CME CREDIT

EDUCATIONAL OBJECTIVE: To update readers on developments in influenza for the 2008-2009 flu season

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2008–2009 Influenza update: A better vaccine match

ABSTRACT

Last year, the influenza vaccine did not match the circulating strains very well, and its overall protective efficacy was only 40%. All three antigens contained in the 2008–2009 vaccine are new. Surveillance data from the Southern Hemisphere during the summer of 2008 show that this vaccine is expected to match well the circulating strains in the Northern Hemisphere.

KEY POINTS

Real-time reverse transcriptase polymerase chain reaction is the most accurate and clinically useful diagnostic test for influenza.

All children age 6 months to 18 years should be vaccinated, and the live-attenuated vaccine is now approved for use in children 2 years old and older.

We should continue to pursue traditional and innovative measures to increase influenza vaccination rates.

Influenza vaccination during pregnancy reduces laboratory-confirmed influenza in infants up to 6 months of age by 63%.

Hygienic measures (particularly hand-washing) aimed at younger children can prevent the spread of respiratory viruses in the community.

Primary viral resistance to oseltamivir (Tamiflu) is rising, but almost all isolates remain susceptible to zanamivir (Relenza).

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Last year, some people may have lost their faith in flu shots. The three antigens chosen for the vaccine in advance by the US Centers for Disease Control and Prevention (CDC) did not match very well the influenza strains that ultimately circulated in North America, and the overall protective efficacy of the vaccine was estimated at only 40%.

Nevertheless, vaccination remains the primary preventive measure for both epidemic and pandemic influenza, especially in view of a rising rate of resistance to the oral antiviral agent oseltamivir (Tamiflu).

In the 2008–2009 influenza season, we hope to do better. All three antigens contained in the 2008–2009 vaccine are new. Surveillance data from the Southern Hemisphere during the summer of 2008 show that this vaccine is expected to be a good match for the strains circulating in the Northern Hemisphere. And with 146 million doses expected to be manufactured this season by six companies—the largest number of doses ever manufactured in the United States—enough should be available for all.

GREAT STRIDES HAVE BEEN MADE, BUT FLU IS STILL A PROBLEM

We are making great strides against influenza. Over the last 50 years, the rate of influenza-related deaths in the United States declined by 95%, from an average seasonal rate of 10.2 deaths per 100,000 population in the 1940s to 0.56 per 100,000 by the 1990s.[1]

However, influenza still accounts for about 10% of patients admitted to intensive care units for acute respiratory failure during epidemics.[2]

Children and the elderly are still hit the hardest: infants age 0 through 23 months and adults age 65 years and older have the highest peak rates of pneumonia and influenza hospitalization and death.[3] School-age children (5–18 years) have an indirect role in anticipating the risk to others and can learn to help avoid spreading the virus by washing their hands more, wearing masks, and adopting other hygienic measures.

In the 1918–1919 pandemic, most deaths were from secondary bacterial pneumonia, a fact that has implications for pandemic preparedness.[4] Currently, *Staphylococcus aureus*, particularly methicillin-resistant strains (MRSA), is an important cause of secondary bacterial pneumonia, with a high mortality rate.[5]

UPDATE ON DIAGNOSIS: PCR IS THE BEST TEST

In the hospital, it is important to identify patients who have influenza so that we can give them appropriate antiviral therapy and also protect other patients from getting the flu. Unfortunately, the sensitivity and positive predictive value of fever, cough, and other symptoms for the diagnosis of influenza in hospitalized patients are 40% or less.[6]

MRSA is an important cause of secondary bacterial pneumonia, with a high death rate

Real-time reverse transcriptase polymerase chain reaction (PCR), compared with direct fluorescent antigen detection or cell culture, has the highest sensitivity (98.7%) and specificity (100%) in both children[7] and the elderly.[8] Furthermore, cell culture is slow and therefore is not useful in clinical practice. Nasopharyngeal wash sampling appears impractical in nursing home residents, owing to their underlying disabilities, and nasopharyngeal swabs tested by PCR are equally sensitive.[8]

However, improvements are needed in molecular detection and subtyping of influenza viruses.[9] If a pandemic breaks out, we will need to identify the virus quickly to have enough time for preventive interventions. The US Food and Drug Administration has recently cleared a new test called the Human Virus Real-Time RT-PCR Detection and Characterization Panel to detect and differentiate between seasonal and novel influenza strains.[10]

UPDATE ON INFLUENZA VACCINE

New recommendations in 2008 by the CDC Advisory Committee on Immunization Practices[11] include annual vaccination for all children age 5 through 18 years, and either the trivalent inactivated vaccine (ie, the shot) or the live-attenuated vaccine (ie, the FluMist intranasal spray) for healthy people age 2 through 49 years. The CDC recommendations are summarized at **www.cdc.gov/flu/professionals/acip/index.htm.**

Has the benefit of vaccination in adults been overestimated?

Jackson et al,[12] in an article published in August 2008, suggested that the effect of influenza vaccination on the risk of community-acquired pneumonia in immunocompetent elderly people during influenza season is less than previously estimated. However, some patients in this study who were classified as not having been vaccinated may have actually been vaccinated by other health care providers without notifying their primary care providers. Moreover, influenza infection may cause only a small proportion of cases of pneumonia in this population.

In another study, Eurich et al[13] suggested that previous observational studies overestimated the benefit of influenza vaccination on reducing deaths in patients with pneumonia outside the flu season. Although they found the incidence of death to be 51% lower in vaccinated than in unvaccinated adults with community-acquired pneumonia (N = 1,813) admitted to six hospitals, they ascribed it to confounding factors, specifically socioeconomic and functional status. This phenomenon was previously called the "frailty bias" or the "healthy user effect." However, this study included only patients hospitalized with pneumonia and did not include data on vaccine-induced immunity or the cause of pneumonia, and measures of the healthy user effect were rudimentary. In addition, only outcomes during hospitalization were included.

Most experts still believe that vaccination prevents 50% of influenza-related deaths (with a smaller effect on rates of all-cause mortality[14]), including deaths in very old people.[15] A recent review found no basis for the

historic concern that the antibody response to the influenza vaccine in people age 60 and older declines more rapidly than in younger people and below seroprotective levels within 4 months of immunization.[16]

Nevertheless, discordance between antibody and T-cell responses to influenza vaccine does exist[17] (ie, the vaccine can induce antibodies while not boosting the T-cell-specific response), and we should continue to seek new vaccines that are more effective.

More people are being vaccinated, but we're still below our goals

Although influenza vaccination rates among adults continue to improve,[18] they remain well below the Healthy People 2010 initiative's target of 90% in adults age 65 and older (the current rate is 72%) and below the target of 60% in people age 18 through 64 who have one or more high-risk conditions, health care workers, and pregnant women[19] (currently 35% in people age 18 through 49 and 42% in people age 50 through 64). Thus, we still need to improve vaccination coverage rates.

Health care providers should offer vaccination at every opportunity between October and May.[20] Offering vaccination in nontraditional settings such as work sites and pharmacies is likely to be cost-saving for healthy adults due to averted morbidity.[21] At many hospitals, health care workers can opt out of being vaccinated, but they must formally state that they are doing so. The use of these declination statements among health care workers is associated with a mean increase of 11.6% in vaccination rates.[22]

Since influenza is the second most frequent vaccine-preventable infection in travelers, the vaccine should be offered to those crossing to the opposite hemisphere during its peak influenza season (eg, to South America in May through September), as well as to those visiting the tropics at any time of year.[23]

Vaccination is safe and effective in high-risk groups

Data on vaccination are reassuring in several at-risk groups.

In pregnancy, there is no indication that infants are harmed if their mothers are vaccinated in the first trimester.[24] The evidence of excess morbidity during influenza epidemics supports vaccinating healthy pregnant women in the second or third trimester and those with comorbidities any time during pregnancy. Influenza vaccination during pregnancy reduces laboratory-confirmed influenza in infants up to 6 months of age by 63% and prevents 29% of all febrile respiratory illnesses in infants and 36% of those in mothers.[25]

In patients with chronic obstructive pulmonary disease, vaccination cuts the rate of outpatient visits and hospitalizations due to acute respiratory illness by 67%.[26] The antibody response to influenza vaccine in patients with rheumatoid arthritis treated with rituximab (Rituxan), a monoclonal antibody directed against CD20 surface antigen-positive B lymphocytes, was lower than in healthy controls, but was not negligible.[27]

Dispelling myths about vaccination in children

One recently published study in children younger than 5 years did not find vaccination to be effective in preventing influenza-related hospitalizations and outpatient visits.[28] However, in both seasons in which this study was conducted, there was a suboptimal antigenic match between vaccines and circulating strains. Moreover, about 60% of participants were unvaccinated and another 20% were only partially vaccinated, making it difficult to assess vaccine effectiveness. Several other studies have shown that, when there is a good match, vaccine effectiveness in children is 85% to 90%.

Experts still believe vaccination cuts flu-related deaths by 50%

Even though the live-attenuated (inhaled) vaccine is more expensive than the inactivated (injected) vaccine, it reduces the number of influenza illness cases and lowers subsequent health care use in children and productivity loss in their parents, with a net total savings of $45.80 relative to the inactivated vaccine.[29] The live-attenuated vaccine provides sustained protection against influenza illness for 12 months following vaccination, as well as meaningful efficacy through a second season without revaccination, although at a lower level.[30]

Several myths about the live-attenuated vaccine should be dispelled.[31] It is well tolerated and causes only mild, transient symptoms

of upper respiratory infection, even in people with asthma or the early stages of human immunodeficiency virus infection. Genetic reversion of the vaccine strain to a wild-type virus requires independent mutation in four gene segments, an event that has not been observed. Finally, although viral shedding is common for several days after vaccination, transmission to another person has been shown in only one person, who remained asymptomatic.

Unfortunately, rates of influenza vaccination are even worse for children than for adults.[32] In children 6 through 23 months old, only 22% are fully vaccinated; in those 24 through 59 months old, only 16.5% are.

One group of immunocompromised children, liver transplant recipients, achieved antibody seroprotection and seroconversion rates similar to those achieved by their healthy siblings, with no vaccine-related serious side effects.[33] As in adults, the cell-mediated immune response to the vaccine was diminished, suggesting that other strategies are needed to provide optimal protection.

IF BIRD FLU BREAKS OUT, WE HAVE A VACCINE

The goal vaccination rate in people age 60 and older is 90%; the rate now is 72%

In the event of an outbreak of avian influenza in humans, the US government now has a vaccine against H5N1, the causative virus. A two-dose regimen of a whole-virus H5N1 vaccine, which is derived from cell culture, induced neutralizing antibodies against diverse H5N1 virus strains in most subjects in one study.[34] Another vaccine, which is egg-independent and adenoviral vector-based and contains conserved nucleoproteins, is broadly protective against globally dispersed H5N1 virus clades.[35] The addition of the MF59 adjuvant to a subvirion H5N1 vaccine increased antibody response, but the addition of aluminum hydroxide did not.[36]

EXERCISE AND HYGIENE PREVENT FLU

Exercise has benefits beyond the usual ones: one study showed that exercising at low to moderate frequency (between once a month and three times a week) is associated with lower rates of influenza-related death.[37]

A recent meta-analysis[38] confirmed that hygienic measures can prevent the spread of respiratory viruses in the community. The investigators calculated that hand-washing at least 10 times daily can prevent a large number of these infections (number needed to treat [NNT] = 4), and wearing surgical masks (NNT = 6), N95 masks (NNT = 3), gloves (NNT = 6), and gowns (NNT = 5) had incremental effects. On the other hand, the value of adding virucidal or antiseptic solutions to normal hand-washing was uncertain. Strict adherence to hand hygiene and masks (including by children) is needed to prevent influenza transmission in the home.[39]

AMANTADINE, RIMANTADINE ARE OUT; OSELTAMIVIR RESISTANCE IS GROWING

The CDC continues to recommend against using amantadine (Symmetrel) or rimantadine (Flumadine) to treat flu, owing to a high rate (> 90%) of resistance to these drugs.

A nonrandomized study suggests that zanamivir (Relenza) is more effective than oseltamivir (Tamiflu) for treating influenza B.[40] A retrospective study in nine lung transplant recipients showed that oseltamivir is well tolerated and may reduce the risk of complications in these patients.[41] Large, randomized, multicenter studies are under way to better assess oseltamivir's preventive and therapeutic efficacy in transplant recipients.

In children, as in adults, oseltamivir is less effective against influenza B than influenza A,[42] and both neuraminidase inhibitors, ie, oseltamivir and zanamivir, are equally effective in reducing the febrile period of influenza.[43]

During the 2007–2008 season, the rate of resistance to oseltamivir increased alarmingly.[44] Resistance was restricted to A (H1N1) viruses carrying the H274Y mutation. In March 2008, the frequency of resistance among A (H1N1) viruses in the United States was 8.6%, 10 times higher than during the preceding influenza season. Resistance rates were much higher in several European countries, including Norway and France. During the Southern Hemisphere's influenza season (May 2008 though September 2008), 46.5% of influenza A (H1N1) viruses received from 14 countries were resistant to oseltamivir.[45] It is worrisome that many of these resistant viruses were isolated from untreated

patients. Fortunately, to date, 99% of these isolates remain susceptible to zanamivir.

Microbiologic tests to detect resistance are not currently available for clinical use. During an influenza pandemic, widespread use of neuraminidase inhibitors will likely promote further development of drug resistance. A mathematical model concluded that combined treatment and prophylaxis with antiviral agents will be necessary to control transmission during a pandemic, and that allocating different drugs to cases and contacts would be most effective in curtailing emergence of resistance.[46]

For now, either oseltamivir or zanamivir is acceptable for patients with flu symptoms and can be started pending results of PCR testing of nasopharyngeal swabs to make sure that the patient really has influenza. The drugs should be taken for 5 days.

Last year, resistance to oseltamivir increased alarmingly

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