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INFLUENZA 2000–2001

Coping with vaccine manufacturing delays

ABSTRACT

With production of influenza vaccine delayed this year, physicians must prioritize and vaccinate those at highest risk first. Antiviral drugs can reduce the duration of symptoms by 1 to 2 days but should not be the first-line strategy for prevention.

KEY POINTS

Persons at high risk of flu complications—who therefore should be given first access to the flu vaccine—are the elderly, persons with chronic medical conditions, nursing home residents, women in the second or third trimester of pregnancy, health care personnel, children receiving long-term aspirin therapy, and family members of persons at high risk.

Antigens in the current US vaccine are A/New Caledonia/20/99-like (H1N1), A/Panama/2007/99-like (H3N2) and B/Yamanashi/166/98-like.

New guidelines from the Centers for Disease Control and Prevention (CDC) recommend vaccinating everyone 50 years of age and older. The previous guidelines recommended universal vaccination starting at age 65. However, owing to delays in vaccine production, persons 65 years and older should be given priority this year until supplies are adequate.

Updated information on the influenza vaccine supply can be found on the CDC's web site (http://www.cdc.gov/nip) or from the CDC's National Immunization Information Hotline at (800) 232-2522.

ALTHOUGH SUPPLIES of influenza vaccine are expected to be adequate this flu season, manufacturing delays are resulting in local shortages, especially early in the flu season when mass immunizations usually take place. Until vaccine supplies stabilize, physicians should concentrate their vaccination efforts on the elderly and those with chronic diseases and wait until later to vaccinate persons at less risk of influenza-related complications.

Antiviral drugs to treat influenza should not be used as a substitute for vaccination, which remains the first line of defense.

LAST YEAR'S FLU SEASON

In the 1999-2000 season, the overall activity level of the influenza virus was similar to that in the previous 5 years, although the percent of deaths attributable to pneumonia and influenza was higher than in previous years, according to a survey of 122 cities conducted by the Centers for Disease Control and Prevention (CDC).[1] This apparent increase in deaths may have been due to changes in the voluntary reporting systems for pneumonia and influenza used during the 1999-2000 season in the cities surveyed. Overall, however, it is safe to say that influenza continues to be a serious national health issue.

Last flu season's viral strains were similar to those of the season before and were well matched with the available vaccine. The predominate strain was influenza A/Sydney/05/97-like (H3N2).

The virus reached its peak activity between December 25 and January 15,[1] which was 4 to 6 weeks earlier than in the 1994-1995,

Influenza: A summary

INFLUENZA is an acute, febrile respiratory illness that occurs globally.

Symptoms. Classic symptoms include high-grade fevers, myalgias, chills, headache, malaise, and upper and lower respiratory symptoms. The onset of symptoms is usually sudden, occurring after an incubation period of 1 to 2 days. In contrast, the common cold has a more gradual onset with upper respiratory symptoms predominating and less-intense constitutional symptoms.

Epidemiology. Influenza epidemics occur every year in the United States and cause an estimated 20,000 deaths and 110,000 hospitalizations each year.[9] Some years are much worse, however: several pandemics in the 20th century together resulted in millions of deaths, specifically in 1918-1919 ("Swine flu"), 1957-1958 ("Asian influenza"), and 1968-1969 ("Hong Kong influenza"). Most flu-related deaths are in the elderly and those with chronic medical illnesses.

Pathogens. Influenza is caused by infection with an RNA virus, influenza type A or B. Type A accounts for most cases. The vaccine has to be changed every year because the virus continually makes gradual changes in its two surface proteins—hemagglutinin (H) and neuraminidase (N)—in a process called antigen "drift." Antigenic "shift," on the other hand, refers to sudden changes that are the cause of pandemics.

1997-1998, and 1998-1999 seasons but about the same as in the 1995-1996 and 1996-1997 seasons.

THIS YEAR'S VACCINE DELAYED BUT NO SHORTAGE FORECAST

The 2000 influenza vaccine contains antigens from two type A strains (A/New Caledonia/20/99-like [H1N1] and A/Panama/2007/99-like [H3N2]) and one type B strain (B/Yamanashi/166/98-like). These represent the CDC's forecast of what viral strains are likely to be circulating in the upcoming season.[2]

This year, difficulties in growing the A/Panama strain and problems at some manufacturing plants are delaying the availability of the influenza vaccine.[2]

While earlier reports raised concern about an overall shortage, it now appears that the vaccine will be available in similar quantities as last year, but at a later date.[3] (In 1999, four manufacturers in the United States produced a total of approximately 80 million doses of the influenza vaccine.[4])

For instance, at the time of this writing, it is estimated that the Cleveland Clinic Foundation will not receive vaccines for widespread patient use until after November 1st—approximately 30 to 45 days later than the vaccine is usually received. Since the optimal time for vaccination is from October to mid-November, this delay will affect the standard strategy of immunization, in which all persons are immunized at the same time.

VACCINATE OLDER PATIENTS, SICKER PATIENTS FIRST

Recent changes in the guidelines from the CDC expand the number of people recommended to be vaccinated this year, but owing to delays in vaccine production, persons with chronic illness and those 65 years and older should be given priority this year until supplies are adequate.

Initial vaccination should focus on high-risk patients

CDC lowers the recommended age for universal vaccination

The CDC Advisory Committee on Immunization Practices (ACIP) updated its 1999 recommendations in a report published in April 2000.[5] This update recommends that the age for universal vaccination be lowered from 65 years to 50 years. The 50-to-64-year age group was added because many persons in this bracket have one or more chronic medical conditions that place them at a higher risk for influenza-related complications.[5]

This recommendation expands the total number of people officially recommended to receive the vaccination.

This year's vaccination strategy

However, as noted above, because of the delay in production, one's initial vaccination strategy this year should focus on patients at highest risk: elderly patients and those with chronic illness.

Initial target groups for vaccination include:

- Persons older than 65 years
- Persons which chronic medical conditions (eg, chronic cardiopulmonary conditions, metabolic disorders, renal dysfunction, hemoglobinopathies, and immunosuppression) that place them at higher risk
- Nursing home residents
- Pregnant women who will be in their second or third trimester during flu season
- Persons who can transmit the virus to at-risk individuals; this large group includes all health care personnel and family members of persons in high-risk groups
- Children 6 months to 18 years old receiving long-term aspirin therapy (who are therefore at risk of Reye syndrome).

To be effective, antivirals must be started within 48 hours of onset

Other people should be vaccinated later in the season, ie, December onward. One concern I have is that some of these people who are at lower risk may not take the time to return for another visit to get their vaccination. For example, a patient not at high risk who is seen for an office visit in early November may not wish to come back 1 month later just for his or her flu shot. But unfortunately the delay in receiving the vaccine makes such a policy necessary.

Updated information on the influenza vaccine supply can be found on the CDC's web site (**http://www.cdc.gov/nip**) or from the CDC's National Immunization Information Hotline at (800) 232-2522.

ANTIVIRAL AGENTS

One of the exciting developments in the last year was the introduction of two new drugs that are effective in treating influenza: zanamivir (Relenza) and oseltamivir (Tamiflu). These drugs, called neuraminidase inhibitors, join amantadine (Symmetrel, generic preparations) and rimantadine (Flumadine) in the treatment of influenza. All were reviewed in detail in a previous issue of the *Cleveland Clinic Journal of Medicine*,[6] but a few words are in order.

Amantadine and rimantadine are effective against only influenza A (the predominate strain) and have indications both in prevention (chemoprophylaxis) and treatment. A meta-analysis by Jefferson et al[7] found both drugs approximately equal in their effectiveness in preventing and treating influenza, but rimantadine was associated with fewer adverse effects. Amantadine may cause central nervous system side effects in 6% to 30% of patients. These effects are more common in the elderly and in patients with renal insufficiency. Also, resistance to either drug may occur in 10% to 30% of cases, as can cross-resistance.

Zanamivir and oseltamivir are effective against both influenza A and B but are currently indicated only in treating influenza, not preventing it. Zanamivir is an inhaled aerosol and may cause cough or bronchospasm. Oseltamivir comes in pill form; its most common adverse effect appears to be gastrointestinal symptoms.

Use of antiviral drugs

To be effective, all anti-influenza drugs must be started within 48 hours of symptom onset. This fact alone limits the widespread use of these medications because many patients present outside of this window. And what do we tell patients who have heard of these medications? Just how effective are they?

A recent multicenter, randomized controlled trial[8] looked at the effectiveness of oseltamivir in the treatment of influenza. Patients were 726 healthy adults with an influenza-like illness of up to 36 hours' duration, who were randomized to receive either oseltamivir (75 or 150 mg) or placebo twice daily for 5 days. Sixty-six percent of the patients proved to have influenza by culture or serology, and more than 95% of the patients with influenza were infected with type A. In the group receiving oseltamivir 150 mg, the duration of the illness was shortened by 35 hours (by 47 hours if the medication was started within 24 hours), and patients were afebrile within 40 hours, compared with

67 hours in the placebo group. Most oseltamivir recipients began to feel better within a day. Of note, this trial did not include people with chronic medical conditions, and such studies are still needed.

Antiviral drugs are no substitute for vaccination

Although effective, these drugs should not be used as a substitute for influenza vaccination. Even with the delay in the influenza vaccines, the CDC and ACIP do not support the routine and widespread use of antiviral agents as chemoprophylaxis.[4] Such a strategy is unproven and expensive and may result in a number of adverse drug events. Vaccination remains the first line of defense.

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