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REVIEW ARTICLE

Influenza and pneumococcus vaccination: current recommendations

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ABSTRACT

Acute asthmatic exacerbation and hospital admission may be associated with severe influenza infection. It has been reported that immunization with inactivated influenza vaccine in patients with persistent asthma decreased respiratory illnesses and asthma-related events. Evidence from more recently published randomized trials indicated that there is no significant increase in asthma exacerbations immediately after influenza vaccination. Similarly, inactivated influenza vaccine in chronic obstructive pulmonary disease (COPD) patients resulted in a significant reduction in the total number of exacerbations when compared with placebo. The highest incidence of invasive pneumococcal disease occurs in children <5 years of age, immunocompromised persons such as HIV, and those ≥65 years of age. Therefore, pneumococcal vaccine has been recommended for all adults ≥65 years of age and in younger patients who have a condition that increases the risk of invasive pneumococcal disease or pneumococcal pneumonia. The development of pneumococcal conjugate vaccines represents a major advance, and the use of such vaccine has reduced the incidence of pneumococcal disease and acute exacerbation in COPD patients. There are limited data about the effect of pneumococcal vaccine on asthmatic patients.

Keywords: Influenza vaccine, Pneumococcal vaccine, Asthma, COPD

Seasonal influenza vaccination in adults

Influenza virus may result in an acute respiratory illness. There are two types of viruses as influenza A and B. Influenza epidemics are reported nearly every year and the risk is highest in the winter season. Influenza vaccines are developed to prevent influenza infection in the population. Scientific researchers reported that influenza viruses change their antigenic characteristics frequently. Therefore, annual influenza vaccination should be redeveloped against these novel antigens [1-4]. The United States Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) held a worldwide network to track influenza virus isolates every year and to predict the appropriate annual influenza vaccine type. New vaccines are produced each year to match viruses over world. Influenza A viruses show periodic changes in the antigenic characteristics of their envelope glycoproteins, the hemagglutinin and the neuraminidase [5]. Major changes of glycoproteins are called as antigenic shifts and minor changes as antigenic drifts and also antigenic drifts in the hemagglutinin have been reported. Ongoing studies screen these changes annualy to produce the well matched vaccines. Current influenza vaccines are trivalent or quadrivalent [4]. The trivalent vaccine contains two influenza A virus antigens and one influenza B virus antigen, the quadrivalent vaccine contains two influenza A antigens and two influenza B antigens. A quadrivalent formulation is favored over a trivalent formulation when possible. Annual immunization is recommended even if the previous year's vaccine contained same virus antigen because immunity declines gradually over time. In a meta-analysis, the overall efficacy of inactivated vaccines in preventing laboratory-confirmed influenza was 60% in 2014 (53 to 66 %) [6]. Commercially, two different types of influenza vaccine are available, inactivated influenza vaccine (IIV) and live-attenuated influenza vaccine (LAIV) [2,4]. The available inactivated trivalent or quadrivalent influenza vaccines are prepared by split virion or subunit vaccines that have been inactivated. The standard-dose of inactivated influenza vaccines are usedintramuscularly in adults of any age. These vaccines are produced in embryonated chicken eggs. Standard-dose quadrivalent LAIV is administered intra nasally and is approved for healthy non-pregnant adults up to 49 years of age. Comparisons of inactivated and live-attenuated vaccines have shown that the differences between the two vaccines were not statistically significant. In this field, there are numerous studies to develop new vaccines with high efficiency and efficacy. Recently, a vaccine using recombinant DNA technology was approved in USA. Currently, vaccine production takes six months from the selection of virus type until production. A single

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dose of an influenza vaccine should be offered soon after the vaccine becomes available, ideally by October in the northern hemisphere and May in the southern hemisphere. Influenza virus usually causes an acute self-limited illness in healthy young adults, however, older adults and patients with different health problems are high risk groups [7,8]. The United States Advisory Committee on Immunization Practices (ACIP) expanded the recommendation for influenza vaccination to include all individuals six months of age and older. Annual influenza vaccination is recommended for healthy non-pregnant adults <65 years of age (Grade 1A). Studies revealed Grade 1B for individuals ≥65 years of age and for other individuals at increased risk for severe influenza (eg, immunocompromised; chronic cardiovascular, pulmonary, or metabolic disease, renal, hepatic, hematologic diseases (including sickle cell disease), pregnancy, obesity, neuromuscular and neurodevelopmental disease, chronic aspirin use, resident of nursing home).

Healthcare personnel and household contacts or caregivers of persons with medical conditions should remain high priority for vaccination. Since influenza infection is associated with excess complications and death in pregnant women, influenza vaccine is recommended for pregnant women with any trimester and women who might be pregnant during the influenza season [2].

For individuals ≥65 years of age, the high-dose inactivated influenza vaccine is favored when available rather than a standard-dose inactivated influenza vaccine. The studies reported that high-dose vaccine is more immunogenic and more effective than the standard-dose vaccine in older patients (Grade 2B).

In a Cochrane meta-analysis, the vaccines were 58% percent effective against influenza in older patients [9]. In the 2012 to 2013 influenza season, influenza vaccine had 40 percent effectiveness and decreased approximately 60,000 hospitalizations among individuals ≥65 years of age in the United States [10]. There is a small number of studies evaluating mortality as an endpoint. A small but significant reduction in mortality in vaccinated older individuals was reported in a cohort study [11].

Co vaccination is an important point, inactivated influenza vaccines do not interfere with the other inactivated or live virus vaccines [2,12]. LAIV can also be administered at the same time with other inactivated vaccines [13]. However it should be administered at least four weeks after live virus vaccines. If possible, individuals on statins should receive the high-dose vaccine, since statins may decrease vaccine responses.

Table I. For 2015–16, ACIP recommends the followings for influenza vaccination [14]:

1. All persons aged ≥6 months should receive influenza vaccine annually.
2. For healthy children aged 2 through 8 years who have no contraindications or precautions, either LAIV or IIV is an appropriate option. LAIV should not be used in the following populations:
   - Persons aged <2 years or >49 years
   - Persons with contraindications listed in the package insert:
     - Children aged 2 through 17 years who are receiving aspirin or aspirin-containing products
     - Persons who have experienced severe allergic reactions to the vaccine or any of its components, or to a previous dose of any influenza vaccine
   - Pregnant women
   - Immunocompromised persons
   - Persons with a history of egg allergy
   - Children aged 2 through 4 years who have asthma or who have had a wheezing episode noted in the medical record within the past 12 months, or for whom parents report that a health care provider stated that they had wheezing or asthma within the last 12 months.
   - Persons who have taken influenza antiviral medications within the previous 48 hours.
3. In addition to the groups for whom LAIV is not recommended above, the "Warnings and Precautions" section of the LAIV package insert indicates that persons of any age with asthma might be at increased risk for wheezing after administration of LAIV. The package insert also notes that the safety of LAIV in persons with other underlying medical conditions that might predispose them to complications after wild-type influenza virus infection (e.g., chronic pulmonary, cardiovascular [except isolated hypertension], renal, hepatic, neurologic, hematologic, or metabolic disorders [including diabetes mellitus]), has not been established. These conditions, in addition to asthma in persons aged ≥5 years, should be considered precautions for the use of LAIV.
4. Persons who care for severely immunosuppressed persons who require a protective environment should not receive LAIV, or should avoid contact with such persons for 7 days after receipt, given the theoretical risk for transmission of the live attenuated vaccine virus to close contacts.

Seasonal influenza vaccination in patients with asthma or COPD

Influenza in asthmatic patients is associated with increased health care services use (hospital admissions, clinic visits, and emergency department visits). Inactivated influenza

vaccine in patients with persistent asthma resulted in decreased respiratory illnesses and asthma-related events. In a Cochrane review, the controlled trials noted no benefit in preventing influenza-related asthma exacerbations, although vaccination might improve specific aspects of asthma-related quality of life among children. Moreover, it has been shown that IIV is not associated with asthma exacerbations 2 weeks after vaccination in children and adults [15]. A few studies support the hypothesis that IIV vaccination might provide protection against influenza-related asthma exacerbations, but these studies were not prospective, randomized, or controlled and thus were excluded from analysis in the Cochrane review [15]. A study noted that vaccination was associated with reduced oral steroid use for asthma exacerbations and a protective effect in reducing severity-adjusted asthma exacerbations by 22% to 45% [16-18].

In patients with COPD, the influenza vaccine annually is recommended to prevent acute exacerbations of COPD (Grade 1B) [19]. In COPD patients, the influenza vaccine effectiveness was up to 76%. Several observational studies showed a reduction in the number of hospitalizations, incidence of pneumonia, risk of death, and number of acute exacerbations in COPD patients who received the influenza vaccine. Wongsurakiat and colleagues described the protective effects of a trivalent split-virus vaccine in patients with COPD by analyzing the number and severity of episodes of total acute respiratory illness. They found that the overall incidence of influenza-related respiratory infection in the vaccinated group was less than one fourth that in the placebo group. The effectiveness of vaccination was not influenced by the severity of COPD [20].

Pneumococcal vaccination in adults

Pneumococcal infections, including pneumonia and invasive disease such as bacteremia and meningitis may result in high risk of morbidity and mortality in children <5 year of age, older adults, and persons immunocompromised. The surface capsular polysaccharide of *Streptococcus pneumoniae* is the main part for production of antibody against bacteria. Pneumococcal vaccines are produced using some of these 90 different pneumococcal capsular serotypes that are identified as causative agent for invasive disease. Pneumococcal vaccination is recommended for all children, for adults who have high risk for pneumonia or invasive pneumococcal disease, and for all adults ≥65 years of age (Grade 1B). Pneumococcal vaccine is recommended especially for following patients [21-23] (Table II).

Table II. High risk groups for pneumococcal vaccination in adults

Chronic lung disease
Chronic heart disease
Diabetes Mellitus
Cerebrospinal fluid leaks
Cochlear implant
Functional or anatomic asplenia
Cigarette smoking
Aged≥ 65
Sickle cell disease/other hemoglobinopathies
Congenital or acquired immunodeficiency
Chronic renal failure
Nephrotic syndrome
Leukemia/lymphoma
Hodgkin disease
Generalized malignancy
Solid organ transplant
Diseases associated with treatment with immunosuppressive drugs or radiation therapy

Two types of pneumococcal vaccines are approved. Pneumococcal polysaccharide vaccine (PPSV23) consists of capsular material from 23 pneumococcal types. Pneumococcal conjugate vaccine (PCV) initially marketed as a 7-valent vaccine, now PCV13 consists of capsular polysaccharides from the 13 most common types that cause disease; it is covalently linked to a nontoxic protein to increase the immunologic response. PCV13 is recommended for all adults ≥65 years of age. United States Advisory Committee on Immunization Practices (ACIP) recommended sequential administration of both PCV13 and PPSV23 [21-23]. In accordance with the ACIP, PPSV23 is recommended alone for persons aged 19 to 64 years who have certain risk factors for pneumococcal infection and/or serious complications of pneumococcal infection [21-23]. The ACIP recommends that both PCV13 and PPSV23 be given sequentially to all adults aged ≥65 years and to adults of any age who have the underlying conditions listed above. When possible, PCV13 should be given first, followed by PPSV23 [21-23] as shown in Fig 1.

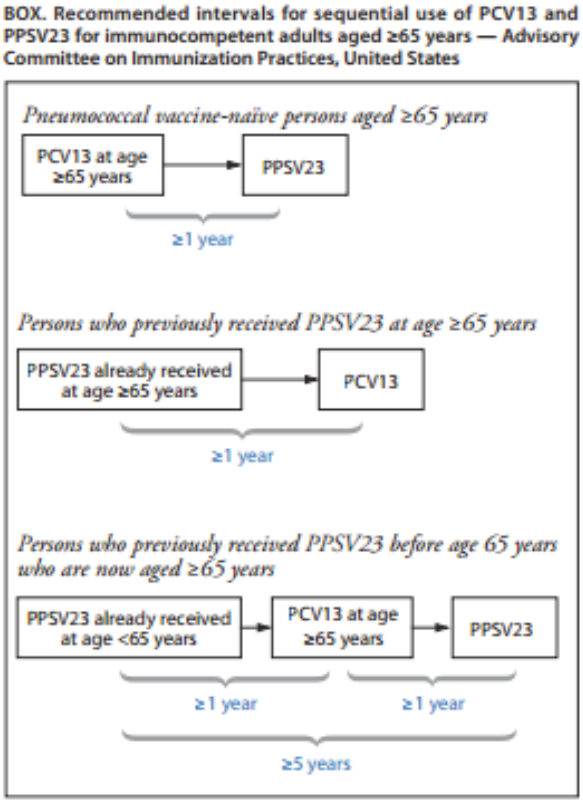

Fig 1. Recommendation of ACIP on intervals between PCV13 and PPSV23 Vaccines (2015).

These pneumococcal vaccines may be given concomitantly with other vaccines. Concurrent use of PPSV23 with the influenza vaccine is safe and does not alter the effectiveness of either vaccine. At the present time, revaccination of adults with PCV13 is not recommended.

Many studies of the pneumococcal polysaccharide vaccine have demonstrated efficacy against invasive and noninvasive pneumococcal disease such as bacteremia and meningitis, but both immunogenicity and efficacy are lower in elderly patients and immunocompromised hosts [24]. The CAPiTA trial, a randomized placebo-controlled trial that included approximately 85,000 adults ≥65 years of age in the Netherlands between 2008 and 2010 and who had not received a pneumococcal vaccine previously. The trial demonstrated 46 percent efficacy of PCV13 against vaccine-type pneumococcal pneumonia, 45 percent efficacy against vaccine-type non-bacteremic pneumococcal pneumonia, and 75 percent efficacy against vaccine-type invasive pneumococcal disease [25].

Several case-control studies, randomized trials, and meta-analyses have shown that the pneumococcal polysaccharide vaccine (PPSV) prevents pneumococcal disease. However, other published studies have failed to demonstrate efficacy for preventing invasive or noninvasive disease [26] or for reducing mortality [27, 28]. A 2013 systematic review and meta-analysis showed PPSV prevented invasive pneumococcal disease, all-cause pneumonia, but not all-cause mortality in adults in 16 randomized trials [27].

Pneumococcal vaccine in patients with asthma or COPD

Pneumococcus colonization occurs more frequently in the airways of patients with COPD when compared to healthy controls. It is associated with a higher risk of COPD exacerbation. Patients with chronic respiratory disease (COPD, chronic bronchitis and/or asthma) are at a higher risk of pneumonia than individuals without these comorbidities. Risk of pneumonia increases with age. Among individuals with COPD, those aged 65–79 or ≥80 years have an increasingly higher risk than those aged 45-65 years [29]. Having COPD, and greater age, lack of pneumococcal vaccination, and corticosteroid therapy have been identified as independent risk factors for recurrent community acquired pneumonia (CAP) in adults [30]. Therefore, pneumococcal vaccine is recommended as part of overall medical management in patients with COPD (Grade 2C). Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) recommended the use of pneumococcal vaccine for all adults aged ≥ 65 years and those aged 19 to 64 years with underlying medical conditions such as COPD [31]. Several retrospective studies showed a reduction in incidence of community-acquired pneumonia, hospitalizations, as well as prevention of invasive disease [32, 33]. However, a 2008 Cochrane review of adults found a reduction in invasive pulmonary disease after pneumococcal vaccination but no reduction in all-cause pneumonia and mortality [34]. Moreover, two studies in Japan showed a reduction in bacterial infections and acute exacerbations of COPD in subjects receiving both influenza and pneumococcal vaccines when compared to either alone [35, 36].

There are limited data available for the role of PPSV23 in asthma. The positive association between asthma and risk of invasive pulmonary disease supports the addition of asthma as a high-risk condition for pneumococcal vaccination. A 2002 Cochrane review found only one study of PPSV23 and asthma which met their entry requirement for review. This

study found a reduction in the number of acute exacerbations following PPSV23 vaccination; however, a study by Lee et al. found no significant difference in the relative risk of hospitalization due to pneumococcal pneumonia after PPSV23 in patients with asthma compared to controls [32,37]. Despite these discrepancies, ACIP and CDC recommend pneumococcal and influenza vaccination for all adults with asthma, COPD, and cigarette smokers [38].

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