures suggest that the average life expectancy in the United States decreased over the short term by 12 years because of the 1918 pandemic.

Although influenza morbidity is extensive, quantifying its full extent has been difficult. The greatest morbidity occurs among children and young adults, falling off with increasing age. The difficulty in quantification results from the fact that typical influenza, that is, an illness that meets a rigorous case definition, including fever, is a criterion often not met by milder cases with virologic evidence of infection. As a result, researchers have developed quantification methods that combine illness detection with laboratory confirmation. Estimates have varied widely, depending on the methods used and the year studied (Table 2).⁴ However, it is clear that the impact of influenza on older children and adults is greater than that of other respiratory infections, because of its longer duration and greater propensity to produce disability and activity restriction.⁵ For many years, epidemiologists have used 10% as the figure for the annual attack rate. However, a study involving randomized, blinded distribution of influenza vaccine to healthy adults showed reduced overall illness rates,

from 140 per 100 to 105 per 100, during the winter, indicating that the attack rate that year was 35%, suggesting that clinicians and researchers underestimated influenza's overall impact in terms of illness (Table 3).⁶

Impact of Type A and B Viruses: Changing Antigenicity

Scientists first isolated influenza viruses from humans in 1933 in the United Kingdom and in 1934 in the

Figure 2. Mortality Rates in Different Influenza Epidemics

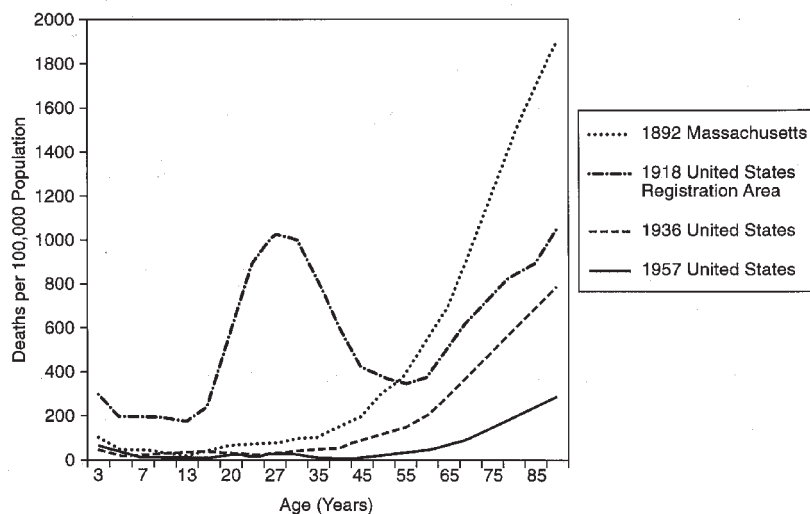


Table 2. Average Annual Number of Influenza-Associated Respiratory Illnesses Per 1000 Per Year, Tecumseh and Houston

Age Group	Tecumseh			Houston Estimates
	Observed Illnesses	Estimated Illnesses Lower	Estimated Illnesses Upper	
<5	103	109	113	349
5 to 14.9	155	164	171	375
15 to 24.9	40	42	44	218
25 to 59.9	19	20	21	153
60+	35	37	39	100
Overall	70	74	83	205

United States. The type B virus was isolated in 1940. Type C was identified later and is not generally considered of importance because it does not cause epidemic disease. Virtually every year since then there has been some influenza activity, usually as a result of the influenza A virus, but in about 1 year in 3 influenza B activity has also occurred. Excess mortality during this time has varied widely, and in many years is clearly associated not only with influenza A activity but with influenza B as well. Therefore, clinicians must be concerned about more than the threat of influenza A. Studies of the role of

influenza vaccine use in reducing hospitalization among older Americans have confirmed this concern for both influenza A and B years.^{7,8}

Influenza represents a continuing public health problem, because the virus keeps reinventing itself, that is, it changes antigenicity. The more common form of antigenic change is referred to as *antigenic drift*, or subtle changes in the virus' surface proteins, resulting from point mutations in the virus that lead to its escape from host immunity. The resultant outbreaks and epidemics are referred to as inter-pandemic influenza (Table 4).

Antigenic shift, on the other hand, refers to a major change in the viral hemagglutinin and sometimes in the surface glycoprotein neuraminidase as well. Changes of this type can lead to the pandemic form of influenza (Table 4). The study of these pandemic viruses has attracted a great deal of interest, because of concern that the world is due for another influenza pandemic. During pandemics, significant mortality occurs, both in the elderly and to a certain extent in healthy young adults. One reason the attack rate is so high is that pandemics have a major impact on every population group, each of which is totally susceptible. Pandemics have occurred unpredictably in recent years, and the world will inevitably be confronted with another one.

Of course, the greatest example of a pandemic occurred in 1918, when the Spanish flu spread worldwide. Then, much of the total excess mortality occurred in young and middle-aged adults. Researchers have

Table 3. Health-Related Benefits Associated with Vaccination (Minnesota, 1994-1995)

Study Outcome	Rate per 100 Subjects		Difference (95% CI)	Vaccine Effectiveness (%)	P value
Primary					
Episodes of URI	140	105	35 (17-53)	25	<0.001
Days of sick leave due to URI	122	70	52 (21-84)	43	0.001
Visits to physicians' offices for URI	55	31	24 (8-40)	44	0.004
Secondary					
Days of URI	974	780	194 (15-373)	20	0.034
Days of sick leave due to all illnesses	203	129	74 (23-125)	36	0.004

URI = upper respiratory illness.

Table 4. Antigenic Drift Versus Antigenic Shift

Change in Influenza Virus	Type Involved	Mechanism	Result
Antigenic Drift	Types A & B	Point mutation	Interpandemic outbreaks
Antigenic Shift	Type A only	Reassortment (replacement of RNA segment)	Pandemics

RNA = Ribonucleic acid.

estimated that as many as 1 to 2 per 100 young adults in the United States died during that pandemic, and as a result, considerable effort has gone toward discovering the specific virus that led to that pandemic. A number of articles in the lay press have been devoted to how influenza hunters are trying to resurrect that particular virus to study it further.

Jeffrey Taubenberger, at the Armed Forces Institute of Pathology, has partly succeeded in doing so. By cloning out segments of viral genetic material from pathology samples of individuals who died in 1918, he has determined that the 1918 virus probably originated in birds and then spread to mammalian species—perhaps to humans directly or else initially through pigs and then to humans—some years before the 1918 pandemic. However, the exact reason for the virus' lethality remains unclear.⁹

Some influenza mortality data indicates that for many years inter-pandemic influenza has been associated with mortality, but precise estimates have varied. Mortality occurs almost every year, including years when H1N1 subtype influenza predominates as well as in years when B viruses have predominated.

Virology of Influenza

Figure 3, which depicts an influenza A virus, shows how the phenomenon of antigenic shift develops. Influenza A, a medium-sized, enveloped virus, features 2 major surface proteins:

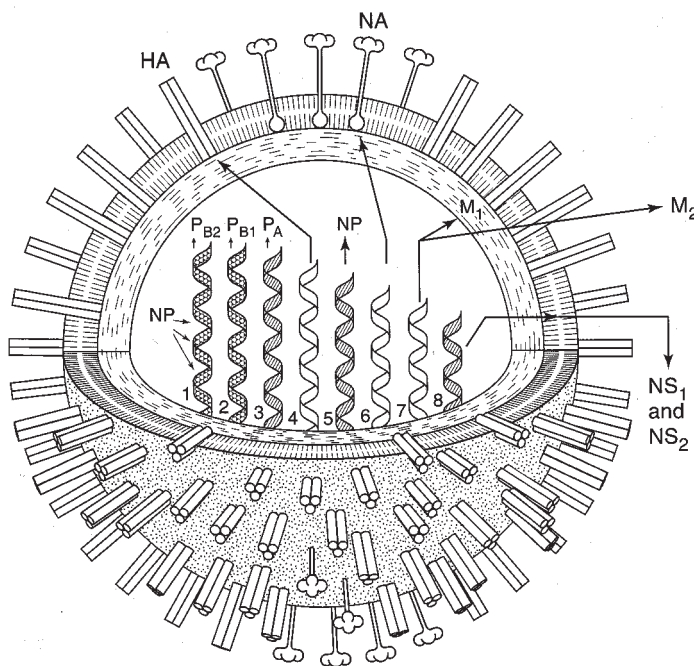
- the rod-shaped hemagglutinin, which is important in getting the virus attached to cells and starting the infection cycle, and
- the club-shaped neuraminidase, a tetramer, which is important in getting the virus out of the cells and allowing it to spread within the respiratory tract.

Hemagglutinin and neuraminidase. The antibody to hemagglutinin and

neuraminidase is protective. Changes in these 2 surface proteins allow the virus to escape from the host immunity. Another important protein in the type A virus is the M₂, which is the site of action of the drugs amantadine and rimantadine.¹⁰ Changes in the M₂ protein are related to resistance to these 2 drugs.¹¹

Inside the influenza A and B viruses, each of the 8 segments of genetic material encodes 1 or more of the proteins that are important either in making the virus itself or in regulating its growth within cells. Because of the genome's segmented nature, it is possible that, when 2 different influenza

Figure 3. Diagram of the Influenza Virus Virion



The glycoprotein spikes are approximately 16 nm long and are of 2 kinds: the hemagglutinin (HA) predominates, and the nucleic acid (NA) occurs in patches. Inside the lipid bilayer are 8 segments of single-stranded ribonucleic acid (RNA), each of which codes for 1 protein (sometimes 2). The nucleoprotein ribonucleic acid (NP-RNA) polymerase complex occurs in a helix not as individual segments indicated by the diagram. P_{B1}, P_{B2}, P_A = Viral polymerase proteins. Source: Webster RG, Bean WJ, Gorman OT, Chambers TM, Kawaoka Y. Evolution and ecology of influenza viruses. *Microbiol Rev* 1992;56:152-157. Adapted with permission from the American Society of Microbiology. NA = Neuraminidase; NS = Nucleocapsid protein.

viruses coinfect the same cell, they can exchange genetic material, leading to the generation of new viruses, a process that has been documented in a number of instances.

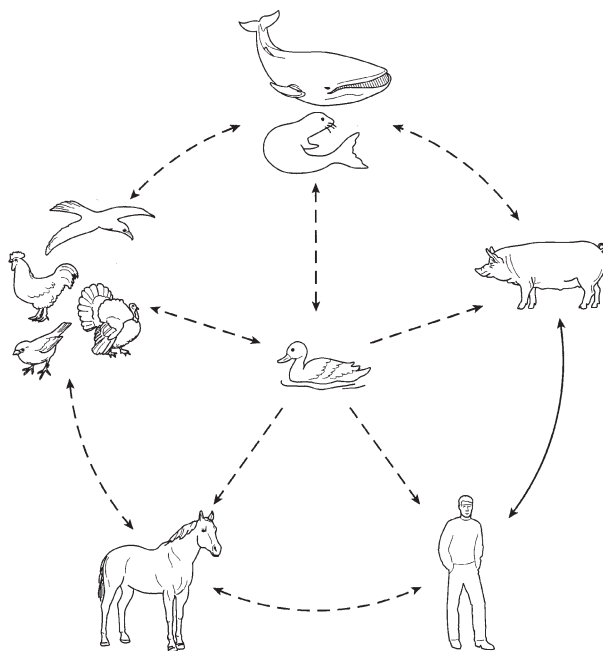
The importance of this process lies in the fact that type A, unlike type B, influenza is not an exclusively human infection. Only 3 different type A hemagglutinin subtypes—of the 15 that are recognized—have circulated widely in humans. A number of other animals, such as pigs or horses, can support the growth of influenza viruses, which have even been reported to have been isolated in seals and whales (Figure 4).

However, birds, especially aquatic waterfowl, harbor virtually all the different influenza viruses that have been recognized in nature. Today, scientists know that there are 15 different influenza A hemagglutinin subtypes and 9 different neuraminidases. Of these 9 neuraminidases, only 2 are currently found in humans. Unlike in the human situation, where the viruses are continually evolving and changing antigenically, influenza viruses are more stable and have a different relationship in their avian hosts. There, they replicate primarily in the gut and are shed in the feces, in a relationship that generally does no harm to the birds—although some examples of viruses from the H5 and H7 subtypes indicate the viruses can lead to lethal disease.

Birds that harbor influenza viruses provide a tremendous reservoir for influenza genes, which can lead to the development of new pandemic strains among humans. Studies documented this in the case of the 1957 pandemic virus, when an avian virus donated 3 genetic elements to that year's particular strain of virus, 2 of which encoded the new surface glycoproteins, the neuraminidase and the hemagglutinin. Then, in 1968, another such recombination occurred, with the sharing of 2 new genetic elements, 1 of which encoded a new hemagglutinin to create the subtype virus H3N2. Such recombinations constitute one of the mechanisms by which a new pandemic virus can be generated.¹¹

The situation in Hong Kong in 1997 presented a special case, in which an influenza A (H5N1) virus spread directly from a bird, or another animal, to humans.¹² Fortunately, in the case of this avian influenza, authorities destroyed all the domestic fowl in the live-bird markets in Hong Kong, stopping transmission of influenza virus from birds to humans. In that instance, 18 clinically recognized cases occurred in humans, one third of which resulted in death. This

Figure 4. Reservoir of Influenza A Viruses



The working hypothesis is that wild aquatic birds are the primordial reservoir of all influenza viruses for avian and mammalian species. Transmission of influenza virus has been demonstrated between pigs and humans (solid lines). There is extensive evidence for transmission between wild ducks and other species, and the 5 different host groups are based on phylogenetic analysis of the nucleoproteins (NPs) of a large number of different influenza viruses.

Source: Webster RG, Bean WJ, Gorman OT, Chambers TM, Kawaoka Y. Evolution and ecology of influenza viruses. *Microbiol Rev* 1992;56:152-157. Adapted with permission from the American Society of Microbiology.

was a lethal virus because the deaths occurred in non-high-risk individuals. Moreover, that virus lacked the properties for efficient person-to-person transmission that are necessary for it to become pandemic, but it demonstrates that if this virus had further adapted to its human host it could have developed into a new pandemic strain.

More recently, cases of another avian influenza caused by an H9N2-type infection have been seen in several children in Hong Kong. One concern is that if such viruses continue to circulate and cause infections in humans at the same time that conventional human viruses are also causing infection, then another recombination of genetic material could occur, resulting in the generation of a pandemic strain.

Another recent epidemiologic event was the appearance of the A/Sydney/5/97 (H3N2) virus in the 1997 to 1998 season. This virus originated in the Southern Hemisphere (its name reflects the fact that it was first isolated in Australia) after the vaccine for that year had already been formulated, so the vaccine antigen for the H3N2 component was a poor match for the circulating strain.¹³ As a result, vaccine efficacy was low, and numerous influenza outbreaks took place in nursing homes.

Influenza appears to be transmitted year-round in some areas of the tropics. Furthermore, researchers have recently recognized that in the Northern Hemisphere influenza viruses, though epidemic in the winter months, can also cause summer activity. Significant outbreaks among travelers occurred in Alaska and the Yukon Territory in the summers of 1998 and 1999.¹⁴ Outbreaks have occasionally occurred in chronic care facilities during the summer. Clinicians, especially those who care for individuals in nursing homes or other chronic care facilities, must recognize that if there is an outbreak of

febrile respiratory illness in the summer, it could be influenza.

Some of the data the CDC developed regarding outbreaks of influenza in chronic care facilities across the

“Influenza appears to be transmitted year-round in some areas of the tropics. Furthermore, researchers have recently recognized that in the Northern Hemisphere influenza viruses, though epidemic in the winter months, can also cause summer activity.”

United States were linked to circulation of the A/Sydney virus, a situation in which there was a poor match between the vaccine antigen and the circulating virus.¹³ Such outbreaks occurred in as many as 44% of institutions in Connecticut. In institutions that experienced outbreaks, the attack rate for influenza-like illness varied widely, but it reached nearly 50% of the residents in some nursing homes. In 3 well-characterized outbreaks of A/Sydney virus, influenza-like illness in those who were vaccinated occurred at rates of 22% to 49%. The estimated vaccine efficacy in patients in these 3 outbreaks was anywhere from -34% (in other words, worse than neutral) to 25% in aggregate. The vaccine afforded no significant antiviral protection in these patients, but it did appear to protect against death. Its efficacy in healthcare workers was also low, which is much different from the usual situation, where vaccine efficacy in healthcare workers typically ranges from 70% to 90%. This was another situation in which a current vaccine was a poor match for the epidemic strain and therefore, not very protective.¹³

Interpandemic Influenza Outbreaks

Interpandemic influenza has had a substantial epidemiologic and financial impact on the United States.

Annual outbreaks typically last 6 to 8 weeks, sometimes longer, as in 1998 and 1999, when both influenza A and influenza B viruses circulated. The

direct costs in medical care are large, with some estimates as high as \$3 to \$5 billion. However, this represents only about 30% of the total cost,

Table 5. Frequency of Visits for Acute Respiratory Disease for Members of an HMO During 2 Influenza Epidemics in Houston, 1981-1983

Age (years)	Weeks 3-12, 1982*		Weeks 2-11, 1983†	
	Visits for ARD	Visits for LRD	Visits for ARD	Visits for LRD
<5	1776 (26.6)	400 (6.0)	2542 (29.3)	464 (5.4)
5-9	1340 (21.5)	240 (3.9)	1150 (15.0)	153 (2.0)
10-19	1247 (11.8)	151 (1.4)	1106 (8.4)	105 (0.8)
20-34	2829 (10.1)	410 (1.5)	2686 (8.0)	357 (1.1)
35-44	999 (13.3)	188 (2.5)	1071 (10.0)	174 (1.6)
44-54	361 (10.2)	86 (2.4)	410 (8.7)	88 (1.9)
>55	212 (12.8)	63 (3.8)	175 (7.6)	39 (1.7)
Total	8764 (13.7)	1538 (2.4)	9140 (11.3)	1380 (1.7)

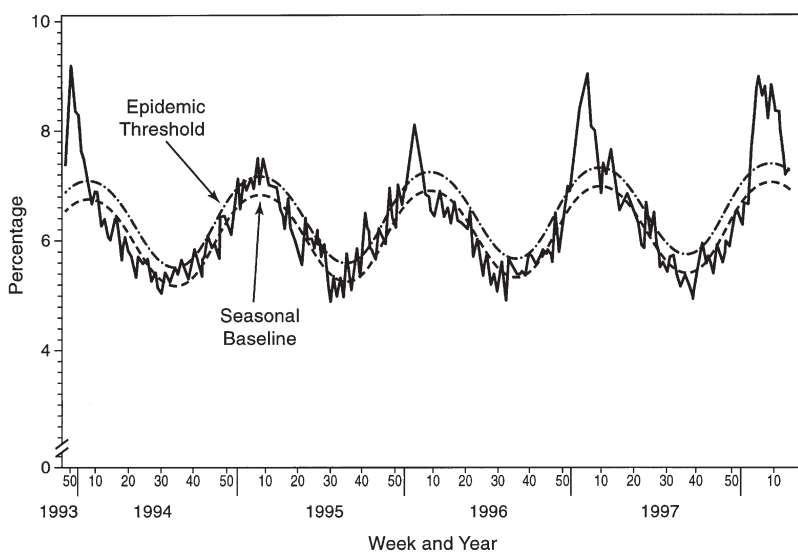
Data are number of visits (percentage of total number of patients in HMO in indicated age group); HMO = health maintenance organization; ARD = acute respiratory disease; LRD = lower respiratory-tract disease.

*Influenza B/Singapore; number of people in HMO: 64,062.

†Influenza A/Bangkok (H3N2); number of people in HMO: 80,707.

Source: Reference 15. Adapted with permission from the University of Chicago Press, Copyright 1989.

Figure 5. Weekly Pneumonia and Influenza Mortality as a Percentage of All Deaths in 122 Cities: United States, December 1993 through March 1998



Source: Update: Influenza activity - United States and worldwide, 1997-98 season, and composition of the 1998-99 influenza vaccine. *MMWR Morb Mortal Wkly Rep* 1998;47:280-284.

because time lost from work can be substantial. Total indirect costs would probably be closer to \$12 to \$14 billion per epidemic in the United States. Influenza not only puts a patient in bed for a few days, but it can also impair his or her performance for some days thereafter.

Influenza is spread primarily by droplets, particularly small particle aerosols. The initial site of infection is usually the lower respiratory tract, specifically the tracheobronchial tree, although infection of the upper respiratory tract can also be present. The incubation period averages 2 days, with a range of 1 to 4 days. Because of its respiratory spread and short incubation period, the influenza virus is capable of causing very explosive outbreaks of febrile respiratory illness.

Classic clinical symptoms include a rapid onset of fever, myalgia, malaise, a sore throat, and cough, which are usually debilitating for 2 or more days. On average, fever lasts for 3 days, although it can last for as long as 5, but cough and malaise may persist for several weeks. This typical flu syndrome accounts for only 20% to 30% of all such infections. Influenza can also cause common colds and other respiratory syndromes that do not exhibit the classic symptoms.

When influenza moves through a community, very discrete periods of increased visits to physicians for febrile

respiratory illness become evident. Data from Houston show the close temporal correspondence between circulating influenza viruses, which typically last about 6 to 8 weeks, and such visits. In some years, as many as 40% of all visits to physicians for febrile respiratory illness among adults occurred during this relatively brief period (Table 5).

The impact on practitioners, not only family physicians but also internal medicine specialists, can be substantial: more than half of all influenza-related consultations are sought by adults, and physician visits increase by 150% to 450% during influenza outbreaks. Although figures vary by country, roughly 40% of all influenza illness among teenagers and adults in the United States result in some kind of primary care physician contact.

CDC Monitoring of Influenza Activity

The Centers for Disease Control and Prevention has monitored influenza activity in this country for many years,¹⁶ with P&I mortality rapidly reported from 122 cities as a way of following the severity of outbreaks (Figure 5). During the 1997 to 1998 flu season, for example, the proportion of deaths attributed to P&I from those cities exceeded the epidemic threshold for 10 consecutive weeks, beginning with the week ending January 3, 1998. As the CDC's figures show, P&I mortality in those 122 US cities has gone beyond expected levels nearly every year; this is how outbreaks are timed.

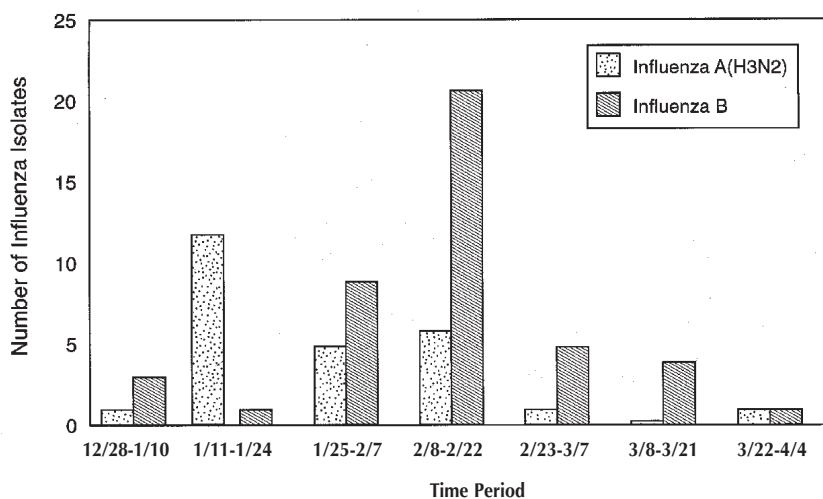
The 1998 to 1999 influenza season featured mixed activity, with both influenza A and B viruses involved and mixed according to each type's predominance in different regions of the country. Overall, influenza A viruses accounted for 80% of isolates and influenza B for 20% during that season. However, influenza B went from a low of 9% of isolates in the New England area to a high of 39% in the East-North Central and East-South Central

regions, so regional variations are significant. Figure 6 shows the situation in Michigan, where total co-circulation of type A and type B viruses during the outbreak is given. Such a situation would have been difficult to handle with a vaccine whose activity was limited to type A.

This mixture of influenza types, their regional predominance, and their unpredictability make using interventions such as amantadine or rimantadine difficult, because they are specific to influenza type A. At present, clinicians cannot distinguish whether an individual patient is experiencing type A or type B influenza on a clinical basis alone.

Both type A and type B influenza viruses cause significant morbidity and mortality every year. Influenza vaccine has shown significant usefulness in preventing complications and death, and clinicians should encourage greater use of it. However, there continues to be unmet needs in the field of influenza prophylaxis, and new interventions, such as improved drugs and vaccines, will be valuable additions to clinicians' annual efforts against influenza.

Figure 6. Isolates for Influenza A and B in Michigan, 1998 to 1999



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