ABSTRACT

Morbidity and mortality attributable to viral influenza appears to be increasing, particularly in preschool- and school-age children. The potential for a major influenza epidemic is increasing because of a confluence of demographic changes, antigenic shift and mutation, and low uptake of influenza vaccine, particularly among high-risk children. A comprehensive immunization strategy should target children who are 5 years of age and younger, pregnant women, and other populations identified as being at increased risk for influenza.


Advances in the diagnosis and treatment of infectious diseases have yet to eliminate the morbidity and mortality burden posed by influenza. In the United States, mortality attributable to influenza remains at about 30,000 deaths per year. Pneumonia hospitalizations among the elderly increased by more than 50% between 1985 and 1995, from 400,000 annually to 685,000, and a large proportion of these are due to influenza virus infection. Worldwide, infections of the lower respiratory tract, including influenza, rank first among causes of disability, accounting for the loss of almost 97 million disability-adjusted life-years and almost 4 million deaths annually (Table 1).

In the United States, the potential exists for the burden of influenza to increase dramatically in the future. Over the next 20 years, a growing number of individuals from the baby-boom generation will cross the age threshold of 65 years, greatly expanding the population at increased risk for influenza morbidity and mortality. The Centers for Disease Control and Prevention (CDC) estimates that the number of deaths attributable to influenza will reach 65,000 by 2020 if no advances are made to improve the control of influenza. Problems presented by the increase in the population of aging Americans will add to the toll influenza already exacts from the most vulnerable population of all, children younger than 5 years of age.

Another reason for concern comes from evidence that influenza has barely scratched the surface of its infectious potential. The hemagglutinin and neuraminidase surface antigens of the influenza virus have thus far had minimal expression in humans. For example, only 3 of 15 known hemagglutinin glycoproteins have been associated with influenza infection in humans. The remaining 12 identified hemagglutinins continue to circulate in avian species. The possibility that some or all of these avian antigens could eventually affect humans deserves serious consideration.

Despite current concerns for the potential damage that can be inflicted by viral influenza, this infection can be prevented. Vaccines with proven efficacy already exist, and ongoing vaccine development should lead to increasingly effective aids to combat the influenza threat. However, the vaccines currently are greatly underused. Extending the use of these vaccines, particularly in populations at increased risk for

*This article is based on a presentation at the 2001 American Academy of Pediatrics National Conference and Exhibition.
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influenza infection, is an important challenge for physicians to accept.

**Virus Origins**

Appreciation of the risk that influenza virus poses begins with an understanding of how viruses make the transition from avian species to humans. As stated previously, only 3 of 15 known hemagglutinin surface antigens on influenza virus have infiltrated the human population. The primary reason for the lack of penetration has been the preference of the hemagglutinin antigens for receptors in the airway epithelium of birds, primarily involving sialic acid moieties present on the respiratory mucosa. That single factor offers a thin barrier of protection for humans.

The classic explanation for the transition from avian to human populations is that the antigen first adapts to an intermediate mammalian host, such as swine, before it is capable of infecting humans. The intermediate host allows for adaptation or mutation of these viruses. For example, swine have receptors for both avian and human viruses, creating the possibility for reassortment of the 2 types of viruses so that the progeny may have new surface antigens of the avian virus but the internal genome of a human virus.

Another possible explanation relates to viral adaptation. A virus may adapt to receptors in swine and in the process acquire the ability to infect humans. A more disturbing possibility is that avian viruses infecting humans may undergo reassortment directly with human viruses, allowing the virus to spread from person to person. Concern about such a scenario played a key role in the decision in 1997 to eradicate Hong Kong poultry flocks infected with avian virus A (H5N1). Public health officials had a valid reason for concern, as the poultry infection arose when Hong Kong was approaching the time of year during which human viruses circulated with increased frequency in the population. No one wanted to take the chance that humans could be infected simultaneously with avian and human viruses, allowing reassortment of viral genomic information.

Still another possibility is that frequent exposure to avian viruses within a specific human population might create an environment whereby an avian virus mutates and takes on characteristics that allow the virus to spread from human to human. The potential for this possibility was realized in 1976, when an infectious agent with all the characteristics of a swine virus spread through Fort Dix, New Jersey. While this type of virus would typically affect only swine caretakers, if any humans at all, it had mutated to the point of being able to be transmitted from human to human. This case should serve as a reminder of the possibility that repeated exposure to an animal virus within a human population eventually may provide the virus with an opportunity to acquire the ability to spread from human to human.

Fortunately, scenarios described above occur rarely, as indicated by the fact that only 3 of the 15 avian hemagglutinin antigens have achieved expression in humans. Nonetheless, the potential for this type of antigenic shift provides ample reason for continued diligence in the monitoring of viruses that do not currently infect humans.

**Mortality Potential of a Pandemic**

The influenza pandemic of 1918 to 1920 was the worst ever to strike the United States. The pandemic offers a glimpse of a worst-case scenario, as the table below illustrates the leading causes of disability—adjusted life-years (DALYs) for the world, 1999.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Cause</th>
<th>DALY's (x1000)</th>
<th>Deaths (x1000)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Lower respiratory tract infections</td>
<td>96 682</td>
<td>3963</td>
</tr>
<tr>
<td>2</td>
<td>Human immunodeficiency virus</td>
<td>89 819</td>
<td>2673</td>
</tr>
<tr>
<td>3</td>
<td>Perinatal conditions</td>
<td>89 508</td>
<td>2356</td>
</tr>
<tr>
<td>4</td>
<td>Diarrheal diseases</td>
<td>72 063</td>
<td>2213</td>
</tr>
<tr>
<td>5</td>
<td>Depression, major unipolar</td>
<td>59 030</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>Ischemic heart disease</td>
<td>58 981</td>
<td>7089</td>
</tr>
<tr>
<td>7</td>
<td>Vaccine-preventable diseases</td>
<td>54 638</td>
<td>1554</td>
</tr>
<tr>
<td>8</td>
<td>Cerebrovascular diseases</td>
<td>49 856</td>
<td>5544</td>
</tr>
<tr>
<td>9</td>
<td>Malaria</td>
<td>44 998</td>
<td>1086</td>
</tr>
<tr>
<td>10</td>
<td>Nutritional deficiencies</td>
<td>44 539</td>
<td>493</td>
</tr>
</tbody>
</table>

infection spread uncontrolled because no one knew what was causing it at that time. The end result was 675,000 deaths, which translates into a crude mortality rate about 200/100,000. The pandemic was especially devastating because of the population it struck. More than 40% of the deaths occurred in healthy young adults between 20 and 39 years of age. Roughly 1% of the US population in that age group died in 1918 during the first wave of the pandemic. Another sobering thought is that the mechanism for the virulence of the 1918 virus has still not been determined. Despite the fact that viral nucleic acids were obtained from autopsy specimens and from exhumed bodies of people who died in 1918, the explanation for the virulence in young adults has not been found.

Although the influenza pandemic of 1918 to 1920 was by far the worst ever to affect the United States, it was not the only pandemic to cause substantial morbidity and mortality. Between 1957 and 1960, the A (H2N2) pandemic resulted in 115,700 deaths, and another in 1968 to 1972 caused by A (H3N2) claimed almost 112,000 lives.

Interpandemic periods illustrate more typical years of influenza activity. Immediately following the 1918 pandemic, the crude mortality associated with influenza declined dramatically from almost 220/100,000 to about 23/100,000 during the period of 1920 to 1933, and the number of influenza-related deaths for the entire period was 368,400—fewer than 30,000 per year. From 1933 until the 1957 pandemic, influenza mortality declined even further to a ratio of 7.5/100,000, with about 10,000 total deaths per year. After a period of a higher influenza-associated mortality rate of 22/100,000 resulting from the 1957 to 1960 pandemic, the influenza-associated mortality declined again to 14,363 deaths, or 7.5/100,000 population. A similar rise and fall occurred during and after the pandemic of 1968 to 1972. Current mortality rates are about 10 per 100,000 with average annual numbers at 30,000 per year (Table 2).

The cause of the waxing and waning of influenza virulence remains unknown. While antigenic shift probably plays a role, this phenomenon occurs infrequently. Viral surface glycoproteins continually acquire mutations, which regularly influence attack rates and virulence. Mutations involving as few as 2 amino acid changes can substantially alter hemagglutinin antibody receptor sites, allowing the virus to escape prevalent antibodies. This subtle variation is usually termed “antigenic drift” and creates the need to update influenza vaccine annually.

To put the problem of antigenic drift into context, consider that between 1968 and 2000, 20 influenza epidemics occurred in the United States that were associated with 16 different variants of influenza A (H3N2). Each of these variants necessitated vaccine changes. Further context for the importance of antigenic variation comes from the realization that most of the influenza mortality over the past 33 years occurred during the H3N2 epidemics.

Another example of the role that antigenic variation plays in influenza infection comes from collaborative investigations with the CDC. Viral specimens were obtained from sequential infections among Houston families involved in a longitudinal study of influenza. Investigators have sequenced the hemagglutinin of viral pairs that were typically obtained from individuals at 2-year intervals. Comparing hemagglutinin amino acid changes associated with the primary infection and reinfection, the number of changes ranged between 9 and 22 in 6 pairs of viruses recovered from 6 different individuals. In most cases, the changes affected the essential antibody-combining sites on hemagglutinin. This type of antigenic varia-

<table>
<thead>
<tr>
<th>Period</th>
<th>Years</th>
<th>No. of excess Death</th>
<th>Annual Average</th>
<th>Crude rate/100,000</th>
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</thead>
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<td>675 000</td>
<td>225 000</td>
<td>218.4</td>
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<tr>
<td>Interpandemic</td>
<td>1920-1933</td>
<td>368 400</td>
<td>28 338</td>
<td>23.0</td>
</tr>
<tr>
<td>Interpandemic</td>
<td>1933-1957</td>
<td>242 600</td>
<td>10 108</td>
<td>7.5</td>
</tr>
<tr>
<td>Pandemic</td>
<td>1957-1960</td>
<td>115 700</td>
<td>38 567</td>
<td>22.0</td>
</tr>
<tr>
<td>Interpandemic</td>
<td>1960-1968</td>
<td>114 900</td>
<td>14 363</td>
<td>7.5</td>
</tr>
<tr>
<td>Pandemic</td>
<td>1968-1972</td>
<td>111 927</td>
<td>27 982</td>
<td>13.9</td>
</tr>
<tr>
<td>Interpandemic</td>
<td>1972-1981</td>
<td>198 800</td>
<td>22 089</td>
<td>10.3</td>
</tr>
<tr>
<td>Interpandemic</td>
<td>1981-1991</td>
<td>c. 200 000</td>
<td>20 000</td>
<td>10.0</td>
</tr>
</tbody>
</table>

*Preliminary estimates
tion confers on viruses the ability to reinfect persons to cause multiple sequential epidemics.

**Current and Future Mortality Trends**

Recognition of the potential for antigenic shift and drift has come at a time when infectious disease mortality appears to be increasing, particularly influenza mortality. Between 1972 and 1984, the number of deaths associated with influenza averaged 15,542 annually. Beginning in 1984, the number of influenza-attributable deaths almost doubled to an annual average of 29,900.1

The recent rise in mortality associated with influenza has occurred against the backdrop of a major demographic shift in the United States, providing more reason for concern. The proportion of individuals 65 years of age and older, one of the most vulnerable to influenza infection, is increasing rapidly with the aging of the baby-boom generation. Not only is the 65-and-older age group expanding, Americans are living longer, with the population of individuals 80 years of age and older one of the fastest growing in the United States.

The expansion of the vulnerable elderly population is expressed by the change in hospitalization rates. Between 1985 and 1995, the number of pneumonia hospitalizations increased from 400,000 to 685,000 among people ≥65 years of age whose numbers increased from 28.4 million to 35.5 million.2 The increase in hospitalization rates is not explained entirely by aging of the population. Stratifying hospitalization rates by age explained only half of the increase. The remainder is thought to be related to increasing severity of influenza epidemics.

More evidence comes from data showing that lower respiratory tract infections are the leading cause of disability worldwide, surpassing human immunodeficiency virus infection, ischemic heart disease, and several other conditions that have better-known reputations for causing disability. Notably, vaccine-preventable diseases rank in the worldwide morbidity top 10, just behind ischemic heart disease.3

**Influenza Threat to Children**

Along with the elderly, the youngest members of society have an increased vulnerability to influenza infection. Surveillance from several health care facilities illustrate that point and provide additional context for the current status of influenza-related infection in the United States.

During 1998 to 1999, an epidemic of influenza A (H3N2) affected many communities, including Houston, Texas. At the Baylor College of Medicine-affiliated pediatric facility, Texas Children's Hospital (TCH), the hospitalization rate for children younger than 6 months of age was 163/10,000. Expanding the age group to all children younger than 1 year of age, the influenza-related hospitalization rate was even higher; 177/10,000. The hospitalization rate declined in populations older than 1 year of age. However, the overall rate for children younger than 5 years of age was 83.1/10,000, which is greater than the hospitalization rate for the elderly in some years.8 At the very least, young children must be viewed as having the same susceptibility to influenza morbidity as that seen in elderly adults. A further consideration is that the patient population at TCH does not have the high frequency of chronic underlying conditions typically associated with the increased vulnerability to infection often seen in the elderly, which may indicate that this naïve patient group is actually more susceptible to influenza morbidity than adults with chronic underlying conditions.

Experience in a pediatric Medicaid population offers another example of disease burden in children.9 Age-specific hospitalization rates for influenza, expressed in terms of 10,000 person-years, ranged from a high of 538 in children younger than 6 months of age to 25 in children between the ages of 5 and 15 years. The figures are consistent with those reported from TCH and other facilities. Notably, the study of pediatric Medicaid patients excluded those who had high-risk conditions; therefore, the data underestimate the total influenza burden but provide an accurate picture of the morbidity in normal, healthy children.

For high-risk children, particularly those with asthma, in the same Medicaid population, the overall hospitalization rate of 222/10,000 was considerably higher than for healthy children in the same age group.10 Influenza is an important trigger for asthma attacks and asthma-related hospitalization. Over a 4-year period, influenza infection was associated with 21% of all hospitalizations of school-aged children, with three fourths of those influenza-related hospitalizations involving patients with asthma.11 Given the increasing mortality and hospitalization rate among
children with asthma, adequate coverage with influenza vaccine should have high priority.

Compared to the general population, preschool- and school-age children are at high risk for influenza infection. Data from the Houston Family Study show that children between 6 and 10 years of age have about a 50% chance of infection each year. Compared to the general population, preschool- and school-age children are at high risk for influenza infection. Data from the Houston Family Study show that children between 6 and 10 years of age have about a 50% chance of infection each year. A field study conducted in the central Texas communities of Temple and Belton provides further evidence of the influenza risk faced by children. Comparing rates for office visits during an 8-week period of the 1997 to 1998 influenza epidemic with an 8-week summer period (during which the risk for infection is low), the investigation showed the influenza-attributable rate of visits of 25 per 100 among children younger than 5 years of age and 15 to 16 per 100 in children ages 5 to 11 years.

The burden of influenza is not limited to the infection in the respiratory tract, as influenza is often complicated by other conditions or produces sequelae that can have potentially devastating consequences. In children, these complications include febrile convulsions, myositis, Reye syndrome, encephalopathy, pericarditis, and myocarditis. The risks posed by these serious problems further reinforce the need to increase coverage with influenza vaccine.

**Benefits of Vaccination**

Considerable evidence supports the beneficial effect of immunization against influenza. The benefits often come not from immunization of vulnerable individuals but from immunization of their necessary contacts—other members of the household, the caregivers, or other social contacts.

An evaluation of community-wide immunization in the late 1960s offers an example of how widespread vaccination can reduce influenza risk. The study involved children in the neighboring communities of Tecumseh and Adrian, Michigan. In this study, about 85% of school children in Tecumseh were immunized against influenza, while Adrian served as a comparison population for which no special measures were taken to increase immunization rates. For all age groups, illness rates were substantially lower for individuals living in Tecumseh than those living in Adrian. Notably, vaccination of children in Tecumseh conferred substantial influenza protection to nonimmunized adults in the community. This demonstrates the indirect effort (and immunity) of influenza vaccine.

The Michigan results were essentially replicated in a study conducted in Australia. When a portion of the community was immunized, the rate of illness was significantly lower for both children and adults in the community than in communities where no vaccine was given. A study of immunization among Russian schoolchildren showed substantial influenza protection of teachers, staff, and other adults at the schools when at least 50% of the student population received influenza vaccine. A recent study from the CDC showed that immunization of preschool-age children in day care resulted in some degree of protection from influenza infection in school-age siblings.

A study from the United Kingdom illustrates the impact influenza immunization can have in vulnerable elderly populations. In contrast to the studies of immunization in schoolchildren, the UK investigation focused on the impact of immunizing caregivers in a nursing home. The result was a substantial reduction in influenza-attributable morbidity and mortality among the nursing home residents. The study raises an important issue: because many high-risk patients have suboptimal responses to influenza vaccine, debilitated patients are best protected by immunization of their contacts.

Beginning in 1962, influenza vaccination was recommended for schoolchildren in Japan. Between 1977 and 1987, influenza vaccination was mandatory for school attendance. The mandate was associated with a substantial decline in total excess mortality attributable to influenza. Beginning in 1988, immunization was left to the discretion of parents, and the immunization program was discontinued altogether in 1994. Predictably, influenza-attributable mortality increased to pre-1977 levels after immunization was discontinued. Japan currently finds itself in a difficult position because its vaccine manufacturers stopped production of influenza vaccines when the school immunization program was discontinued.

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The cause of the waxing and waning of influenza virulence remains unknown. While antigenic shift probably plays a role, this phenomenon occurs infrequently.
Despite the abundance of evidence favoring influenza immunization, uptake of influenza vaccine remains low, particularly among high-risk children, such as those with asthma and other conditions that predispose them to influenza complications. Immunization rates also are low among pregnant women, although this population is in the unique position of being able to provide protection to their newborn children through passive immunization. This protection persists for the first 3 to 6 months of life.

**Conclusion**

Influenza virus infection poses a significant risk for morbidity and even mortality in all age groups, although the risks are particularly high for otherwise healthy children 5 years of age or younger. For this young population, the influenza hospitalization rates exceed those of high-risk adults. Protection of children begins with immunization of pregnant women who will deliver during or just prior to influenza season. Children with chronic conditions, such as asthma, have the lowest uptake of influenza vaccine among all risk groups. Immunization of children against influenza could provide the added bonus of reduced spread of the illness in the household and in the community.

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**REFERENCES**