CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will vaccinate all people older than 6 months against influenza this season

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Influenza: Still more important than Zika virus in 2016–2017

ABSTRACT

Influenza kills and hospitalizes many people every year. Although the 2015–2016 influenza season was relatively mild, we should remain vigilant in our efforts to reduce the impact of future epidemics or pandemics by implementing universal influenza vaccination and early initiation of antiviral therapy for suspected cases. We don't expect influenza vaccine to prevent all cases of influenza, since immune response varies depending on age, underlying diseases, and immunosuppression.

KEY POINTS

Influenza vaccine remains the most effective way to prevent influenza. Healthcare providers should continue to vaccinate all people older than 6 months.

For the 2016–2017 influenza season, only the inactivated influenza vaccine, not the live-attenuated vaccine, is recommended, regardless of age group or underlying disease.

Early initiation of a neuraminidase inhibitor is advised for an influenza-like illness while awaiting a confirmatory diagnostic test.

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The mass media and the medical literature have been saturated in the last few years by concerns about a variety of emerging viral epidemics such as Ebola and Zika. We must always remember that influenza will continue to affect many more patients worldwide.

The *Cleveland Clinic Journal of Medicine* periodically publishes updates on influenza, a topic befitting the large proportion of internists and internal medicine subspecialists who regularly read the *Journal*. This series began in 1975 with an article by Steven R. Mostow, MD,[1] which followed three pandemics that changed the world's attitude about influenza.

A lot has changed since then, including another pandemic in 2009–2010. Here, I review recent information relevant to daily practice.

NO REASON FOR COMPLACENCY

The relatively mild 2015–2016 influenza season is no reason for complacency this season.

Influenza activity in 2015–2016 was milder than in most seasons in the last decade.[2] Activity peaked in mid-March and resulted in fewer outpatient visits, hospitalizations, and deaths than in previous seasons. Influenza A (H1N1)pdm09 has remained the predominant circulating virus since 2009. Although the overall rate of influenza-related hospitalization was less than half that in previous years, the hospitalization rate of middle-aged adults was relatively high (16.8 per 100,000 population). Importantly, 92% of adults with influenza illness that required hospitalization had at least one underlying medical condition, alerting us as healthcare providers that there is plenty of room for improvement in preventing such hospitalizations.

We should remain vigilant. We should put forth our best efforts in vaccinating all individuals above the age of 6 months and in diagnosing influenza early in the course of the illness in order to prescribe antiviral therapy within 48 hours of onset of symptoms. These actions not only shorten the illness and prevent hospitalization and secondary bacterial infection, but also reduce contagion and thus reduce overall healthcare costs.

School closure as a measure to halt epidemics has been lately called into question,[3] since there are not enough data to support doing this routinely. School closure in Western Kentucky during the 2013 influenza epidemic did not reduce transmission but caused additional economic and social difficulties for certain households.[4]

STUDIES REINFORCE EARLIER DATA THAT INFLUENZA VACCINE WORKS

In the several decades since influenza vaccine became available, hundreds of studies have demonstrated the value of the "flu shot." A few recent papers that support these well-established data:

- In adults who sought medical care for acute respiratory illness, influenza vaccine was 58.4% effective in preventing laboratory-confirmed influenza illness in adults age 50 and older.[5]
- In the same age group, influenza vaccine was 56.8% effective in preventing laboratory-confirmed influenza hospitalizations.[6]
- Influenza vaccination in patients with heart failure reduced all-cause hospitalizations, particularly cardiovascular hospitalizations (30% reduction) and hospitalizations for respiratory infections (16% reduction).[7] This effect lasted up to 4 months after influenza vaccination.
- Patients who were hospitalized with community-acquired, laboratory-confirmed influenza pneumonia were 43% less likely to have received the influenza vaccine than patients hospitalized with community-acquired pneumonia due to other pathogens.[8]

INFLUENZA VACCINE IS EVEN MORE VALUABLE DURING PREGNANCY

Influenza vaccination during pregnancy prevented one in five preterm deliveries in a developing country[9] and reduced the risk of stillbirth by 50% in Australia.[10]

An interesting collateral benefit was demonstrated in a survey conducted in Minnesota, where children of mothers who self-reported prenatal influenza vaccination were more likely to complete their routine childhood vaccination series.[11]

ADDITIONAL BENEFITS OF INFLUENZA VACCINATION

A recently appreciated benefit is that influenza vaccine induces cross-reactive protective immune responses ("heterologous immunity") to viral strains not included in the vaccine, even in immunosuppressed individuals such as kidney transplant recipients.[12] Interestingly, patients were more likely to seroconvert for a cross-reactive "heterologous" antigen if they also seroconverted for the vaccine-specific "homologous" antigen.

In a study in mice, an influenza vaccine with an adjuvant protected mice not only from influenza virus challenge, but also from a *Staphylococcus aureus* superinfection challenge.[13] This novel idea suggests that influenza vaccine protects not only against influenza virus infection, but also against a potentially fatal secondary bacterial infection. This has significant implications for curbing antibacterial use, with an expected reduction in antimicrobial resistance.

Another important benefit of influenza vaccination was recently demonstrated when ferrets were intranasally inoculated with the highly pathogenic influenza A(H5N1) strain and then received either influenza vaccine or prophylactic oseltamivir. Ferrets that received the vaccine were less likely to develop severe meningoencephalitis.[14] Since influenza A(H5N1) is much more virulent than the current circulating influenza strains, and since it may be the cause of the next pandemic, preventing such a serious complication of influenza would be lifesaving.

The 2015–2016 influenza season was milder than most in the last decade

SAFETY OF INFLUENZA VACCINATION

Hundreds of studies involving thousands of people have established the safety of influenza vaccination.

Issues related to Guillain-Barré syndrome have long been put to rest. A large retrospective study found no evidence of increased risk of Guillain-Barré syndrome following vaccination of any kind, including influenza vaccination.[15]

Local reactions after vaccination are transient and do not interfere with the ability to perform daily activities.

In this era of utilization review, it is reassuring to know that giving influenza vaccine to hospitalized surgical patients was not associated with an increased rate of postdischarge fever or other clinical concern for infection requiring emergency room visits or rehospitalization.[16]

WHY INFLUENZA VACCINE MAY NOT PREVENT ALL CASES OF INFLUENZA

Whether neutralizing antibodies to influenza virus hemagglutinin antigen should be the main immune correlate of protection for influenza vaccines remains in question. Although prepandemic avian influenza vaccines are poorly immunogenic in inducing neutralizing antibodies, they confer considerable protection. A recent study showed that antibody-dependent cell-mediated cytotoxicity to hemagglutinin antigen in an avian influenza vaccine was a better predictor of protective capacity than neutralizing antibodies.[17]

Hundreds of studies have established the efficacy and safety of influenza vaccination

Patterns of immunity induced by the live-attenuated influenza vaccine and the inactivated influenza vaccine are different.[18] In fact, no single cytokine or chemokine measurement predicts protection.

Even though adults age 50 and older mount statistically significant humoral and cell-mediated immune responses to the inactivated vaccine, two-thirds do not reach hemagglutination inhibition antibody titers of 40 or higher for influenza A(H1N1), and one-fifth do not reach hemagglutination inhibition antibody titers of 40 or higher for influenza A(H3N2).[19] While age had some negative effect on vaccine responsiveness, prevaccination titers were much better at predicting postvaccination antibody levels.

ONGOING DEBATE OVER LIVE-ATTENUATED INFLUENZA VACCINE

Several studies had shown that the live-attenuated influenza vaccine, given intranasally, was not only more protective in vaccinated children, but also provided herd protection in unvaccinated contacts. However, a recently published study conducted in Canadian Hutterite children showed that the live-attenuated vaccine did not result in herd immunity when compared to the inactivated influenza vaccine.[20]

On June 22, 2016, the US Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices recommended against the use of the live-attenuated vaccine for the 2016–2017 season,[21] based on data showing negligible protection conferred by the live-attenuated influenza vaccine in the three preceding influenza seasons.

This decision created significant debate among experts in the field. It is unclear why the live-attenuated influenza vaccine was much less protective in the last three seasons than in prior seasons. Recommending against its use in the United States will essentially eliminate any possibility of reassessing its efficacy in this country. Of note, the quadrivalent live-attenuated influenza vaccine had recently replaced the previous trivalent live-attenuated vaccine, which may have introduced some "competition" among the vaccine strains to infect enough cells to allow viral replication and subsequent immune response. Another potential explanation is that consistent annual vaccination may have resulted in a cumulative immunity that could hamper response to subsequent doses.

COMPOSITION OF THE 2016–2017 INFLUENZA VACCINE

The 2016–2017 quadrivalent inactivated influenza vaccine will contain[22]:

- A/California/7/2009 (H1N1)pdm09-like virus
- A/Hong Kong/4801/2014 (H3N2)-like virus
- B/Brisbane/60/2008-like virus (B/Victoria lineage)
- B/Phuket/3073/2013-like virus (B/Yamagata lineage).

This represents a change in the A (H3N2) component compared with the 2015–2016 vaccine.

Influenza vaccine manufacturers estimated they would produce 170 million doses for distribution in the United States for the upcoming influenza season. The previously mentioned recommendation against the use of the live-attenuated vaccine, which accounts for approximately 8% of the influenza vaccine supply, may affect vaccine uptake, particularly in children.

NEW ANTI-INFLUENZA AGENTS AND UPDATE ON EXISTING AGENTS

Neuraminidase inhibitors are the only class of antiviral drugs currently recommended for prevention and treatment of influenza. The three products currently available in the United States are oseltamivir, zanamivir, and peramivir. Oseltamivir is administered orally, and the first generic version was approved by the US Food and Drug Administration on August 3, 2016. Zanamivir is administered by oral inhalation. Both oseltamivir and zanamivir are approved for treatment and prevention of influenza. Peramivir is administered intravenously as a single dose and is approved only for the treatment of acute influenza, not prevention.

Unfortunately, the influenza vaccination rate during pregnancy in the United States remains only around 50%.[23] Physicians' recommendations are strongly associated with vaccine uptake, particularly when they emphasize protective effect on the newborn. Influenza during pregnancy carries higher mortality than in the general population, with collateral fetal loss.

Early initiation of antiviral therapy is particularly imperative during pregnancy. A recent study showed that starting antiviral therapy within 2 days of onset of illness in pregnant women hospitalized with severe influenza reduced length of stay by 5.6 days compared with those in whom therapy was started more than 2 days after illness onset.[24]

A single dose of laninamivir octanoate, a long-acting neuraminidase inhibitor currently approved in Japan for treating influenza, was recently shown to be effective as postexposure prophylaxis.[25] This option may be convenient for people who prefer not to take a daily medication for several days, or in an outbreak in a healthcare facility.

Early initiation of antiviral therapy is particularly imperative during pregnancy

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