ABSTRACT

Seasonal influenza is a significant cause of morbidity and mortality, measured in terms of illness, loss of days from school or work, hospitalizations, and death. The best means to limit that impact is prevention through vaccination, the use of nonpharmacological interventions, and, in some settings, the use of prophylactic treatment with antiviral medications. Healthcare workers (HCWs) with influenza that is symptomatic or asymptomatic can become a vector for transmission of infection to others, yet vaccine acceptance nationwide among HCWs is only 42%, thus efforts to prevent nosocomial transmission of seasonal influenza in hospitals are essential. Antivirals, including oseltamivir and zanamivir, are both effective in preventing influenza infection and in reducing the duration of symptoms and secondary disease transmission in families when administered within 48 hours of symptom onset. During the “Spanish Flu” pandemic of 1918 to 1919, as many as 500,000 individuals in the United States became infected, and between 50 and 100 million individuals died worldwide. Most of the 322 reported cases of H5N1 influenza among people to date have been teenagers or young adults. If H5N1 influenza mutates so that it is easily spread from person to person, and if it drives a pandemic that is the equivalent of the 1918 pandemic in terms of morbidity and mortality, meeting the needs of pandemic influenza patients in the United States would require twice the numbers of hospital beds and ventilators, and nearly 5 times the intensive care unit capacity, than are currently available. Guidelines for pandemic planning describe the components of a comprehensive plan to manage influenza, should a pandemic develop. (Adv Stud Med. 2007;7(11):331-349)

SEASONAL INFLUENZA: EPIDEMIOLOGY AND CLINICAL PRESENTATION

Influenza is a respiratory illness that may lead to serious complications or death. The highest illness rates occur among school-age children, but approximately 20% of all adults are also affected (Figure 1).1

The clinical presentation of influenza differs by age (Figure 2). Adults and adolescents are most likely to present with fever, chills, cough, headache, sore throat, and myalgia.2 Common physical signs of influenza infection include fever, flushed face, hyperemic mucous membranes, and nasal discharge. However, in children, influenza may present as gastrointestinal symptoms, such as nausea, vomiting, abdominal pain, and diarrhea. Elderly patients may initially have only high fever or cough.2,3

THE IMPACT OF SEASONAL INFLUENZA

The impact of seasonal influenza can be measured on both an individual and institutional level. Individuals may feel the impact from mild illness, as...
the average adult loses 2.8 days of work due to influenza annually, and those that continue to work are less effective at their jobs. The personal impact is especially high if complications develop. For example, up to 45% of young children with influenza may develop otitis media. As many as 17% of adults and adolescents develop secondary bacterial infections that require treatment with antibiotics.

Influenza or its complications are reportable to public health authorities in most states in the United States. Data derived from laboratory-reported cases of influenza from individual health departments is concatenated by the Centers for Disease Control and Prevention (CDC) weekly from October through May during the influenza season (Figure 3). Although influenza peaks during the influenza season from November to March each year, the disease occurs year round.

Between October 2006 and May 2007, there were 23,753 laboratory-confirmed cases of seasonal influenza reported to the World Health Organization (WHO) and National Respiratory and Enteric Virus Surveillance System collaborating laboratories in the United States. Four-fifths (79%) of specimens tested were influenza type A, and 21% were type B. Based on the most commonly circulating strains, the US Food and Drug Administration (FDA) recommended only a slight change to the influenza A (H1N1) component of the trivalent influenza vaccine; the influenza A (H3N2) and influenza B components of the vaccine did not change.

**Figure 2. Symptoms of Clinical Influenza by Age Group**

<table>
<thead>
<tr>
<th>Sign/Symptom</th>
<th>Children</th>
<th>Adults</th>
<th>Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough (nonproductive)</td>
<td>++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Fever</td>
<td>++++</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Myalgia</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Headache</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Malaise</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Sore throat</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Rhinitis/nasal congestion</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Abdominal pain/diarrhea</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>++</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

Children are more likely to present with gastrointestinal symptoms than are adults or the elderly.

++ = most frequent sign/symptom; + = least frequent; – = not found.

Data from Cox and Subbarao; Monto et al.

**Figure 3. Influenza Cases Sent to the US/WHO Laboratory 2006–2007**

[Graph showing influenza cases by week and year with different influenza strains depicted.]

Laboratory-confirmed influenza data collected during the entire year, including the peak influenza season, in the US, 2006–2007.

The magnitude of the economic impact of seasonal influenza each year is huge (Figure 4). In particular, seasonal influenza leads to up to 500,000 hospitalizations, which last an average of 5 days, and for which hospitals typically recoup only 66% of their costs because influenza care is typically reimbursed by insurance companies at a lower rate than surgical procedures are (Figure 5).

Determining whether a surge in hospitalizations is due to true influenza or other illnesses is difficult. There are approximately 226,000 hospitalizations due to pneumonia and influenza per year; a large proportion of these hospitalizations are in the elderly. Physician and emergency department visits tend to increase during the peak influenza season. Based on laboratory-confirmed influenza, during interim periods between influenza seasons, approximately 8.75% of all physician visits are due to respiratory complaints compared to 17.7% of all visits during peak influenza season. For every 100 cases of influenza in a community, ambulance and emergency room (ER) diversion increased by approximately 2.5 hours a week in an average ER.

Glezen and Couch looked at the impact of an influenza outbreak on healthcare resources (Figure 6). The number of isolations of influenza A from January through March in the Houston area is shown on the bottom of the graph on the left. Above that is the percentage of ER visits that were due to respiratory complaints. The surge in emergency department visits corresponds with the surge in influenza cases. The graph on the right shows a similar correspondence between the influenza surge and hospital admissions due to pneumonia in the pediatric and adult populations. Pediatric admissions surged prior to adult admissions, indicating that children are the vectors of influenza spread in adults. This increase in admissions is occurring in the face of declining numbers of ERs and hospital beds nationwide.

Figure 7 illustrates data from the New Vaccine Surveillance Network, which is a prospective

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**Figure 4. Impact of Epidemic Influenza in the United States**

| Cases: | 25–50* million cases |
| Days of illness: | 100–200 million days |
| Work and school loss: | Tens of millions |
| Hospitalizations: | 85 000–550 000* |
| Deaths: | 34 000†–51 000‡ |
| Costs: | Billions of dollars |

Epidemic influenza continues to have a huge annual impact.

Data from Thompson et al8; Adams et al10; Bridges et al11.

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**Figure 5. Impact of Influenza: Costs of Seasonal Influenza**

- Average length of stay: 5.32 days
- Average total hospital charges: $15 135
- Average total hospital cost: $6527
- Average total hospital reimbursed amount: $4332


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**Figure 6. Impact of Influenza: Healthcare Visits Houston, 1978**

laboratory-based surveillance network in Rochester, Cincinnati, and Nashville. Among children aged 5 years or younger, 50 visits per thousand children were attributable to laboratory-confirmed influenza during a mild season (2002–2003) compared to 95 visits per 1000 children during a severe season (2003–2004). The estimated number of outpatient visits due to influenza in this population per thousand children ranged from 357 to 711, with a similar pattern seen for emergency department visits. These data were primarily responsible for the broadening of national recommendations to vaccinate children up to 5 years of age.

The current Advisory Council for Immunization Practices (ACIP) recommendations are to prioritize providing influenza vaccine to 218 million people (72.7% of US population), including children 6 months to 59 months old, adults older than 50 years, high-risk individuals 5 years to 49 years of age, pregnant women, healthcare workers (HCWs)/caregivers, and household contacts of children younger than 5 years.

Another way to measure the burden of influenza is from statistics about mortality from influenza or pneumonia. Seasonal influenza causes approximately 36,000 deaths in the United States annually. Influenza may exacerbate chronic respiratory and cardiovascular diseases, but death certificates (which are used to collate mortality statistics) ascribe the primary cause of death as the underlying illness, not influenza. Thus, the burden of influenza may be underestimated.

**Impact of Seasonal Influenza on the Workforce**

Absenteeism is of particular concern in the healthcare field, as staff shortages may compromise patient care. Presenteeism, the opposite problem, occurs when individuals come to work even though they are sick. Individuals exposed to influenza virus experimentally shed virus within 24 hours of inoculation (Figure 8). Assuming this process occurs with naturally acquired influenza infections, HCWs with early, asymptomatic influenza may thus become a vector for transmission of infection to patients, visitors, and other staff. One study found that 76.6% of HCWs came to work with an influenza-like illness, and they worked a mean of 2.5 days while sick.

Nosocomial outbreaks of influenza have been documented on general medical, organ transplant, oncol-

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**Table:**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Visits for Acute Respiratory Tract Infection or Fever Associated with Confirmed Influenza</th>
<th>Mean Rate of Visits for Acute Respiratory Tract Infection or Fever, 1998–2002</th>
<th>Estimated Rate of Visits Attributable to Influenza</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient clinics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–5 mo</td>
<td>4.6 (0.1–15.5)</td>
<td>9.7 (4.0–19.0)</td>
<td>611 (428–794)</td>
</tr>
<tr>
<td>6–23 mo</td>
<td>7.3 (4.0–11.9)</td>
<td>17.5 (12.8–23.1)</td>
<td>711 (555–869)</td>
</tr>
<tr>
<td>24–59 mo</td>
<td>14.9 (4.0–11.9)</td>
<td>24.8 (19.0–23.1)</td>
<td>357 (277–437)</td>
</tr>
<tr>
<td>0–59 mo</td>
<td>10.2 (7.5–13.6)</td>
<td>19.4 (16.0–23.1)</td>
<td>489 (387–591)</td>
</tr>
<tr>
<td>Emergency departments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–5 mo</td>
<td>0.0 (0–4.1)</td>
<td>18.2 (11.8–26.2)</td>
<td>127 (95–159)</td>
</tr>
<tr>
<td>6–23 mo</td>
<td>5.5 (2.6–10.2)</td>
<td>26.2 (20.9–32.1)</td>
<td>150 (127–173)</td>
</tr>
<tr>
<td>24–59 mo</td>
<td>11.4 (6.0–19.1)</td>
<td>39.0 (32.0–46.4)</td>
<td>60 (49–71)</td>
</tr>
<tr>
<td>0–59 mo</td>
<td>5.9 (3.7–8.9)</td>
<td>28.8 (25.0–32.7)</td>
<td>94 (78–110)</td>
</tr>
</tbody>
</table>


ED = emergency department.

ogy, and pediatric units, in neonatal intensive care units, and in long-term care facilities. The incidence of nosocomial influenza has been measured as 3 per 1000 admissions, but this rate may be an underestimate. As lengths of stay get shorter at hospitals, individuals may get exposed to influenza in the hospital but do not develop respiratory illness until after discharge. Data from these cases are not captured as nosocomial infections.

These data highlight the importance of ensuring that the hospital workforce be vaccinated against the seasonal influenza each year to minimize both staff absenteeism and the risk of nosocomial spread from staff to patient. The ACIP recommends that all HCWs be vaccinated annually against influenza, yet vaccine acceptance nationwide among HCWs is only 42%. Hospitals should provide vaccination free of charge in-hospital and during all shifts to ensure uptake and minimize nosocomial infections. One 600-bed hospital provided influenza vaccinations to HCWs using a mobile cart, and vaccination rates increased from 4% in 1987 to 1988 to 67% in 1999 to 2000 ($P < .0001$). Proportions of nosocomial-acquired influenza cases among employees or patients both declined significantly ($P < .0001$).

As of January 1, 2007, the Joint Commission on the Accreditation of Healthcare Organizations requires that hospitals offer influenza vaccinations to all HCWs who have close patient contact and report HCW vaccination rates as part of the accreditation process. Other professional organizations, including the Healthcare Infection Control Practices Advisory Committee (HICPAC), the ACIP, and the Society for Healthcare Epidemiology of America (SHEA), have officially recommended that all healthcare personnel be vaccinated annually against influenza.

**TRANSMISSION AND PREVENTION OF SEASONAL INFLUENZA**

For an influenza virus to spread sufficiently to cause an outbreak there must be a chain of infection—an infectious virus, a susceptible host, and a method of transmission. In humans, influenza is transmitted via respiratory droplets released during coughing or sneezing, from one person to another who may be up to 3 feet away. Or someone may touch a porous surface that is contaminated with influenza virus and transmit the virus to mucous membranes in the eyes, nose, ears, or mouth. Thus, an effective method of preventing transmission of influenza is frequent hand washing. In addition, nurses/physicians treating influenza patients should use droplet precautions for the duration of the patients’ illnesses. Droplet precautions involve placing the patient in a private room, wearing a mask when working within 3 feet of the patient, and having the patient wear a mask when being transported within the hospital.

**IMMUNOPROPHYLAXIS: SEASONAL INFLUENZA VACCINATION**

In the United States, 2 types of influenza vaccines are available for immunoprophylaxis. Trivalent inactivated influenza vaccine is administered as an injection, and approved for all individuals 6 months of age and older. Live attenuated influenza vaccine is administered nasally, and is approved for healthy individuals 5

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**Figure 8. Viral Shedding in Experimental Influenza**

Oseltamivir (100 mg once or twice daily) was dispensed to 24 healthy adults; 12 controls received placebo. All participants were then inoculated with H1N1 influenza virus 26 hours later. Viral titers in oseltamivir-treated patients dropped to undetectable levels within 36 hours.

*Viral shedding: mean 107 hours.
Vaccines for seasonal influenza include 3 strains (2 of influenza type A and 1 type B) and are reformulated each year in an attempt to match the most commonly circulating viral strains. The number of influenza cases at Johns Hopkins Hospital from 2000 to 2007 is shown in Figure 9. If the annual influenza vaccine matches the subtypes that are circulating, the pattern of the line graph (the epidemiological curve) can be used to anticipate the likely pattern of influenza cases for the upcoming year. The dotted lines of the graph for 2004 to 2005 illustrate what happened when the annual influenza vaccination did not match the circulating influenza subtypes well.

Vaccinating children in a community against seasonal influenza has the potential to confer herd immunity (Table 1) on the entire population. This phenomenon happens because children have the highest attack rates for influenza, and play an active role in introducing influenza into the household and the community at large.

One study carried out at 2 sites in Moscow, Russia, provided proof of the concept that if the majority of school children were vaccinated against influenza, the entire population would develop herd immunity. Investigators immunized 57% of preschool children and 72% of school children against influenza. They subsequently compared rates of influenza and complications in unvaccinated community-dwelling adults 60 years of age and older (Figure 10). Fewer than 1% of elderly adults in the intervention and control communities were vaccinated against influenza because of a shortage of influenza vaccination during the study period. The rates for influenza-like illness, pneumonia, asthma, and bronchitis in adults older than 60 years were significantly lower at the intervention site than at the control site. Only a minuscule percentage of elderly adults developed an influenza-like illness—.07% in the intervention group and .24% in the control group (P <.01). Most children lived in 3-generation households, thus the grandparents had direct contact with the children who were immunized during the program. The 28 000 doses of vaccine that were administered not only protected 64% of the children from developing influenza, but also protected the 82 000 high-risk individuals older than age 60 who were not immunized.

Influenza vaccines generate optimal immune responses in healthy school children and working adults. Thus, one way to maximize “herd immunity” is to eliminate barriers to vaccination of school children and working adults by establishing school- or workplace-based vaccination clinics. Similarly, vaccinating a majority of HCWs in a hospital against influenza would subsequently help protect at-risk, hospitalized patients.

Elderly individuals, particularly African Americans, do not mount as effective an immune response to influenza vaccination as do younger individuals. Although vaccination may not prevent influenza in nursing home residents, among those who were vaccinated, rates of pneumonia, hospitalization, and death from respiratory illness were reduced approximately 50% in nursing home residents who were vaccinated.
Antiviral Medications

There are 2 classes of antiviral medications available in the United States for treatment of seasonal influenza (Table 2). One class, to which amantadine and rimantadine belong, targets the M2 protein channels in the influenza virus. On the recommendation of ACIP, neither amantadine nor rimantadine were used for prophylaxis or treatment during the 2005 to 2006 and 2006 to 2007 influenza seasons, although these drugs had been widely used for prophylaxis in earlier years because of evidence that more than 90% of influenza virus circulating in the United States had developed resistance to these drugs.22

Another class of antiviral medications, the neuraminidase (NA) inhibitors, which includes oseltamivir and zanamivir, is most effective when given early in the infection, and all benefit is largely gone once symptoms have been present for more than 48 hours. When administered within 12 hours of symptom onset, oseltamivir reduces the duration of illness by an average of 3 days.32 When administered within 48 hours of symptom onset, oseltamivir and zanamivir reduce both the duration of influenza symptoms by 1 to 2 days and secondary disease transmission in families.33-36 Oseltamivir reduces the duration of fever by 1 to 2 days and acute otitis media in children by 44%.37,38 Zanamivir reduces antibiotic use by approximately 30%.6

Although there is evidence that oseltamivir is effective in preventing flu pneumonia in patients treated early enough, there is no evidence that antivirals are effective in treating patients who present with influenza that has already progressed to flu pneumonia because participants in oseltamivir and zanamivir clinical trials were eligible only if symptoms had lasted for 2 days or less.39

Adverse events that were more frequent in adults with influenza treated with oseltamivir than those receiving controls were nausea (10% vs 6%, respectively) and vomiting (9% vs 3%, respectively).40 Among pediatric patients treated with oseltamivir, the only adverse event that occurred more often in the treatment group than in controls was vomiting (15% vs 9%, respectively).40 Physicians should be aware that 32 children with influenza who were treated with oseltamivir experienced neuropsychiatric symptoms, such as delirium, abnormal behavior, hallucinations, convulsions, and encephalitis, although it could not be determined whether these events were secondary to the underlying influenza itself or due to the drug.41

For all that antivirals play an important therapeutic role, physicians should be aware that there is some evidence that influenza viruses started to develop resistance to oseltamivir within the first 3 years of their use.

<table>
<thead>
<tr>
<th>Table 1. Glossary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Term</strong></td>
</tr>
<tr>
<td>Epidemic</td>
</tr>
<tr>
<td>Hemagglutinin</td>
</tr>
<tr>
<td>Herd immunity</td>
</tr>
<tr>
<td>Isolation</td>
</tr>
<tr>
<td>Mitigation</td>
</tr>
<tr>
<td>Neuraminidase</td>
</tr>
<tr>
<td>Nosocomial</td>
</tr>
<tr>
<td>Pandemic</td>
</tr>
<tr>
<td>PPE</td>
</tr>
<tr>
<td>Quarantine</td>
</tr>
<tr>
<td>SARS</td>
</tr>
<tr>
<td>Surge capacity</td>
</tr>
</tbody>
</table>

CDC = Centers for Disease Control and Prevention.
However, strains that were oseltamivir resistant usually retained sensitivity to zanamivir.42

**Antiviral Prophylaxis to Prevent Influenza**

Oseltamivir and zanamivir are both approved by the US FDA for prevention of seasonal influenza in the United States. During a community outbreak, if prophylactic antivirals are given simultaneously with influenza vaccination, the duration of antiviral treatment can be stopped after 2 weeks, once the immune response from the vaccination occurs. Several agents including oseltamivir are safe and effective as prophylaxis for up to 6 weeks in individuals for whom vaccine is contraindicated, so long as dosing is continuous (Roche, oseltamivir label).

Indications for oseltamivir or zanamivir prophylaxis include the need for an adjunct to vaccination in high-risk individuals or in immunodeficient individu-

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**Figure 10. Herd Protection of Elderly by Mass Influenza Immunization of Children: Moscow, 2001–2002**

The rates for influenza-like illness, pneumonia, asthma, and bronchitis in adults older than 60 years were significantly lower at the intervention site than at the control site.

ILI = influenza-like illness.

Data from Ghendon et al.27

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**Table 2. Antiviral Medications Complement Vaccination**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Effective Against</th>
<th>How Administered</th>
<th>Treatment</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M2 Protein Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amantadine*</td>
<td>A</td>
<td>Oral</td>
<td>1–12 years</td>
<td>See package insert†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;12 years to &lt;65 years</td>
<td>Two 100-mg tablets once daily until 24–48 hours after signs and symptoms disappear‡</td>
<td></td>
</tr>
<tr>
<td>Adults &gt;65 years</td>
<td>One 100-mg tablet once daily‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rimantadine*</td>
<td>A</td>
<td>Oral</td>
<td>≥10 years</td>
<td>100 mg twice daily for 7 days‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥1 year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100 mg twice daily‡</td>
</tr>
</tbody>
</table>

**Neuraminidase Inhibitors**

| Osel tamivir       | A & B              | Oral             | ≥1 year | 75 mg twice daily for 5 days (if <88 lbs refer to the weight base table for children) |
|                   |                    |                  |         | ≥13 years |
| Zanamivir         | A & B              | Inhalation       | ≥7 years| 10 mg (2 inhalations) twice daily for 5 days‡ |
|                   |                    |                  |         | ≥13 years |

*Not used during 2005–2006 influenza season.


als who are likely to have a poor response to vaccine, unvaccinated individuals caring for high-risk individuals, or individuals with contraindications to influenza vaccine such as severe egg allergy.22

Hayden et al pretreated 24 healthy adults with oseltamivir (100 mg either once or twice daily) and 12 participants with placebo, then inoculated all participants with H1N1 influenza virus 26 hours later.18 Unlike patients receiving placebo, those receiving an NA inhibitor shed virus for a shorter period of time (Figure 8). This study has important implications for hospitals because eliminating viral shedding among patients and HCWs would likely be an advantage in preventing nosocomial infections.18

Prophylaxis with NA inhibitors is also effective among the elderly in long-term care facilities (LTCFs). In 1 randomized study, residents in US and European LTCFs received placebo or oseltamivir before and during a 6-week-long local influenza outbreak. Laboratory-confirmed, clinical influenza dropped 92%.43 Among 494 nursing home residents (only 9% of whom were vaccinated against seasonal influenza) who were randomized to zanamivir or placebo, the percentage who developed symptomatic, culture-proven influenza was statistically the same (zanamivir, 6%; placebo, 9%; \( P = .355 \)).44 However, zanamivir use was associated with a 70% reduction in laboratory-confirmed influenza (2% vs 6%; \( P = .043 \)), as a secondary end point. Zanamivir was 91% effective in preventing influenza among 50 nursing home residents with multiple comorbidities who were exposed to both influenza A and B during a community outbreak.45

CHALLENGES IN MANAGING SEASONAL INFLUENZA

One challenge in managing seasonal influenza involves poor vaccine acceptance among consumers. In a recent survey at a large teaching hospital of 153 individuals caring for children ages 6 to 23 months, 20% believed that influenza vaccine can cause influenza.46 Nearly 33% of the more than 2000 individuals who participated in a CDC survey believed the same.47 Parents may perceive wrongly that influenza is not serious enough to justify vaccinating their children, and some physicians apparently do not recommend influenza vaccination appropriately.48 Disturbingly, only 29% of children aged 2 to 17 years with asthma got immunized for influenza during the 2004 to 2005 influenza season, even though such children are a recognized high-risk group.49 Approximately 65% of individuals older than 65 years received influenza vaccination in 2004, well below the national health objectives for the 2010 goal for 90% coverage in this age group.50 Physicians can encourage vaccine acceptance by reviewing the ACIP recommendations and recommending vaccination to those patients that meet the high-priority criteria. Other methods to improve vaccine acceptance among patients include providing standing orders for vaccinations, establishing special influenza clinics, posting signs encouraging vaccination in public areas, and notifying patients with a computer-based reminder system.51,52

Another challenge is the availability of vaccine. During the 2004 to 2005 influenza season, there was a shortage of vaccine because of the temporary shutdown of a manufacturing plant belonging to a major vaccine supplier to the United States.53 Some large pharmacy or grocery chains received vaccine for distribution early in the season, whereas many hospitals or doctor’s offices received supplies later or not at all. Influenza vaccine manufacturers and distributors eventually addressed these concerns about allocation of influenza vaccine. Although availability has not been a problem during recent influenza seasons, national policies to assure distribution to high-risk patients and caregivers of high-risk patients may facilitate distribution of vaccine moving forward.

Prevention of seasonal and pandemic influenza will hinge on primary and secondary means. Primary prevention hinges on effective vaccination. However, hand hygiene, isolation, and separation are important interventions to prevent transmission of respiratory diseases, including influenza. Hand hygiene, whether with soap and water or alcohol hand rub, kills influenza virus and interrupts transmission from direct or indirect sources. Hand hygiene has been shown to decrease transmission of influenza-like illness or respiratory illness in schools, among college students, and military recruits and other settings.54-56 Likewise, cohorting and isolation have been shown to decrease transmission of influenza in outbreak settings.57 Hospital visitors pose another challenge to minimizing the spread of seasonal influenza. As recommended in the recently released CDC HICPAC isolation guidelines, respiratory etiquette policies should be established.58 At the height of the influenza season, hospitals might consider offering masks to individuals and cohorting, or placing individuals with
respiratory symptoms on one side of the waiting room and other noninfectious emergencies on the other. Per CDC guidelines, sick patients should be isolated or cohorted with patients who have similar disease. Transmission-based precautions (droplet precautions) are indicated and have been shown to decrease transmission and nosocomial disease.

Outside of acute care, LTCFs face particular challenges in managing influenza, as they have a minimal capacity to deal with influenza outbreaks. Short-term residents arrive from the hospital having been discharged more quickly than in the past. Physicians may visit only once every 30 days and laboratory results may take 7 days. These facilities generally have only part-time infection control practitioners and have no airborne isolation rooms.

THE ROLE OF THE PHYSICIAN IN SEASONAL INFLUENZA

Physicians and other providers have a responsibility to correct misperceptions among their patients (eg, that influenza is not a serious disease or that immunizations cause the flu). Physicians should be role models for their patients by being vaccinated against seasonal influenza each year and by encouraging their coworkers to also be vaccinated.69 Physicians should also try to limit unnecessary exposures to influenza patients in the office or emergency department by following standard precautions (hand hygiene and cleaning stethoscopes), and possibly droplet precautions (ie, wearing masks and maintaining a 3-foot perimeter), even before the diagnosis is made. When the symptomatic patient is triaged, such procedures should be implemented to prevent transmission.

Now is the time for physicians and staff to get into the habit of asking patients with respiratory symptoms if they have recently traveled to countries in which H5N1 is circulating. The physician should plan to provide an adequate number of vaccine doses, within the context of recent disruptions in vaccine availability. They should encourage simple infection prevention strategies, including hand hygiene (alcohol hand rub) and separation.

PANDEMIC INFLUENZA

Health professionals and consumers throughout the United States are concerned with the possibility that the H5N1 strain of avian influenza currently circulating among birds in Asia, Europe, and the Middle East, and associated with limited disease in humans, will develop the potential to cause a pandemic. Although H5N1 is the most likely candidate, other circulating avian strains, given the correct set of circumstance, could also become candidate strains for a pandemic strain.

INFLUENZA STRUCTURE AND GENETICS

Influenza are single-stranded RNA viruses that belong to the group Orthomyxidae.60 Two surface proteins on the influenza virus determine the naming conventions that identify subtypes of infection. The first part of the name refers to the hemagglutinin (HA) antigen, of which there are 16 subtypes. HA allows the virus to attach to the host cell. Birds are the natural reservoir of influenza and they are susceptible to all 16 HA subtypes.60,61 To date, influenza subtypes H1, H2, and H3 cause most disease in humans.

The second antigen of importance is NA, of which there are 9 subtypes.61 After the virus replicates within a host cell, NA allows mature virus particles to be released from host cells.

The genes that encode for HA and NA within the same subtype of influenza viruses mutate from year to year, a process known as antigenic drift. This process drives the need for a new seasonal influenza vaccine every year to match the most common circulating variants.60 In contrast, in rare instances, portions of the HA and NA genes reassort within host cells, usually within pigs. This process results in a new influenza subtype that has characteristics of avian strains but can cause human disease, and is known as genetic shift. When genetic shift occurs, the risk for a pandemic increases because humans, never having been exposed to the new virus before, have not developed antibodies to it.60 Pandemics occur rarely, but when they do, the impact on the world population is immense.

POTENTIAL IMPACT OF PANDEMIC INFLUENZA

The currently circulating H5N1 influenza is highly pathogenic to birds, and transmits easily from bird to bird. Experts are concerned that infected poultry transmit H5N1 influenza to wild, migratory birds, which are at least partially responsible for the spread of the virus beyond its epicenter in Asia. Currently,
H5N1 influenza does not transmit easily from person to person, and human to human transmission of H5N1 has been postulated only rarely. However, because H5N1 is rapidly mutating, public health experts are concerned that H5N1 has pandemic potential.

The worst pandemic in the 20th century, the so-called “Spanish Flu,” occurred between 1918 and 1919. It is estimated that 500,000 individuals in the United States became infected, and between 50 and 100 million individuals died worldwide. The epidemiology of the Spanish Flu was unusual in that many young, seemingly healthy individuals quickly developed severe respiratory symptoms and died. Thus, the combined influenza and pneumonia mortality curve for this pandemic is W-shaped, in contrast to the U-shape of the interpandemic period from 1911 to 1917 (Figure 11).63

If the current H5N1 mutates so that it is easily spread from person to person, meeting the needs of pandemic influenza patients in the United States would require twice the numbers of hospital beds and ventilators, and nearly 5 times the intensive care unit capacity than are currently available. Depending on the severity of such a potential pandemic, 675,000 to 1.9 million people could die in the United States alone. In preparation for this eventuality, several companies have developed prepandemic vaccines. The US FDA recently approved one of these vaccines. Hence, if H5N1 mutates into a pandemic strain, the goal will be to produce 300 million doses of an up-to-date vaccine that matches the new strain within 6 months. Unfortunately, the manufacturing capacity to rapidly meet this goal does not exist at this time. However, recently, Yang et al developed vaccines and monoclonal antibodies to H5N1 mutants in which the receptor binding domain, which originally targeted avian receptors, had been altered to bind to human receptors. This new approach could be used to identify H5N1 strains that are most likely to become adapted to humans before they actually do so, which would permit development and production of a prepandemic vaccine much more quickly.

As of May 2007, there has been no evidence of highly pathogenic H5N1 among birds or humans in North America. It is not guaranteed that the currently circulating H5N1 will develop pandemic potential. However, there are a number of other avian strains that periodically become transmitted to humans, any of which could become a pandemic strain.

**Current Status of Human Cases of H5N1 Influenza Worldwide**

Of the 322 reported cases of H5N1 influenza among people that have occurred from 1997 to date, approximately 80% have been from Asia, although human cases have been identified in Azerbaijan, Egypt, Iraq, Nigeria, and Turkey. The majority of H5N1-infected individuals have been teenagers or young adults (Figure 12). Almost all H5N1-infected people had direct contact with sick poultry at live bird markets, on farms, or from backyard flocks, but there have also been 10 clusters of H5N1 among family members. The disease has an incubation period of 2 to 5 days, after which the patient quickly develops lower respiratory tract symptoms, multiorgan failure, and sepsis. Of the 322 reported human cases, 195 (60.6%) have died.

Although research indicates that oseltamivir and zanamivir are effective in preventing H5N1 virus from replicating in the lungs of mice,70,71 no randomized clinical trials of oseltamivir or zanamivir treatment during the Spanish Flu pandemic of 1918–1919, many young, seemingly healthy individuals died from influenza, leading to a mortality curve that is W-shaped.
have been done in H5N1 patients. In a series of 8 Vietnamese patients with H5N1, 50% died despite being treated with 75 mg of oseltamivir twice daily. Two of the 4 deceased patients exhibited resistance to oseltamivir, but 1 of them had not started treatment until 6 days after symptom onset.72

**FINANCIAL COSTS OF PLANNING FOR PANDEMIC INFLUENZA**

It would likely cost $1 million for an average hospital (164 beds) to develop and buy the supplies to implement a pandemic influenza preparedness plan (Figure 13). Once the plan is complete, hospitals would also need to budget for drills or tabletop exercises and recurring annual costs of $200 000 to maintain preparedness for a large-scale health emergency.14 Hospitals may want to consider sharing resources (eg, educational campaigns) with other local facilities to minimize some costs.

Many hospitals already operate at slim (1.9%) profit margins—30% are losing money.14 Add an ongoing shortage of personnel, and a pandemic would likely cause some to close. The question then is, if it’s so expensive, why bother with planning? Only with planning will there be a chance to prevent a pandemic strain from adapting to humans and acting like a human seasonal influenza.

**LESSONS FROM SARS: THE PANDEMIC THAT COULD HAVE BEEN**

The city of Toronto learned many valuable lessons while handling the SARS (severe acute respiratory syndrome) outbreak that can be applied to planning for pandemic influenza.73,74 Prior to that outbreak, HCWs didn’t use special precautions with patients who had community-acquired pneumonia. The coronavirus that causes SARS is spread via airborne transmission of tiny droplet nuclei as well as by direct and indirect contact with large droplets.75 The SARS experience taught HCWs to use droplet precautions with all patients, and airborne precautions (private room with negative air pressure; N95 respirator) with patients with SARS. Hospitals relaxed precautions too early, which led to a second outbreak, in which 44 people died, approximately 45% of whom were HCWs. HCWs who used precautions consistently were significantly less likely to become infected with influenza (Figure 14). Hospitals learned to screen patients and HCWs carefully by taking the temperature and obtaining a history of every individual who entered into the healthcare setting to prevent transmission of disease.

**THE PANDEMIC PLANNING PROCESS**

The process of planning for a potential influenza pandemic involves input from agencies on the international, federal, state, and local level.
**INTERNATIONAL LEVEL**

On the international level, the WHO drives planning strategies based on 6 pandemic alert levels:

- **Interpandemic period**
  - Phase I: A new influenza virus subtype circulates in animals, but has not been detected in humans. The risk of human infection or disease is considered to be low.
  - Phase II: A new influenza virus subtype is circulating in animals and poses a substantial risk of human disease, although the virus has not been detected in humans.

- **Pandemic alert period**
  - Phase III: Human infection(s) with a new viral subtype but no human-to-human transmission, or at most rare instances of transmission to a close contact. As of March 29, 2007, this is the phase that the world is in currently.
  - Phase IV: Small, highly localized cluster(s) of human-to-human transmission exist, suggesting that the virus is not yet well adapted to humans.
  - Phase V: Larger, but localized, cluster(s) but human-to-human transmission, suggesting that the virus is adapting to humans but may not be fully transmissible (substantial pandemic risk).

- **Pandemic period**
  - Phase VI: Increased and sustained viral transmission throughout the world.

**NATIONAL LEVEL**

On the national level, pandemic planning is driven by documents developed by the Department of Health and Human Services (DHHS) and the Homeland Security Council (HSC).

Recommendations to improve the HSC Implementation Plan for the National Strategy for Pandemic Influenza were offered by the Task Force on Influenza, a joint effort of the Infectious Diseases Society of America (IDSA) and SHEA. These recommendations included providing sustainable long-term funding for pandemic planning and developmental of national clinical management guidelines for treating pandemic influenza. The recommendations pointed out that implementing social distancing might be difficult to do because of the need for local coordination and the possibility that the public might not comply.

To supplement the federal pandemic plan, the CDC released a plan for community mitigation strategies. The goal of these strategies is to delay the peak of any potential pandemic in the hopes that a well-matched vaccine can be developed and distributed. Implementation of 1 or more of these strategies would be triggered by identification of a pandemic strain in the community, which would be triggered depending on the severity of the pandemic, as defined by the case fatality rate. These strategies include:

- Isolating and treating (if medications are available and appropriate) of ill individuals at home
- Voluntary quarantining of asymptomatic individuals who have been exposed to sick family members at home
- Closing of universities, schools, and childcare facilities
- Canceling of large public gatherings or alternating workplace schedules

The CDC plan included a warning that the effectiveness of community mitigation measures had not been proven definitively. That statement has now been superseded by data from a retrospective study of 43 US cities. This study showed that in cities in which multi-

**Table 14. Lessons from SARS: PPE Effectiveness for Influenza**

<table>
<thead>
<tr>
<th>Type of PPE</th>
<th>Consistent</th>
<th>Inconsistent</th>
<th>Relative Risk (95% CI)</th>
<th>2-Tailed Fisher Exact P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gown</td>
<td>3/20 (15)</td>
<td>5/12 (42)</td>
<td>0.36 (0.10–1.24)</td>
<td>.12</td>
</tr>
<tr>
<td>Gloves</td>
<td>4/22 (18)</td>
<td>4/10 (40)</td>
<td>0.45 (0.14–1.46)</td>
<td>.22</td>
</tr>
<tr>
<td>N95 or surgical mask</td>
<td>3/23 (13)</td>
<td>5/9 (56)</td>
<td>0.23 (0.07–0.78)</td>
<td>.02</td>
</tr>
<tr>
<td>N95</td>
<td>2/16 (13)</td>
<td>5/9 (56)</td>
<td>0.22 (0.05–0.93)</td>
<td>.06</td>
</tr>
<tr>
<td>Surgical mask</td>
<td>1/4 (25)</td>
<td>5/9 (56)</td>
<td>0.45 (0.07–2.71)</td>
<td>.56</td>
</tr>
<tr>
<td>N95 versus surgical mask</td>
<td>2/16 (13)</td>
<td>1/4 (25)</td>
<td>0.50 (0.06–4.23)</td>
<td>.51</td>
</tr>
</tbody>
</table>

During the SARS outbreak in Toronto, Canada, healthcare workers who used precautions consistently were significantly less likely to become infected with influenza.

Cl = confidence interval; PPE = personal protective equipment; SARS = severe acute respiratory syndrome.

ple nonpharmaceutical strategies (eg, isolation and quarantine, school closure, and bans of public gatherings) were instituted early and consistently, the pandemic influenza outbreaks were significantly delayed and mortality was significantly less severe than in cities that did not institute them.80

**STATE/REGIONAL LEVEL**

All 50 states have posted pandemic influenza plans on the Internet (Sidebar). These detailed plans show substantial variation in basic approaches to such pivotal issues as surveillance and social distancing measures.

The availability and distribution of vaccine and antiviral drugs, and the guidelines and accountability for their use, will also be determined on a regional level.

**LOCAL/HOSPITAL LEVEL**

There is essentially no surge capacity, or ability to respond to an unexpected increase in demand for healthcare services, in this country. Yet, the DHHS and the Department of Homeland Security continue to remind healthcare providers that preparations must be “local.” In other words, hospitals and local public health authorities should identify and coordinate their resources, as federal support will be limited. The challenges faced by hospitals in fulfilling the need for pandemic planning fall into 6 major categories, all of which will compromise a hospital’s ability to mount a medical response to a 1918-like pandemic:

- Hospital preparedness is not clearly defined in the DHHS Pandemic Plan itself, although there is a nonspecific checklist for hospitals to use as a starting point, but it does not include such basics as guidelines for infection control or identifying ways to increase surge capacity (see Web links later in this article).
- Some key preparedness tasks, such as planning for alternate care facilities when hospitals are full, cannot be accomplished by hospitals individually. Yet, cooperation among competitive healthcare institutions is the exception rather than the rule.
- The demand for healthcare will exceed capacity. There are fewer hospitals and ERs available today, and hospital bed capacity continues to decrease. In addition, 48% of emergency departments are already at or over capacity.
- There is a nationwide critical shortage of hospital workers, especially nurses. Hospital workers may be absent from work because they are themselves ill, are caring for ill family members, or are afraid of becoming infected. The Health Resources and Services Administration (HRSA) is developing plans for the Emergency System for Advance Registration of Volunteer Health Professionals, which will require standardized recruiting, credentialing, and deploying of volunteer medical professionals. HRSA has not yet released data on how well this program is progressing.
- Federal funding levels for hospital preparedness are inadequate. Until 2006, HRSA provided funds to hospitals to increase surge capacity in case of bioterrorism or other health emergencies; pandemic influenza counted as an eligible event. It is unclear if this program has been extended beyond 2006. Further information is available from each state’s hospital preparedness coordinator.
- A severe pandemic may threaten hospitals’ solvency. As it is, 30% of hospitals are losing money, and those in the black make only a 1.9% profit margin. There is no federal support to develop surge capacity, or to reimburse hospitals that already provide $25 billion per year in uncompensated care for the 45 million uninsured people in the United States.
- However, with these caveats in mind, nurses/physicians/pharmacists who are involved in pandemic planning on the local level have resources on which to draw. Checklists that include the necessary elements of a pandemic plan are available for hospitals, LTCFs, and medical offices and clinics, and some hospitals have posted their site-specific plans on the Internet (Sidebar).

**ROLE OF THE PHYSICIAN IN PANDEMIC INFLUENZA**

 Physicians should keep abreast of the news about H5N1 influenza worldwide. The physician’s responsibilities during a pandemic would be the same described earlier in this article for a seasonal outbreak. However, fulfilling those roles will be more difficult in an environment of scarce resources. In order to be able to care for patients when a pandemic develops, community-based physicians must prepare just as hospitals and public health departments do. Physicians should consider taking part in local pandemic planning efforts...
Once a pandemic influenza strain starts to circulate in the United States, physicians will play a vital role in detecting cases and progression to a local outbreak. Physicians should train staff about protecting themselves and implementing public health procedures, such as transmission of nasopharyngeal specimens to the public health laboratory, isolation of patients with putative pandemic influenza, and quarantine of healthy individuals exposed to a known pandemic influenza case. They will play a key role in educating patients and the community about prevention strategies. Although a vaccine against a pandemic strain would not be immediately available, it is possible that components in the seasonal influenza vaccine (eg, N1) may provide some immunity against H5N1, thus all staff should be immunized against seasonal influenza.

Ideally, clinics and private practices should try to establish isolation areas for patients with respiratory symptoms. If that is not possible, clinicians should consider scheduling influenza-related patient care in separate blocks of time from all other care. All healthcare professionals, whether hospital-based or practicing in a community, clinic, or university setting, should understand the concepts of isolation versus quarantine.

Physicians need to know how to prescribe and administer antiviral medications appropriately. They may be asked to make difficult decisions—if supplies are limited, they may be able to provide therapy only to “high-risk” patients. An office/clinic plan must anticipate the possibility that staff will stay home because they or a family member are ill. Physicians should also ensure in advance of need that their own family members will be cared for if they become infected with pandemic influenza.

Obtain supplies of personal protective equipment, antiviral medications, antibiotics, insulin, and other commonly prescribed drugs for patients with chronic illness, in case the pharmaceutical supply line is disrupted.

**RESEARCH STILL NEEDED**

Despite many advances, there is still much research into H5N1 influenza that needs to be done:

- New methods are needed to produce 300 million doses of a vaccine directed to a new pandemic influenza variant within 6 months of recognition of a pandemic strain. New vaccines should require only a single dose with an effective adjuvant (an ingredient that facilitates or modifies the action of the vaccine), and production methods cannot be egg based. New strategies to provide vaccine should also be investigated (eg, intradermal or nasal administration).

- Healthcare institutions need access to rapid, accurate, and inexpensive point-of-care diagnostics for H5N1 influenza. As one step in that direction, in December 2006, the CDC awarded $11.4 million in grants to 4 companies developing new diagnostic tests that doctors and field epidemiologists could eventually use to quickly and accurately test patients for avian influenza H5N1 and differentiate influenza A H5N1 from seasonal human influenza viruses within 30 minutes. In addition, the National Institutes of Health anticipates providing $20 billion in funding in 2007 for research into new vaccines, diagnostic tests, and medications for influenza.

- The optimal dosages for existing antiviral medications for prophylaxis or treatment of patients with H5N1 influenza needs to be determined.

- New antiviral medications need to be developed that are effective against late-stage influenza.

- There is a need for actual data on whether com-
munity mitigation actions, such as closing schools and businesses, restricting travel, and quarantine, result in measurable slowing of influenza spread. In addition, similar strategies must be evaluated in acute and alternative healthcare settings to further assure disease transmission will be limited.

• There is a need for data on transmission of seasonal and pandemic influenza viruses and their prevention and control in healthcare settings.

**POLICY CHANGES ARE NEEDED**

• Financial
  – Given the financial challenges facing hospitals attempting to develop pandemic plans, policy changes are needed on every jurisdictional level. Ideally, the federal government should provide funding for pandemic influenza planning and to assure coverage for costs of caring for flu patients, as it would to care for individuals affected by a major hurricane or other natural disaster.

• Manpower
  – HRSA is developing a plan to standardize the qualifications and credentials to retired healthcare professionals who wish to volunteer their services if a pandemic develops. This plan is still in its early stages, and HRSA has not released any statistics about how many people have volunteered.
  – In addition, workplace leave policies will need to be modified to provide paid furloughs so that clinical staff will voluntarily stay home if they have respiratory symptoms. Current policies drive HCWs back to work because they are afraid to use up all their paid sick and vacation time. Hospitals also need to develop methods for personnel whose jobs do not require direct patient contact to work from home.
  – Credentialing rules need to facilitate the use of healthcare workers from different settings to assure maximal staffing.

• Surge capacity
  – US hospitals do not have the beds, equipment, or personnel to build surge capacity for equivalent of a pandemic with the severity of 1918, but it may be possible to build enough capacity to care for as many patients as were affected by the 1958 pandemic.

• Supply sources
  – Multiple, reliable, domestic sources of hospital supplies need to be developed. Approximately 80% of hospital supplies come from offshore sources that are likely to collapse rapidly should a pandemic develop.

• Leadership
  – The federal government needs to supplement the efforts of the states by providing reliable public health leadership about ethical issues, vaccine distribution, antiviral priorities, liability coverage, insurance reimbursement, emergency credentialing, etc.
  – There needs to be a standardized but flexible ethical framework to prioritize who receives the vaccine and antivirals when supplies will be scarce. If a pandemic develops in the near future, for example, all available vaccine and antiviral medications will be prioritized to the military and those involved in vaccine and antiviral production. Healthcare is not a priority.

• There needs to be official federal policy about stockpiling supplies, such as N95 respirators, ventilators, surgical masks, gloves, and gowns.
  – Similarly, a policy needs to be established about the use of antivirals prophylactically as a substitute for vaccine, thus healthcare institutions can be eligible for reimbursement by HRSA.
  – Inform health insurers that they will need to be flexible about what documentation will be required to ensure reimbursement. In a crisis, pharmacists will be concentrating on providing services for the maximum number of patients, not on thorough documentation.
  – The government should provide legal assurances that healthcare professionals will be exempt from liability during an influenza pandemic during which limited resources might result in a lower standard of patient care than usual.

**CONCLUSIONS**

Seasonal influenza is often misperceived as a minor disease. The disease and its complications have a major impact on individuals and healthcare institutions. Although vaccines and antiviral medications are effective in preventing and treating seasonal influenza, it
still needs to be determined if that is true for H5N1 influenza. This influenza subtype, currently circulating widely among birds, causes high mortality among the relatively few humans that have been infected with it.

Many resources exist to help hospitals develop a comprehensive pandemic plan, but knowledge gaps and shortages of vaccine, antiviral medications, equipment, and supplies will pose challenges to preventing and treating pandemic influenza.

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