**Program Name:** Adult Pneumococcal Disease Prevention

| Planning Committee: | Dr. Alan Kaplan  
|                     | Dr Jennie Johnstone  
|                     | Dr Louis Valiquette  
|                     | Dr. Jacques Bouchard  
|                     | Dr. Andrew Cave  
|                     | Dr. Kenneth Bayly  
|                     | Dr. Robert Woodland  

| Accreditation Information: | This version of the program is unaccredited and intended for informational purposes only. An accredited version was available online at www.advancingin.com until March 13, 2013.  

| Sponsor: | This program was supported by an educational grant from Pfizer.  

© Copyright 2011  
The following content is unaccredited and intended for informational purposes only.  
An accredited version was available online at www.advancingin.com until March 13, 2013.
LEARNING OBJECTIVES

- To understand the clinical manifestations and risk factors for pneumococcal disease
- Discuss current pneumococcal vaccine recommendations for adults
- Review data on emerging pneumococcal vaccines in adults

INVASIVE PNEUMOCOCCAL DISEASE (IPD)

Pneumococcal disease is caused by *Streptococcus pneumoniae* (pneumococcus), a gram-positive diplococcus. *S. pneumoniae* is a common cause of community-acquired pneumonia (CAP), meningitis, and bacteremia in children and adults. [1]

![Figure. S. pneumoniae: Gram stain of blood culture](image)

PATHOGENESIS AND PATHOPHYSIOLOGY

Pneumococci are common inhabitants of the respiratory tract and may be isolated from the nasopharynx of 5-70% of asymptomatic healthy adults, although only 5-10% of adults without children are carriers. Rates of asymptomatic carriage vary with age, environment, and the presence of upper respiratory infections. [2] Pneumococcal disease occurs in adults when a change in the host's immune system allows the pneumococcus to invade otherwise sterile body sites. Pneumococcal virulence factors (see figure below) include the capsular polysaccharide, a cytotoxin (pneumolysin), and surface proteins (e.g., pneumococcal surface proteins A and C [Psp A, Psp C], pneumococcal surface adhesin A [PsaA] protein, pneumolysin) which help the organism to survive the
host’s immune response. The capsule helps the organism to evade phagocytosis, and the pneumococcal surface proteins contribute to its virulence. [3, 4]

Figure. Schematic diagram of the virulence factors of *S. pneumoniae* [5]

*S. pneumoniae* can cause both non-invasive and invasive disease. The organism can cause disease of the lower respiratory tract, i.e., pneumococcal pneumonia, which by itself is not considered to be “invasive” disease, even though it can be life-threatening. However, pneumonia can serve as a focus for bloodstream invasion, which can result in invasive pneumococcal disease (IPD), i.e., disease in which the bacterium enters a sterile site such as blood, cerebrospinal fluid (CSF), pleural fluid, joint fluid or pericardial fluid. The capsular polysaccharide is considered to be the most important virulence factor enabling the pneumococcus to survive in the bloodstream. Pneumococci can also establish systemic invasion in the absence of a clinically evident focus of infection. [4, 6]

**Serotypes**

There are more than 91 known serotypes of *S. pneumoniae*. Antigenically-related types are included in groups (e.g., 9A, 9L, 9N, and 9V), and types without close antigenic relationship are given numbers (e.g., types 1, 2, 3, 4, 5). [7, 8] The 10 most common serotypes are estimated to account for about 62% of all invasive disease worldwide. [2] The Canadian Bacterial Surveillance Network (CBSN) study in adults [9] found that from 2000 to 2009, IPD due to serotypes in 7-valent conjugate vaccine (PCV7) decreased significantly (56% to 18%), while serotypes not in PCV7, but in PCV13, increased (18% to 43%), as did those due to non-conjugate vaccine serotypes (26% to 40%). The majority of the increase in PCV13 serotypes was due to 19A (1% to 15%). In 2009, 19A, 7F and 3 were the most common serotypes in adult IPD, representing 15%, 13% and 10% of isolates. National laboratory surveillance (April 1 to December 31, 2010) of IPD in Canada showed that serotypes 7F and 19A are most prevalent in all age groups, representing 18% and 21% of child isolates, 23% and 10% of adult isolates, and 11% and 13% of isolates in the elderly (≥ 65 years), respectively. Prominent serotypes in adults include 12F, 22F and 6C. In the elderly age group, proportions of serotype 22F, 6C and 15A are elevated (see figure below). [10]
Figure. Age distribution of invasive *S. pneumoniae* serotypes in Canada (April 1 to December 31, 2010) [10]

**Question**

1. The most common serotypes causing adult IPD in 2009 were
   (a) serotypes 1, 2, 3, 4 and 5.
   (b) serotypes 19A, 7F and 3.

**PATIENT PROFILE 1**

John is a 55-year old smoker, with a history of coronary artery disease. He does not have any other medical conditions. John is being considered for pneumococcal vaccination. He has not previously received the pneumococcal vaccine.

1. Which of the following statements most correctly describes the association between cigarette smoking and John’s risk for invasive pneumococcal disease (IPD)?
   (a) Smoking does not increase John’s risk for IPD.
   (b) Smoking only marginally increases John’s risk for IPD; less than 5% of otherwise healthy adults with IPD are cigarette smokers.
   (c) Coronary artery disease increases John’s IPD risk but cigarette smoking does not.
   (d) John’s IPD risk is related to the number of cigarettes he smokes per day.

2. What is the interaction between IPD and coronary artery disease (CAD)?
   (a) Persons with CAD who develop IPD have an increased risk of adverse cardiac events.
   (b) CAD increases the risk for developing IPD.
   (c) CAD does not increase IPD risk, and IPD does not increase the risk of an adverse cardiac event in CAD patients.

3. Should John receive the pneumococcal vaccine?
   (a) John should not receive the vaccine because it is not indicated for adults aged <65 years.
(b) John should receive the vaccine because it is recommended for individuals who have not been vaccinated previously and who are at higher risk of IPD.

**RISK FACTORS**

IPD is *most common in* the very young and the elderly. In addition to age, several medical conditions are recognized as potential risk factors. Outbreaks of IPD may occur in crowded settings such as schools, long-term care facilities, jails, hospitals, and closed communities. Recent acquisition of a virulent strain, poverty, alcoholism and cigarette smoking may also contribute to IPD risk. [11, 12]

<table>
<thead>
<tr>
<th>Table. Risk factors for IPD [1, 11, 13, 14]</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Extremes of age</td>
</tr>
<tr>
<td>– &lt; 2 years; ≥ 65 years</td>
</tr>
<tr>
<td>– Exposure to cigarette smoke, multiple children in household</td>
</tr>
<tr>
<td>• Comorbidities (in alphabetical order)</td>
</tr>
<tr>
<td>– Alcohol abuse</td>
</tr>
<tr>
<td>– Asthma</td>
</tr>
<tr>
<td>– Cerebrospinal fluid leaks</td>
</tr>
<tr>
<td>– Chronic liver disease, including cirrhosis</td>
</tr>
<tr>
<td>– Chronic lung disease</td>
</tr>
<tr>
<td>– Cigarette smoking</td>
</tr>
<tr>
<td>– Cochlear implant</td>
</tr>
<tr>
<td>– Congestive heart failure</td>
</tr>
<tr>
<td>– Diabetes mellitus</td>
</tr>
<tr>
<td>– Neurological disorders</td>
</tr>
<tr>
<td>– Recent influenza infection</td>
</tr>
<tr>
<td>• Certain special groups</td>
</tr>
<tr>
<td>– Canada’s First Nations, American Indians, Alaska Natives, African Americans in the US</td>
</tr>
<tr>
<td>– Homeless people</td>
</tr>
<tr>
<td>– IV drug users</td>
</tr>
<tr>
<td>• Immune deficiencies (in alphabetical order)</td>
</tr>
<tr>
<td>– Asplenia, functional hyposplenism, splenectomy</td>
</tr>
<tr>
<td>– B cell or T cell defects</td>
</tr>
<tr>
<td>– Chronic renal failure</td>
</tr>
<tr>
<td>– Deficiencies of early components of classical pathway of complement</td>
</tr>
<tr>
<td>– HIV infection</td>
</tr>
<tr>
<td>– Hematological or solid malignancies</td>
</tr>
<tr>
<td>– Immunosuppressive drugs</td>
</tr>
<tr>
<td>– Nephrotic syndrome</td>
</tr>
<tr>
<td>– Organ transplant recipients</td>
</tr>
<tr>
<td>– Sickle cell disease</td>
</tr>
</tbody>
</table>
**Age**

During the period 2000-2004, children < 1 year of age accounted for 7% (mean 130 cases/year) of Canadian IPD cases, those aged 1-4 years accounted for 18% (mean 345 cases/year) of cases, and adults ≥ 60 years accounted for 37% (mean 711 cases/year) of cases. Age-specific incidence rates (per 100,000 population per year) were 39.8, 24.6 and 13.3 among infants < 1 year of age, children aged 1-4 years and adults aged ≥ 60 years respectively. [15]

**Smoking**

Approximately half of otherwise healthy adults with IPD are cigarette smokers, and smoking is considered to be the strongest independent risk factor for IPD among immunocompetent non-elderly adults; smoking cessation reduces the risk. [13, 16] A clear dose-response relationship exists, with IPD risk being related to current number of cigarettes smoked per day, number of pack-years of smoking, and the time since quitting. The biological mechanisms by which smoking increases IPD risk is unclear, although smoking is known to impair mucociliary clearance, enhance bacterial adherence, and disrupt the respiratory epithelium. Immunoglobulin levels may also be lowered. [16]

**Underlying medical conditions**

Persons who have certain underlying medical conditions are at increased risk for developing pneumococcal infection or experiencing severe disease and complications (see table below).

Respiratory conditions such as COPD and asthma are associated with increased risk. COPD is the most common comorbidity among patients with severe community acquired pneumonia requiring hospitalization. [17] Community-acquired pneumonia in COPD patients is associated with higher mortality rates. [18] Chronic airway inflammation in asthma and COPD may contribute to impaired immunity and predispose to infection. [19] The risk is even greater in active smokers with COPD. [20]

Asthma causes alterations in the airway that can lead to impaired clearance of pathogenic bacteria, and can serve as a focus for infection. [19] Pneumococcal carriage is more common in asthmatic subjects than non-asthmatic subjects. [21] In a study [19] that examined the association between asthma and IPD in persons 2-49 years of age, asthma more than doubled a person’s risk of IPD (adjusted odds ratio 2.4; 95% C.I., 1.9-3.1). The annual incidence of IPD in subjects without other coexisting conditions was 4.2 episodes per 10,000 persons with high-risk asthma (i.e., hospitalization for asthma, prescription for corticosteroids or ≥ 3 β-agonist medications during the previous year) and 2.3 episodes per 10,000 persons with low-risk asthma (i.e., all other subjects), as compared with 1.2 episodes per 10,000 persons without asthma.

Influenza-related mortality is usually mediated by superinfection with bacteria, mainly involving pneumococci. The influenza virus alters the lungs in a way that predisposes to adherence, invasion, and induction of disease by pneumococcus. Alteration of the immune response may contribute to the severity of the resulting infection. The most obvious example of the association between the influenza virus and *S. pneumoniae* infection was the influenza pandemic of 1918 which killed an estimated 40-50 million people, most likely due to secondary bacterial pneumonia. [22]

IPD causes stress on the heart by increasing myocardial oxygen demand. In patients with pre-existing heart disease, IPD increases the risk of an acute cardiac event such as myocardial infarction, serious arrhythmia, and/or new or worsening congestive heart failure. In a study [23] of the medical records of all patients hospitalized for pneumococcal pneumonia during a 5-year period, 19.4% of patients had ≥1 concurrent major cardiac event.
Diabetes is associated with abnormalities in immune function that can result in increased morbidity and mortality from infection. Patients with diabetes may also have end organ complications involving the heart and kidney which further increase their risk for IPD. [24] In one study, [25] type 1 diabetes was associated with a 4.4-fold increased risk of a pneumonia-related hospitalization, and type 2 diabetes was associated with a 1.2-fold increased risk. Poor long-term glycemic control and longer diabetes duration increased the risk of pneumonia-related hospitalization. The relative impact of diabetes was greatest in younger adults and in subjects without coexisting morbidity. Bacteremic pneumococcal pneumonia occurs relatively commonly in diabetic individuals, [26] with one study finding a 1.5-fold increased risk of community-acquired pneumococcal bacteremia in patients with diabetes compared with individuals without diabetes. [27]

The incidence of IPD among hematopoietic stem cell transplant recipients is significantly greater compared to the general population, and the risk remains increased long after transplantation. [28, 29] The risk of pneumococcal infections in also increased in recipients of solid organ transplants including heart, lung and kidney. [30-32] In HIV patients, the incidence of IPD remains high, together with its associated morbidity and mortality, despite measures to prevent pneumococcal disease including the widespread use of highly active antiretroviral therapy (HAART) and pneumococcal immunization. [33] S. pneumoniae is the leading cause of invasive bacterial respiratory disease in patients with HIV infection. [34]

Homelessness

Homelessness is associated with a higher risk of serious pneumococcal infection. Prospective, population-based surveillance [35] for IPD in homeless adults in Toronto showed that the incidence of IPD in homeless adults was 273 infections per 100,000 persons per year, compared to 9 per 100,000 persons per year in the general adult population. The proportion of patients with recurrent disease was five-fold higher for homeless than other adults.

Aboriginal populations

Aboriginal peoples in first-world countries often experience higher rates of many vaccine preventable diseases including IPD. [36] The International Circumpolar Surveillance System, a population-based surveillance network for invasive bacterial disease in the Arctic, found high rates of IPD, i.e., 43 and 38 cases per 100,000 population in 1999-2005, among indigenous persons in Alaska and northern Canada respectively. [37]

PATIENT PROFILE 2

Mary is a 65-year old homeless woman with asthma. She has come to receive her annual flu shot, and pneumococcal vaccination is being considered. She received the pneumococcal vaccine for the first time 7 years ago, and has never been revaccinated.

1. Regarding the effect of underlying respiratory conditions on Mary’s risk for IPD:
(a) Chronic obstructive pulmonary disease (COPD), but not asthma, increases the risk for IPD.
(b) High risk asthma (i.e., hospitalization for asthma, prescription for corticosteroids or ≥ 3 β-agonist medications during the previous year), but not low risk asthma (i.e., all other subjects), increases the risk for IPD.
(c) Pneumococcal carriage is more common in asthmatic subjects than non-asthmatic subjects.
2. Compared to subjects without asthma, the risk of IPD in patients with asthma is
(a) Marginally increased.
(b) Up to 1.2 times higher.
(c) Up to 1.6 times higher.
(d) More than doubled.

3. Compared to the general adult population, the incidence of IPD in homeless persons has been shown to be increased by a factor of
(a) 3.
(b) 10.
(c) 30.
(d) 100.

4. Should Mary be revaccinated against IPD?
(a) Re-immunization should be considered 5 years after the first dose for individuals like Mary who are at high risk for IPD.
(b) Mary should not be revaccinated until ≥ 10 years have elapsed since receiving the first dose of pneumococcal vaccine.
(c) Revaccination is not recommended because of insufficient data regarding its clinical benefit.

**CLINICAL MANIFESTATIONS AND COMPLICATIONS**

The most common form of pneumococcal disease is pneumococcal pneumonia, although pneumonia alone is not considered to be “invasive” disease. The symptoms of pneumococcal pneumonia include abrupt onset of fever and chills or rigors, pleuritic chest pain, productive cough with mucopurulent rusty sputum, dyspnea, tachypnea, hypoxia, tachycardia, malaise, and weakness.

![Figure. Pneumococcal pneumonia. The chest radiograph reveals a left lower lobe opacity with pleural effusion](image)

Manifestations of pneumococcal meningitis are similar to other forms of purulent bacterial meningitis, and include headache, lethargy, stiff neck, fever, disorientation, seizures and coma. Pneumococcal bacteremia may present with symptoms similar to pneumonia and meningitis, along with joint pain and chills. [2]

Approximately 30% of patients with CAP require admission to hospital, and in-hospital mortality occurs in ~10% of patients. [38] Of adults who survive hospitalization, > 50% die within 5 years. [39] Pneumococcal meningitis is associated with mortality rates of up to 30%, and long-term sequelae in more than 50% of cases in adults. [40] The
overall case-fatality rate for pneumococcal bacteremia is about 20% but may be as high as 60% among elderly patients. [2] A systematic review and meta-analysis [41] of serotype-specific disease outcomes for patients with pneumococcal pneumonia and meningitis found an increased risk of death with infection with serotypes 3, 6A, 6B, 9N, and 19F compared with infection with serotypes 3, 6A, 6B, 9N, and 19F. Outcomes among meningitis patients did not differ significantly among serotypes.

THE PROBLEM OF BACTERIAL RESISTANCE TO ANTIBIOTICS

Early and effective antimicrobial therapy provides a substantial survival advantage in severe IPD. However, drug-resistant *S. pneumoniae* infection is becoming increasingly common. Penicillin-resistant pneumococcal strains were first noted in the mid 1970s, and resistant clones have now spread worldwide. [42] In Canada, *macrolide resistance increased from 3.7% in 1995 to 19.0% in 2005*. [43] Resistance is prevalent to various antibiotics and antibiotic classes including the beta-lactams, macrolides, trimethoprim-sulfamethoxazole, and fluoroquinolones. Multi-resistant pneumococci are becoming increasingly common. [12, 42, 44]

As per a Canadian Bacterial Surveillance Network (CBSN) study, [9] resistance to at least one antibiotic class increased from 16 to 27% between 2000 and 2009, and multidrug resistant (MDR; resistance to ≥3 classes) increased from 1 to 5%. Resistant *S. pneumoniae* were more likely to be serotypes covered by PCV13 than non-resistant isolates (resistant: 67% due to PCV13; non-resistant: 56% PCV13; MDR: 90% due to serotypes in PCV13); serotypes 15A, 33A, 9V, and 19A were most likely to be resistant (69%, 68%, 53%, 52% respectively). Increasing resistance of *S. pneumoniae* to macrolides, in particular, represents a challenge for clinicians. During the 2000-2001 season, 474 strains of *S. pneumoniae* were collected in Quebec through a surveillance network. Macrolide resistance was 20.2%, and significantly higher in non-invasive strains versus invasive ones (22.4% versus 14.8%), and in children (30%) versus adults (14.8%). Among the 96 macrolide-resistant strains, 56 (58%) were *erm(B)*, 35 (37%) carried the *mef(A)* gene, four were carrying both genes and one none. [45]

Microbial resistance to antimicrobial therapy poses challenges for treating pneumococcal infections, and highlights the importance of judicious antibiotic use and disease prevention by immunizing persons at high risk. [46]

POLYSACCHARIDE AND CONJUGATE VACCINES

Pneumococcal polysaccharide vaccines were developed more than 50 years ago and have progressed from 2-valent vaccines to the current 23-valent polysaccharide vaccine (PPV23) and 13-valent conjugate vaccine (PCV13).

**Polysaccharide vaccines**

Polysaccharide vaccines contain bacterial capsular polysaccharide. These vaccines do not incite a T-cell response, and are therefore poor inducers of immunologic memory. [47, 48] Two 23-valent pneumococcal polysaccharide vaccines (PPV23) are available in Canada, i.e., Pneumovax® 23 (Merck Frosst Canada) and Pneumo 23® (Sanofi Pasteur). The serotypes contained in the 23-valent vaccines are 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F.
Figure. **The immune response to polysaccharide and protein-polysaccharide conjugate vaccines** [49]

a) Polysaccharides from the encapsulated bacteria that cause disease in early childhood stimulate B cells by cross-linking the B-cell receptor (BCR) and drive the production of immunoglobulins. This process results in a lack of production of new memory B cells and a depletion of the memory B-cell pool, such that subsequent immune responses are decreased. 

b) The carrier protein from protein–polysaccharide conjugate vaccines is processed by the polysaccharide-specific B cell, and peptides are presented to carrier-peptide-specific T cells, resulting in T-cell help for the production of both plasma cells and memory B cells. CD40L, CD40 ligand; TCR, T-cell receptor

**Conjugate vaccines**

In the conjugate vaccine, the capsular polysaccharide is linked to a carrier protein, which converts it into a T-cell-dependent antigen, and results in improved immunogenicity. Conjugate vaccines induce both a B-cell and T-cell response, which is long-lasting. There is also substantial enhancement of antibody responses on boosting. [47, 48]  

A comparative study [47] of conjugate and polysaccharide vaccines found that an initial dose of PCV7 was more likely to elicit higher and potentially more effective levels of antipneumococcal antibodies in elderly adults than PPV23.

In 2010, a 13-valent pneumococcal conjugate vaccine (PCV13, Pfizer Canada) was made available in Canada. PCV13 contains the serotypes contained in the earlier 7-valent vaccine PCV7 (4, 6B, 9V, 14, 18C, 19F, 23F) and the 10-
valent vaccine PCV10 ((1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) together with additional serotypes (3, 6A, 19A). It also includes a modification of the conjugation for serotype 19F to improve stability. [50]

**Question**

Polysaccharide vaccines induce both a B-cell and T-cell response, which is long-lasting.
(a) True
(b) False

**BENEFITS OF PNEUMOCOCCAL VACCINATION**

Pneumococcal vaccination of children with the pneumococcal conjugate vaccine has led to a significant decline in the incidence of IPD. The CASPER study [51] showed that after the introduction of PCV7 infant vaccination in Calgary in 2002, there was a 94% decline in the incidence of vaccine serotype IPD and a 79% decline in overall IPD in children <2 years of age. Interestingly, there was also a 92% decline in vaccine serotype IPD in adults aged 65-84 years and a near-significant 29% decline in overall IPD (see figures below). The decline in IPD adults is thought to be related to the herd effect of immunizing infants, which reduces nasopharyngeal colonization, thereby reducing transmission and subsequent disease in adults. [52]

[Figure. Incidence of invasive pneumococcal disease in Calgary, by serotype grouping, for children aged 0-23 months, 1998-2007] [51]
Vaccination can help to reduce the problem of pneumococcal resistance by reducing infection rates and consequently, antibiotic use. [53] This is particularly important because mortality due to pneumonia, meningitis, and septicemia remains high in Canada, [54] while resistance is an increasing concern.

In a Cochrane review, [55] both randomized controlled trials (RCTs) and non-RCTs provided strong and consistent evidence of the effectiveness of PPV against IPD, but efficacy against all-cause pneumonia was inconclusive. Pneumococcal vaccination is particularly beneficial for subjects with risk factors for pneumococcal infection. A retrospective cohort study [56] evaluating the effectiveness of a pneumococcal vaccine (PPV23) in high-risk individuals found a decrease in the risk of hospital admission for asthma, acute otitis media, COPD and other respiratory infections in vaccinated compared with non-vaccinated subjects. Although PPV23 does not prevent community-acquired pneumonia (CAP), it might improve outcomes in those who develop pneumonia. In a large population-based cohort study [57] of hospitalized patients with CAP, patients who had received prior PPV showed about a 40% lower rate of mortality or ICU admission compared with those who were not vaccinated.

Despite the presence of abnormalities in immune function, patients with diabetes generally exhibit appropriate humoral immune responses to vaccination. Pneumococcal vaccination is effective in reducing life-threatening bactemeric disease in diabetes patients, but whether vaccination is effective in preventing nonbacteremic disease is not clear. [24] In HIV patients, the incidence of IPD is significantly lower post-immunization both for serotypes covered by the PPV23 and for all serotypes. [33] In a study [58] involving 62,918 adults hospitalized with community-acquired pneumonia, pneumococcal vaccination was associated with improved survival, decreased chance of respiratory failure or other complications, and decreased length of stay.

**FUTURE VACCINE STRATEGIES**

**Immunogenicity** is the ability of a vaccine to induce an immune response (antibody- and/or cell-mediated immunity) in a vaccinated individual and is distinct from the term ‘immunity’ which refers to the ability to prevent infection or disease. **Vaccine efficacy** refers to the reduction in attack rates in vaccinated compared to
unvaccinated populations monitored within a clinical trial setting, whereas vaccine effectiveness refers to the level of protection afforded by a vaccine under ordinary field conditions of a public health program. No studies have compared the effectiveness of conjugate vaccine with that of polysaccharide vaccine in adults, although measurements of surrogate outcomes including IgG levels and/or opsonic activity suggest that conjugate vaccine may be as good as and possibly better than polysaccharide vaccine in inducing immunity to pneumococcal infection against serotypes included in the respective vaccines. [59]

Polysaccharide vaccine is recommended for adults at higher risk of IPD, but there exists some uncertainty about its protective efficacy; PPV23 reduces the risk of invasive disease but does not appear to reduce the risk of pneumonia in elderly patients or younger adults with co-morbidities. [60, 61] Antibody responses to pneumococcal vaccination may be lower in patients who have alcoholic cirrhosis, COPD, and insulin-dependent diabetes mellitus than among healthy young adults. In immunocompromised patients, antibody responses are often diminished or absent. [62] HIV-infected individuals have significantly lower antibody responses than in healthy individuals. [63] Polysaccharide vaccine may elicit insufficient antibody titers in elderly subjects; and these may be maintained for 1-2 years, but reduce substantially after 5 years. [47, 64, 65] Revaccination with polysaccharide vaccine is associated with an antibody response that may be of lesser magnitude than with a first vaccination. Repeated dosing with polysaccharide vaccine is also associated with increased reactogenicity and immunological hyporesponsiveness. [47, 66]

By contrast, conjugate vaccine has demonstrated efficacy in susceptible adults in some selected populations. In a trial [67] using PCV7 compared to placebo in HIV-infected individuals, the vaccine prevented 74% of recurrent episodes of IPD caused by vaccine serotypes or serotype 6A in patients with HIV infection. Conjugate vaccine also enhances the response to a subsequent dose of vaccine. In a study [68] of two groups of adults aged 60 through 64 years and 50 through 59 years, PCV13 enhanced opsonophagocytic responses to subsequent PCV13 or PPSV23 vaccination in both groups, suggesting that PCV13 establishes an immunological memory state that augments the antipneumococcal response to subsequent administration of conjugated or unconjugated polysaccharide. In a trial [69] involving subjects aged 60-64 years, initial use of PCV13 permitted subsequent administration of PPV23, with opsonophagocytic responses that were noninferior for all, and statistically superior for a number of the serotypes. PPV23 administration established an immunologic state resulting in a diminished response to subsequent administration of PCV13. Local reactions were increased when PPV23 was given after PCV13.

A recent meta-analysis [70] of clinical trials that compared pneumococcal polysaccharide vaccine with a control concluded that vaccination did not appear to be effective in preventing pneumonia in adults, even in populations for whom the vaccine is currently recommended. A Cochrane review [55] found evidence for the effectiveness of polysaccharide vaccine against IPD; however, vaccine efficacy appeared to be poorer in adults with chronic illness although the difference was not statistically significant. While PCV13 has been approved for use in children <5 years of age, [50] the only pneumococcal vaccine advised for use in adults is PPV23, which is recommended for all individuals ≥5 years of age who have not received the vaccine previously and who are at higher risk of IPD. PPV23 provides partial protection against IPD in immunocompetent elderly individuals, but has not been definitively shown to impact the overall risk of pneumonia in the elderly or younger adults with comorbidities. Although PCV13 is licensed for use in Canada in adults >50 years to prevent IPD, it is not yet clear based on available evidence how to best use this vaccine. At this time, there are no guideline recommendations regarding use of PCV13 in adults. Research in this area is ongoing and PCV13 remains a promising option for the future. Perhaps PCV13 may be indicated in very high risk patients, but its use in adults should be considered in consultation with an infectious diseases physician.

A placebo-controlled trial of PCV13 in patients aged ≥65 years is currently being performed in the Netherlands, and is likely to provide more information about the protective effect of PCV13 against pneumococcal pneumonia in adults, but the results are not anticipated to be available until 2012. [71] Meanwhile, the limitations of conjugate vaccines must be noted; these include a lesser breadth of coverage (i.e., 13 pneumococcal serotypes with PCV13 versus 23 serotypes with PPV23) and the appearance of replacement strains that with widespread use of the vaccine can emerge as common causes of pneumococcal disease. Newer conjugate vaccine formulations will
protect against the most prevalent of the current replacement strains, but replacement strains can be expected to emerge. Conjugate vaccines are also more costly than polysaccharide vaccines, and cost-effectiveness considerations may be a barrier to widespread use of conjugate vaccine in adults. [59]

PATIENT PROFILE 3

Tom is a 72-year old male with diabetes. He received the pneumococcal vaccine 6 years ago.
1. Regarding diabetes and IPD:
(a) Pneumococcal vaccination is ineffective in patients with diabetes because of abnormalities in immune function among these patients.
(b) The risk for IPD is not increased in patients with diabetes.
(c) Bacteremic pneumococcal pneumonia occurs relatively commonly in diabetic individuals.
(d) Pneumococcal vaccination is effective in preventing bacteremic and nonbacteremic IPD.

2. Should Tom be revaccinated against pneumococcal disease?
(a) Tom should be revaccinated because he received the vaccine > 5 years ago.
(b) Revaccination is not recommended for individuals who have received the vaccine at or after the age of 65 years.

VACCINE USAGE

Pneumococcal polysaccharide vaccination is recommended for all individuals ≥ 65 years of age. Individuals with unknown immunization histories should receive the vaccine. [15] Vaccination of adults aged <65 years is also recommended for those who have not been vaccinated previously and who have the following risk factors for IPD [14, 15] (in alphabetical order):

- Aboriginal populations
- Chronic medical conditions (e.g., chronic cardiac and pulmonary disease such as bronchopulmonary dysplasia, diabetes mellitus, chronic renal disease or CSF leak)
- Cirrhosis, alcoholism, cigarette smoking
- HIV infection
- Immunocompromising conditions (e.g., primary immunodeficiencies; malignancies; conditions resulting from immunosuppressive therapy, solid organ transplantation, or use of long-term systemic corticosteroids; nephrotic syndrome)
- Persons receiving cochlear implants
- Sickle cell disease, other sickle cell hemoglobinopathies, functional or anatomic asplenia

Re-immunization should be considered 5 years after the first dose for persons aged 19-64 years at highest risk of invasive infection, including those with functional or anatomic asplenia or sickle cell disease; hepatic cirrhosis, chronic renal failure or nephrotic syndrome; HIV infection; and immunosuppression related to disease or therapy. Multiple revaccinations are not recommended because of insufficient data regarding clinical benefit. Revaccination is not recommended for individuals who have received the vaccine at or after the age of 65 years. [13, 15]

Click here to access the Canadian Immunization Guide recommendations.
For publicly funded immunization programs in Canada, including pneumococcal vaccination, click here.
KEY LEARNING POINTS

- Invasive pneumococcal disease (IPD) is associated with adverse outcomes including death.
- Pneumococcal vaccination of children has led to a significant decline in the incidence of IPD.
- Increasing antibiotic resistance highlights the importance of disease prevention by immunizing persons at high risk.
- Available pneumococcal vaccines include 23-valent polysaccharide vaccines and a 13-valent conjugate vaccine.
- Polysaccharide vaccines do not incite a T-cell response, and are therefore poor inducers of immunologic memory. Conjugate vaccines induce both a B-cell and T-cell response, which is long-lasting. There is also substantial enhancement of antibody responses on boosting.
- Pneumococcal vaccination of adults with PPV23 is recommended for all individuals ≥ 65 years of age. Pneumococcal vaccination is also recommended for those with unknown immunization histories and those who have not been vaccinated previously and who are at higher risk of IPD.
- Routine re-immunization with PPV23 is not recommended for those who have been previously vaccinated against IPD. However, re-immunization should be considered 5 years after the first dose for persons aged 19-64 years at highest risk of invasive infection, including those with functional or anatomic asplenia or sickle cell disease; hepatic cirrhosis, chronic renal failure or nephrotic syndrome; HIV infection; and immunosuppression related to disease or therapy.

DISCUSSION FORUM

- What are the pros and cons of currently available pneumococcal polysaccharide and conjugate vaccines?
- In your opinion, what are the main practice gaps impacting the prevention of IPD?
RESOURCES

- NACI Update on Pediatric Invasive Pneumococcal Disease and Recommended Use of Conjugate Pneumococcal Vaccines (2010)
- NACI Statement on the recommended use of pneumococcal 23-valent polysaccharide vaccine in homeless persons and injection drug users (2008)
- CDC: Updated Recommendations for Prevention of Invasive Pneumococcal Disease Among Adults Using the 23-Valent Pneumococcal Polysaccharide Vaccine (PPSV23)

POST-TEST

1. Which organism is the most common cause of community-acquired pneumonia in adults?
   (a) Streptococcus pneumoniae  
   (b) Hemophilus influenzae  
   (c) Staphylococcus aureus  
   (d) Mycoplasma pneumoniae

2. The 10 most common serotypes are estimated to account for about 60% of invasive pneumococcal disease (IPD).
   (a) True  
   (b) False

3. The pneumococcal capsular polysaccharide is linked to a carrier protein for improved immunogenicity in
   (a) the polysaccharide vaccine.  
   (b) the conjugate vaccine.  
   (c) both polysaccharide and conjugate vaccines.  
   (d) neither polysaccharide nor conjugate vaccines.

4. In adults, the pneumococcal polysaccharide has not been found to be very effective for preventing
   (a) any form of pneumococcal disease.  
   (b) invasive pneumococcal disease.  
   (c) pneumococcal pneumonia.
REFERENCES


© Copyright 2011
The following content is unaccredited and intended for informational purposes only.
An accredited version was available online at www.advancingin.com until March 13, 2013.
69. Gurtman A, Frenck R, Strout CB, et al. A Phase 3, Randomized, Active-Controlled Trial to Evaluate the Safety, Tolerability, and Immunogenicity of Sequential Administration of 13-Valent Pneumococcal Conjugate Vaccine (PCV13) and 23-Valent Pneumococcal Polysaccharide Vaccine (PPSV23) Administered at 1-year Intervals in PPSV23-naïve Adults 60-64 Years of Age. Presented at the 49th Annual Meeting of the Infectious Diseases Society of America (IDSA), October 20–23, 2011, Boston, MA, US.