REVIEW

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Influenza update 2007–2008: Vaccine advances, pandemic preparation

ABSTRACT

Influenza vaccination remains our best measure to prevent epidemic and pandemic influenza. We must continue to improve vaccination rates for targeted populations. Antiviral options are currently limited to the neuraminidase inhibitors.

KEY POINTS

Recent research suggests that influenza vaccination has unexpected benefits, such as protecting against strains not included in the vaccine, reducing the rate of death from any cause, and, with live-attenuated vaccine, protecting household contacts of vaccinated children.

Only 20% to 69% of people for whom influenza vaccines are indicated are actually being immunized. Measures to improve these rates should be implemented.

Since 96% of the widely circulating influenza A (H3N2) viruses in the United States are resistant to amantadine (Symmetrel) and rimantadine (Flumadine), only the neuraminidase inhibitors zanamivir (Relenza) and oseltamivir (Tamiflu) should be prescribed.

Anticipating a pandemic of avian influenza, the US Department of Health and Human Services is stockpiling human H5N1 influenza vaccine, oseltamivir, and zanamivir. Social distancing measures such as school closures, public-gathering bans, and travel restrictions will also be required to slow the course of a pandemic.

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INFLUENZA, which annually infects about one-fifth of the world's population, has received much attention lately due to the expanding avian influenza epizootic and the related limited human epidemic.

Vaccination remains the main defense against influenza, and there is ongoing research into improving the vaccine, such as trying to find ways to streamline production without using embryonated eggs and developing a universal vaccine that would be effective against all strains of the virus.

Work is also continuing on developing a vaccine against the potential pandemic strain of avian influenza. In fact, in April 2007, the US Food and Drug Administration (FDA) approved the first prepandemic human avian H5N1 inactivated intramuscular influenza vaccine.

This review highlights recent developments in the field and reemphasizes the value of vaccination as our main defense against epidemic and pandemic influenza.

UPDATE ON EPIDEMIOLOGY

Influenza activity in the 2006–2007 flu season in the United States peaked in mid-February 2007.[1] Influenza A (H1) predominated overall, and influenza A (H3) and influenza B were more frequently identified later in the season. Similar types of viruses circulated during the latest influenza season in the southern hemisphere, which ended in August 2007.

Influenza C virus is difficult to isolate. Most influenza C infections occur in children younger than 6 years, and hospitalization due to lower respiratory tract complications is more likely in children younger than 2 years.[2]

Influenza virus was detected by polymerase chain reaction 7 or more days after the onset of symptoms of influenza in 54% of hospitalized older adults with underlying chronic medical conditions.[3] This finding implies that the adequate duration of isolation to prevent nosocomial transmission may need to be longer than 1 week, as opposed to the 5 days that is standard now.

VACCINATION IS STILL OUR MAIN DEFENSE

It was 2005 when I last wrote about developments in influenza vaccine in this journal.[4] Since then, more studies have reiterated the value of vaccination and added to a vast body of literature already published. Findings:

Vaccination may have unexpected benefits

Ohmit et al[5] found that even when most of the circulating influenza viruses were dissimilar to those included in the vaccine, both the inactivated and the live-attenuated vaccines prevented about 70% of cases of laboratory-confirmed symptomatic influenza in healthy adults.

Furthermore, Spaude et al[6] found that adults who had been vaccinated against influenza and who were hospitalized with community-acquired pneumonia during the influenza season were less likely to die than people who had not been vaccinated. In other studies, Nichol et al[7] found that influenza vaccination reduces older adults' risk of hospitalization by 27% and the risk of dying of any cause by 48%. (Influenza doesn't kill by respiratory disease only: it has been linked to a surge in deaths due to coronary heart disease, causing an estimated 92,000 deaths from myocardial infarction in the United States each year.[8])

Hospitalized flu patients may need to be isolated longer than 7 days from the onset of symptoms

Higher doses may be better

Keitel et al[9] found that higher doses of the inactivated vaccine than are usually used significantly improved its immunogenicity among ambulatory patients 65 years and older, which should lead to enhanced protection against influenza.

The live-attenuated vaccine is safe and effective

King et al[10] found that vaccinating school children with the live-attenuated vaccine not only reduced school-reported absenteeism, but also significantly reduced influenza-like illness in their households. The live-attenuated vaccine is significantly more efficacious than the inactivated vaccine in children 6 to 59 months of age and is safe in those who do not have a history of asthma or wheezing.[11] Vesikari et al[12] calculated that the probability of transmitting the live-attenuated vaccine strain to a child after contact with a single vaccinated child was 0.58% (95% confidence interval 0–1.7%), and they observed no clinically significant illness in the children to whom the vaccine virus was transmitted.

A novel manufacturing process

In an attempt to avoid the current time-consuming and labor-intensive process of manufacturing influenza vaccines using embryonated eggs, a novel influenza virus hemagglutinin vaccine has been produced in insect cells using recombinant baculoviruses. It was found to be safe and immunogenic in healthy adults.[13]

Toward a universal vaccine

An ideal influenza vaccine would be universal: being less sensitive to the viral antigenic evolution, it could in theory protect against all strains of influenza.[14] This vaccine would be based on antibodies specific for conserved viral components in humans. It would not require annual updating and thus could be manufactured continuously, and people could be immunized at any time of the year. More importantly, it could be stockpiled in advance of a pandemic or used routinely to ensure population protection against future pandemics.

Several universal vaccines are under study, although none of the ones studied thus far in animals has achieved the level of protection provided by current vaccines. One such vaccine, directed against the relatively conserved extracellular domain of matrix protein 2 of influenza A, is currently in phase I trials in humans.

Supply is adequate, but vaccination rates are suboptimal

With one more company manufacturing the influenza vaccine in the United States this

year, bringing the total to six companies, the FDA anticipates an ample supply of 134 million doses of vaccine this season, 14 million more than in the 2006–2007 flu season. Unfortunately, 15% of last year's vaccine supply was not used and was discarded, since the vaccine is updated annually.

Vaccination rates are still suboptimal: only 20% in children age 6 to 23 months, 30% in adults 18 to 49 years old with high-risk conditions, 36% in people age 50 to 64 years, 40% in health care workers, and 69% in people 65 years and older.[15] The 2007 guidelines of the Advisory Committee on Immunization Practices[16] continue to recommend influenza vaccination for children 6 to 59 months old, adults 50 years and older, pregnant women, residents of chronic care facilities, people with conditions that put them at increased risk of influenza-related complications regardless of their age, and all health care workers, household contacts of the above-mentioned groups, and contacts of children younger than 6 months. The intramuscular inactivated vaccine is approved for all these age groups, and the live-attenuated vaccine, as an aerosolized nasal spray, has recently been approved for healthy children 2 to 5 years old (it had already been approved for healthy people 5 to 49 years old).

Clearly, we need to improve these vaccination rates. Strategies include continuing education for health care providers, use of reminder systems and standing orders, giving the vaccine at locations outside the doctor's office, and providing feedback to providers.[17]

The level of influenza vaccination coverage among health care workers is a valid measure of patient safety quality programs. Mandatory vaccination of health care workers has its supporters (including myself)[18] and its opponents.[19] Cleveland Clinic requires all its employees to either be vaccinated or declare (on an internal Internet site) that they decline vaccination; last year, 89% of employees participated, and 55% were vaccinated, compared with a 38% vaccination rate in 2004—a substantial improvement.[20]

The United States seems to be slowly moving towards a universal influenza vaccination program,[21] similar to the one implemented in Ontario, Canada, in 2000.

PROMPT DIAGNOSIS IS CRUCIAL

Early diagnosis of influenza can reduce the inappropriate use of antibacterial agents and give us the opportunity to use antiviral therapy.[22] However, diagnosing influenza clinically on the basis of symptoms alone has limited accuracy.

Diagnostic tests available for the practical management of influenza include rapid antigen testing, reverse transcriptase polymerase chain reaction, and immunofluorescence assays.[23] Viral culture and serologic tests are critical for surveilling circulating strains and for monitoring antiviral resistance.

ANTI-INFLUENZA DRUGS: LIMITED OPTIONS

Patients presenting within 2 days of the onset of an influenza-like illness during epidemic periods should be considered for antiviral treatment.[16] These drugs should also be considered in patients hospitalized with severe influenza-related complications, even though the evidence of their effectiveness is primarily from studies of outpatients with uncomplicated influenza.

Chemoprophylaxis is not a substitute for vaccination, but it may be appropriate for household contacts of patients with confirmed cases of influenza, for people at high risk of influenza-related complications for whom vaccination is contraindicated, and for controlling outbreaks in nursing homes and other closed settings.

Currently, only about 40% of health care workers are vaccinated

Only two drugs are currently recommended for preventing or treating influenza: the neuraminidase inhibitors zanamivir (Relenza) and oseltamivir (Tamiflu) (**TABLE 1**).[24] In contrast, the adamantanes amantadine (Symmetrel) and rimantadine (Flumadine) are not currently recommended, since 96% of the widely circulating influenza A (H3N2) viruses are resistant to these drugs.[25]

Oseltamivir is less effective for influenza B than for influenza A in shortening the duration of fever, and 50% of patients with influenza B may continue to shed the virus after 4 to 6 days of treatment, compared with 16% of patients with influenza A.[26] Paradoxically, influenza B viruses with reduced sensitivity to oseltamivir were not found to arise as often as

TABLE 1

Neuraminidase inhibitors: Recommendations for treatment and prevention of influenza

	OSELTAMIVIR (TAMIFLU)	ZANAMIVIR (RELENZA)
Formulation	Capsules or oral suspension	Powder in 5-mg blister on Rotadisk; requires Diskhaler inhalation device
Treatment dosing, adults	75 mg orally, twice a day	10 mg (two blisters) by oral inhalation, twice a day
Duration of treatment	5 days	5 days
Prophylactic dosing, adults	75 mg orally, once a day	10 mg (2 blisters) by oral inhalation, once a day
Duration of prophylaxis (same for both drugs)	10 days for family postexposure prophylaxis 2 weeks for institutional outbreak 6–8 weeks when given as seasonal prophylaxis	
Dosing adjustments	Half the dose for patients with creatinine clearance 10–30 mL/min	Not required
Adverse effects	Nausea and vomiting	Bronchospasm in patients with underlying airway disease; therefore, not recommended in these patients
Cost*	$71 for 10 capsules	$51 (5 Rotadisks with 4 powder blisters each, plus Diskhaler device)

*Approximate Cleveland Clinic formulary price, November 2007

resistant influenza A viruses.[27] Fortunately, these oseltamivir-resistant variants have not yet circulated widely within communities, they are less fit than wild-type virus, and most remain susceptible to zanamivir.[28]

Cases of delirium and self-injury in adolescents who received oseltamivir have been reported, mainly from Japan.[29] It is unclear whether these events were drug-related or due to the higher rates of encephalitis associated with influenza in Japan.

We still lack an intravenous formulation of an anti-influenza drug for seriously ill patients with life-threatening influenza who cannot take an oral (oseltamivir) or an inhaled (zanamivir) agent. Peramivir, an agent currently in phase II studies, may help fill that void.

AVIAN INFLUENZA: THE 'IMPENDING' PANDEMIC

Since the onset of the current H5N1 avian influenza epizootic in December 2003 in southeast Asia, 65 countries have had animal outbreaks, including 26 that were newly added in 2007, up to the time of this writing. Twelve countries have had confirmed human cases, including 5 countries added in 2006 and 2 in 2007, bringing the total number of cases to 329, in which 61% of the patients have died.

The westward spread of the H5N1 virus to countries in Asia, Africa, and Europe has been associated with continued viral evolution.[30] We are learning that this virus causes a spectrum of illness in humans that can be difficult to diagnose.[31] Statistical methods have provided evidence of human-to-human transmission in family clusters in Indonesia, but this has not been shown in Turkey.[32]

Since the seasonal patterns of human influenza in tropical and subtropical areas of southeast Asia are not pronounced, the possibility of a human becoming simultaneously infected with human and avian influenza strains—a pandemic starting point—is not restricted to a short season.[33] In the event that H5N1 causes a pandemic similar to the 1918–1920 pandemic, an estimated 62 million

people (range 51–81 million) worldwide would die (96% of them in the developing world), increasing global mortality by 114%.[34]

What could be done if a pandemic occurs?

During the 1918–1920 pandemic, nonpharmaceutical interventions such as closing schools and banning public gatherings significantly limited the death rate in the United States.[35] In addition, patients with Spanish influenza pneumonia who received influenza-convalescent human blood products had a 21% lower risk of death (95% confidence interval 15%–27%), particularly if the blood products were given within 4 days of onset of illness.[36]

Standard influenza vaccine might offer some protection against avian influenza. Sandbulte et al[37] found that mice immunized against the neuraminidase of a contemporary human H1N1 strain were partially protected from lethal challenge with H5N1 virus. In the same study, analysis of human sera showed that antibodies to human influenza H1N1 neuraminidase provided cross-protection against avian influenza H5N1 in about 20% of subjects.

A simulation model to investigate the mitigation strategies for pandemic influenza in the United States suggested that the best option would be to have a large stockpile of avian-based vaccine with potential pandemic influenza antigens, in conjunction with the capacity to rapidly manufacture a vaccine matched to the human strains.[38] Even if the vaccine is not well matched to the circulating strains, it could slow the spread of disease and limit the number of victims to less than 10% of the population. Ten million vaccine doses must be distributed weekly to affected regions.

In our highly mobile population, social distancing policies including restricting travel do not appear to be effective control strategies but would be required in order to delay the time course of the outbreak, thus allowing time for production and distribution of sufficient amounts of vaccine. Alternatively, timely distribution of a stockpile of 20 million courses of antiviral drugs could be sufficient to contain the national spread of an outbreak.

What has been done already

In April 2007, the FDA approved the first prepandemic human avian H5N1 inactivated intramuscular influenza vaccine. The vaccine was safe and immunogenic in 58% of healthy adults who received two doses, 90 µg each, given 28 days apart.[39] As of July 2007, the US Department of Health and Human Services (HHS) had stockpiled 12 million doses of this vaccine, enough to protect 6 million people. The goal over the next 5 years is to produce enough vaccine to cover all US residents within 6 months of the onset of a pandemic.

More recently, a recombinant H5N1 vaccine engineered by reverse genetics was found to be immunogenic even against a drifted H5N1 isolate, allowing for significant antigen sparing that could increase the production capacity of pandemic influenza vaccine.[40]

The HHS has already stockpiled 48 million courses of oseltamivir and zanamivir, with the goal of stockpiling 81 million courses by December 2008. A recent survey found that 42% of respondents who are part of the Infectious Disease Society of America Emerging Infections Network were asked by patients, family members, or friends for a neuraminidase inhibitor prescription for personal stockpiling.[41] The US Centers for Disease Control and Prevention recommends against this practice.

The HHS has stockpiled enough avian flu vaccine for 6 million people

The HHS is also investing in developing the intravenously administered neuraminidase inhibitor peramivir. In addition, it has purchased 104 million N95 respirators and 52 million surgical masks for use as personal protective equipment in the event of a pandemic. ■

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