Influenza Vaccine in the Elderly and Chronic Obstructive Pulmonary Disease

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Influenza viruses are RNA viruses that are a major determinant of morbidity and mortality caused by respiratory disease. Influenza is highly contagious and has caused epidemics and pandemics for centuries. Most influenza infections are self-limited, but lower respiratory tract and cardiac complications can result in increases in hospitalizations and deaths. The recommended composition of influenza vaccine is updated annually in order to provide a vaccine that is antigenically well matched with the new influenza virus strains that are expected to cause epidemics. Influenza vaccination significantly reduces mortality; however, approximately one third of elderly Americans are not immunized annually. The nation's goal is to increase the influenza vaccination rate among the elderly to 90%. Vaccination is the most effective measure for reducing the impact of influenza and is a cost-effective preventive health intervention for the elderly and individuals with chronic obstructive pulmonary disease.

Introduction

There are three distinct types of influenza viruses (A, B, and C); however, the A and B types are responsible for most human illness. They are RNA viruses belonging to the family of Orthomyxoviridae. Influenza viruses have in common the presence of a host-cell derived envelope covered with surface glycoproteins. The glycoproteins may possess hemagglutinin or neuraminidase activity. The hemagglutinin protein of influenza virus binds virus particles to susceptible cells, and hemagglutinin is the major antigen against which neutralizing antibodies are directed. Neuraminidase is an enzyme that catalyzes the removal of sialic acid residues from glycoproteins, which releases virus particles from the surface of host cells.

Type A influenza strains are characterized by the type of hemagglutinin and neuraminidase present in the viral outer membrane envelope. There are currently fifteen hemagglutinins and nine neuraminidases known to exist in influenza viruses that infect animals (wild aquatic birds, domestic poultry, pigs, seals, and other mammals). Influenza A viruses are named according to the location and first year of isolation, and the hemagglutinin and neuraminidase subtypes. For example, Influenza A/Taiwan/86H1N1 is an influenza A strain of the H1N1 subtype first isolated in Taiwan in 1986. A remarkable feature of influenza viruses is the frequent antigenic changes that occur in the hemagglutinin and neuraminidase. Hemagglutinin and neuraminidase undergo antigenic variation independent of each other. Minor antigenic changes are termed antigenic drift, and the development of antigenic variants through antigenic drift results in seasonal epidemics. In temperate climates in either hemisphere, epidemics occur almost exclusively in the winter months (October through April in the Northern Hemisphere). Reports of increased numbers of children with febrile respiratory illness will often be the first indicator of influenza in a community; however, occasionally an outbreak in a nursing home will be the first indication of influenza.

Major antigenic change in hemagglutinin or neuraminidase called antigenic shift can result in the appearance of a new subtype of influenza A. The mechanism for antigenic shift is genetic reassortment between human and avian influenza A viruses. Pandemics are severe outbreaks that rapidly progress to involve all parts of the world. An antigenic shift may result in a worldwide pandemic if there is little or no pre-existing immunity in the world's population, if the virus has the potential to infect humans (causing clinically apparent illness), and if the virus transmits readily from person to person. To date only three hemagglutinins (H1, H2, and H3) and two neuraminidases (N1 and N2) have been firmly implicated in pandemic influenza. Avian viruses might also be directly introduced into human populations without prior reassortment. In 1997, the occurrence of a number of cases of influenza in Hong Kong involving a highly virulent avian A/H5N1 virus prompted a pandemic alert; however, clinically apparent illness was rare, albeit severe (18 people were hospitalized, six died), and significant person-to-person transmission did not occur. The last pandemic was in 1968, but there remains a constant threat of pandemic influenza viruses emerging from animal reservoirs.

Clinical Illness and Complications of Influenza

Influenza virus spreads from person to person by coughing, sneezing, talking, or by contact with contaminated

hands or surfaces. The virus attaches to and penetrates columnar epithelial cells in the larynx, trachea, and bronchial tree. Subsequently, viral replication begins and leads to cell death by cell necrosis and apoptosis. Prevention of attachment and penetration may occur by the mechanical action of the mucociliary apparatus and by specific secretory antibody (immunoglobulin A). The incubation period for influenza is 1 to 4 days, and a typical uncomplicated presentation is characterized by an abrupt onset of fever and chills accompanied by headache, myalgias, dry cough, malaise, sore throat, and rhinitis [1]. Pulmonary complications include primary influenza viral pneumonia and secondary bacterial pneumonia (*Haemophilus influenzae*, *Staphylococcus aureus*, *Streptococcus pneumoniae*). Influenza can exacerbate underlying medical conditions such as pulmonary or cardiac disease and has been associated with encephalopathy, myocarditis, pericarditis, myositis, and Reye's syndrome.

Epidemics of influenza typically occur during the winter months in temperate regions. In the United States during 1990 to 1999, influenza was responsible for an average of 36,000 deaths per year [2]. The risks for complications, hospitalizations, and deaths from influenza are higher among the elderly and persons with certain underlying medical conditions (*eg*, chronic pulmonary disease or cardiovascular disease, in particular those with reduced pulmonary function and cardiac insufficiency). During major epidemics, hospitalization rates for those at high risk for influenza complications may increase several-fold, depending on the age group [1].

Influenza Vaccine

The most effective method to prevent the medical consequences of an influenza epidemic is annual vaccination of patients at risk. Antiviral drugs may serve as adjuncts to vaccine. Despite influenza vaccine being a covered benefit under Medicare Part B since 1993, approximately one third of elderly Americans are not immunized annually [1]. The Healthy People 2010 goal is to increase influenza vaccination rates among the elderly to 90% by 2010 [3]. Two types of influenza vaccine are available in the United States—inactivated (*ie*, killed virus) and live, attenuated influenza vaccine (LAIV). Inactivated vaccine is administered by intramuscular injection and approved for persons aged older than 6 months, whereas LAIV is an intranasal spray and approved for healthy persons aged 5 to 49 years. Both the inactivated and live, attenuated vaccines are formulated as trivalent preparations containing one example each of influenza A(H1N1) virus, A(H3N2) virus, and influenza B virus. Virus strains to be included in the vaccines are decided annually by the World Health Organization on the basis of epidemiologic and antigenic analysis of currently circulating strains. The efficacy of trivalent inactivated influenza vaccine for preventing culture-proven influenza A illness in adults is approximately 75% [4]; however, in high-risk populations such as the elderly, there are few prospective trials of protective efficacy. In one placebo-controlled prospective trial in the elderly, inactivated vaccine was approximately 58% effective in preventing laboratory-documented influenza [5].

Efficacy of Influenza Vaccine in the Elderly

It has been estimated that persons aged older than 65 years account for more than 80% of all pneumonia- and influenza-like deaths. In 70% to 90% of healthy individuals aged younger than 65 years, influenza vaccine prevents influenza-related illness when the vaccine and infecting virus are antigenically similar. In the elderly, influenza vaccine efficacy is reduced and the exact mechanism is unknown. A randomized controlled trial in the Netherlands among 1838 patients aged 60 years or older demonstrated 58% efficacy of influenza vaccine for a laboratory-confirmed influenza illness [5]. A recent 2002 meta-analysis of the effectiveness of influenza vaccine in persons aged 65 and older living in the community found that when there is a good match between influenza strains in the vaccine and those in circulation, vaccination would prevent approximately one in five cases of influenza-like illness, one in four hospitalizations for pneumonia and influenza, and one in four deaths following hospitalization for these conditions. The authors concluded that influenza vaccine reduced all-cause mortality by 50% and hospitalization for pneumonia or influenza on the average by 33% [6••]. An earlier meta-analysis in 1995 of the efficacy of influenza vaccine determined that influenza vaccination was highly effective among elderly residents of long-term care facilities, reducing pneumonias on average by 53%, hospitalizations by 48%, and deaths by 68% [7]. A serial cohort study of elderly members of three managed care corporations in the United States assessed the risk of hospitalization or death associated with influenza and the effectiveness of influenza vaccination over two influenza seasons. Influenza vaccine was effective in reducing hospitalizations or death by 48% in healthy elderly persons and in those elderly with high-risk medical conditions [8]. A prospective observational cohort study in Taiwan demonstrated that influenza vaccination reduced the rates of hospitalizations for all-causes, lung diseases, congestive heart failure, renal disease, and cirrhosis [9]. The data support vaccination of the elderly regardless of whether they are healthy or have high-risk chronic medical conditions. Influenza vaccination saves lives and decreases hospitalization rates.

Influenza Vaccination and Cardiovascular/Cerebrovascular Disease

Death rates from cardiovascular diseases increase during epidemics of influenza [10], and recent studies suggest influenza may play a role in atherogenesis or atherothrombosis [11]. In a recent case-control study in patients with known coronary artery disease, influenza vaccination was

associated with a 67% reduction in the risk of myocardial infarction in the subsequent influenza season [12]. In a population-based case-control study of 342 married persons who had had out of hospital primary cardiac arrest, influenza vaccination during the prior 12 months was associated with a 49% reduction in the risk of cardiac arrest [13]. Another case-control study reported a 50% risk reduction in stroke risk in patients vaccinated during the year of the study and a 48% risk reduction in patients vaccinated during the past 5 years [14]. An unblinded, controlled trial of vaccination among 200 patients with acute myocardial infarction and 101 patients who were undergoing angioplasty or stent placement in Argentina found that influenza vaccination was associated with a lower risk of cardiovascular death [15]. In an observational study of two large community-dwelling elderly cohorts during the 1998 to 1999 and 1999 to 2000 influenza seasons, influenza vaccination was associated with a reduction in the risk of hospitalization for cardiac disease (reduction of 19%), cerebrovascular disease (reduction of 16%), and all-cause mortality (reduction of 48%) [16••]. These findings continue to highlight the benefits of influenza vaccination and the need to improve the rate of vaccination among the elderly; however, further studies are needed to confirm and quantify the cardiovascular and cerebrovascular benefits of influenza vaccination.

Influenza Vaccine in Chronic Obstructive Pulmonary Disease

Influenza vaccine is underused [3], and elderly individuals with chronic lung disease are especially at high risk for influenza complications. There are few studies designed to test the efficacy of the vaccine in persons with specific underlying medical conditions. A retrospective multiseason cohort study for the 1993 to 1994, 1994 to 1995, and 1995 to 1996 influenza seasons that included elderly members of a managed care organization with chronic lung disease found that influenza vaccination was associated with a 52% reduction in hospitalizations for pneumonia and influenza and a 70% reduction in deaths from all causes. Vaccinated individuals in the cohort also had fewer outpatient visits for pneumonia and for all respiratory conditions. The clinical effectiveness of vaccination in this study was similar to that seen in earlier studies of non–high-risk elderly individuals [17]. A stratified, randomized, double-blind, placebo-controlled trial in 2004 in Thailand revealed that the effectiveness of influenza vaccination was not modified by the severity of chronic obstructive pulmonary disease (COPD; mild, moderate, severe) [18••]. The concern among practitioners that influenza vaccine may induce acute exacerbations in those with COPD has contributed to suboptimal rates of vaccine uptake in this group [19,20]. A population-based cohort study of 12,000 elderly individuals with COPD or asthma in 2003 found no increased risk of adverse acute outcomes in the first 2 weeks after influenza vaccination [21]. These studies strongly suggest that influenza vaccine is safe and effective in the elderly COPD population and is associated with substantial health benefits.

Approaches to Improved Influenza Vaccination in the Elderly

Inactivated influenza vaccine is most efficacious among young healthy individuals and least effective in the high-risk elderly. This is in part because response rate and postvaccination antibody levels achieved are lower in the elderly [22]. Studies with nasal LAIV simultaneously administered with inactivated influenza vaccine have been performed in an attempt to improve the benefit of vaccination against influenza in the elderly. LAIV induces local immunity, which may be an important step in preventing initial infection with influenza virus. A randomized, double-blind, placebo-controlled study conducted during a 3-year period (1987–1989) compared the protective efficacy of combined monovalent LAIV with inactivated influenza vaccine with that of inactivated influenza vaccine alone in elderly residents of long-term care institutions. The results of the study indicated that monovalent LAIV conferred additional protection against influenza A when administered simultaneously with inactivated influenza vaccine in nursing home residents, and further studies were recommended [23]. Recently, a large study assessed whether trivalent LAIV provided additional protection when coadministered with inactivated influenza vaccine in patients with COPD. The study did not demonstrate statistically significant added protection from LAIV [24]. There is currently insufficient evidence to recommend simultaneous administration of LAIV with inactivated vaccine to improve vaccine efficacy in the elderly or individuals with COPD.

Cost Effectiveness of Inactivated Influenza Vaccine in the Elderly

A review in 2000 of available evidence regarding the pharmacoeconomics of influenza vaccination in the elderly generally found influenza vaccination to be cost saving. However, in several of the studies reviewed there was a distinction in cost effectiveness in high-risk and non–high-risk (*ie*, healthy) elderly patients. In those studies, influenza vaccination costs exceeded the benefits for non–high-risk individuals, whereas vaccination for high-risk individuals had cost savings [25]. A large study in Minnesota spanning six consecutive influenza seasons (1990–1991 to 1995–1996) looked at cost effectiveness of influenza vaccination for healthy persons aged between 65 and 74 years. Influenza vaccination in this group was associated with net cost savings and substantial reductions in the risk of hospitalization and death [26•]. These studies support an age-based strategic approach to influenza vaccination beginning at the age of 65 years, regardless of risk category.

Conclusions

Influenza can be a serious illness in the elderly, and complications include pneumonia and exacerbations of underlying cardiorespiratory conditions. Influenza vaccination of elderly persons living in the community and in long-term facilities is associated with reduced hospitalizations from complications from influenza, fewer deaths during the influenza season, and with direct health care cost savings. Vaccination of the elderly with inactivated influenza vaccine is effective, regardless of whether they are healthy or have high-risk chronic medical conditions. Simultaneous administration of LAIV with inactivated vaccine to improve vaccine efficacy in the elderly or in individuals with COPD has not succeeded and therefore is not recommended. The possible benefits of influenza vaccination with respect to cardiovascular and cerebrovascular disease need further study in order to be confirmed and quantified. In the elderly COPD population, influenza vaccine is safe and effective and associated with substantial health benefits.

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