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Pneumococcal Vaccine and Patients with Pulmonary Diseases

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Abstract

Chronic pulmonary diseases describe chronic diseases that affect the airways and lung parenchyma. Examples of common chronic pulmonary diseases include asthma, bronchiectasis, chronic obstructive lung disease, lung fibrosis, sarcoidosis, pulmonary hypertension and cor pulmonale. Pulmonary infection is considered a significant cause of mortality in patients with chronic pulmonary diseases. Streptococcus pneumoniae is the leading isolated bacteria from adult patients with community-acquired pneumonia, the most common pulmonary infection. Vaccination against S. pneumoniae can reduce the risk of mortality especially from more serious infections in both immunocompetent and immunocompromised patients. Patients with chronic pulmonary diseases who take steroids or immunomodulating therapy (e.g., methotrexate, anti-TNF inhibitors), having concurrent sickle cell disease or other hemoglobinopathies, primary immunodeficiency disorders, human immunodeficiency virus infection / acquired immunodeficiency syndrome (HIV/AIDS), nephrotic syndrome, and hematologic or solid malignancies should be vaccinated with both 13-valent pneumococcal conjugate vaccine (PCV13) and the pneumococcal polysaccharide vaccine 23-valent (PPSV23).

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Conflict of Interest
Mehdi Mirsaeidi, Golnaz Ebrahimi, Mary Beth Allen and Stefano Aliberti have no conflicts of interest to disclose.

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Introduction

Pneumococcal disease describes many infectious processes caused by *Streptococcus pneumoniae* (*S. pneumoniae*), including meningitis, pneumonia, bacteremia, bronchitis, sinusitis, and otitis media. Pneumonia is the most common presentation of pneumococcal disease in adults. In the US, pneumococcal pneumonia is responsible for 30% of adult community-acquired pneumonia cases and 400,000 hospitalizations annually. (1) Pneumococcal pneumonia represents a common complication of many disease processes.

Chronic pulmonary diseases, as mainly defined by asthma, bronchiectasis, chronic obstructive lung disease (COPD), interstitial lung disease, sarcoidosis, pulmonary hypertension and *cor pulmonale*, represent the third leading cause of death and account for more than 140,000 deaths in 2011.(2) Pneumococcal pneumonia is a frequent complication in patients with chronic pulmonary disease. Mortality is a frequent outcome in these cases, regardless of whether the patients have developed invasive disease. (3) For this reason, the management of pneumonia exists as a major contribution to the economic burden of chronic respiratory diseases. The cost of pneumonia treatment for Medicare beneficiaries alone was reported in excess of $13 billion in 2008.(4)

Streptococcus pneumoniae serotypes

Streptococcus pneumoniae (*S. pneumoniae*) is classified based on the presence of capsular polysaccharides on the organism. More than 90 different serotypes of *S. pneumonia* have been identified. (5) Each organism has been classified into 46 distinctive subgroups based on immunological similarities. (6) Although invasive pneumococcal disease may occur with all serotypes, almost 60% of cases are caused by the same 23 serotypes. (7, 8) Furthermore, certain serotypes seem to be more commonly isolated from specific organ systems. For instance, serotype 1 and 3 are more frequently isolated in pneumonia and serotypes 6, 10 and 23 are regularly isolated in meningitis.(9, 10) Regional variations also exist in *S. pneumoniae* serotype disease etiology. A recently published meta-analysis showed that isolated serotypes from young children with invasive pneumococcal disease varied significantly in respect to geography. In addition, serotype 14 was the most common isolate from all over the world and serotypes 1, 5, 6A, 6B, 14, 19F, and 23F were isolated in 50% of individuals.(11, 12)

Pneumococcal disease

Pneumococcal disease can manifest in numerous body systems. Even though *S. pneumoniae* is the leading isolated bacteria from adult patients with community-acquired pneumonia globally, pneumococcal disease can present in many other forms.(13-15) Acute otitis media is one of the most commonly diagnosed diseases in children less than 5 years old in the US. (16) *S. pneumoniae* is the most common bacterial cause of AOM acute otitis media.(17) *S. pneumoniae* is the leading bacterial cause of meningitis, and the mortality rate is especially high. (18) Prompt antibiotic therapy is indicated for pneumococcal infection. However, increasing drug resistant strains and lack of development of new antibiotics are main concerns in the battle against these bacterial infections. (12)

Pneumococcal disease is commonly categorized as invasive or noninvasive pneumococcal disease. Invasive pneumococcal disease is defined as a serious condition with major organ involvement or bacteremia, in which *S. pneumoniae* isolates from normally sterile biofluids such as blood, cerebrospinal fluids, pleural fluid, and peritoneal fluid. The case fatality of invasive pneumococcal disease is reported at least 10%. However, it is higher in elderly and immunocompromised patients.(19) An estimated 5,000 adults died due to invasive *S. pneumoniae* infections nationwide in 2009.(20) NIPD Noninvasive pneumococcal disease addresses less serious conditions such as otitis media and nonbacteremic pneumococcal pneumonia.(21, 22)

Conditions predisposing to pneumococcal disease

Pneumococcal infection is common in patients with immunocompromising conditions (23), central nervous system and spleen anatomical abnormalities (24), hemoglobinopathies (25), chronic pulmonary diseases (26), heart failure (27), chronic kidney disease (28), smokers (29), and elderly (30). Patients who have low antibody level and ineffective serum opsonizing against *S. pneumonia* are at a higher risk as well.(31)

Pneumococcal vaccines

Pneumococcal vaccination targeting common serotypes is the current recommended standard of prevention. Pneumococcal vaccines work by stimulating the humoral immune system that facilitates anticapsular antibody. The first large trial assessing the efficacy of pneumococcal vaccine goes back to 1911 in South Africa.(32) The first advanced pneumococcal vaccine was approved in the US by the Food and Drug Administration (FDA) in 1977. This vaccine included coverage of 14 serotypes. Invasive pneumococcal disease in immunocompetent children and adults has been declining after introduction of pneumococcal vaccines in the US. The rate of the disease declined 32% in 20-39 years old group, 8% for 40-64 years old, and 18% for individuals 65 years and older.(33) Although vaccines are the only current proven method for acquired pneumococcal resistance, emerging research indicates that cell-mediated immunity may also be achieved by CD4+ T cells regardless of antibody status or capsular type as observed in laboratory mice.(34)

PPSV23 vaccine

In 1983, additional serotypes were added to the original pneumococcal vaccine in order to form the pneumococcal polysaccharide vaccine 23-valent (PPSV23).(35) PPSV23 covers serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F.(36, 37) (Table 2)

In a study evaluating PPSV23 against invasive pneumococcal disease, Butler et al. demonstrated an efficacy of 75% for the immunocompetent elderly (age>65 years old), 84% for patients with diabetes mellitus (DM), 77% for patients with anatomic asplenia, and 65% for patients with chronic pulmonary disease. (38) The Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) recommended PPSV23 immunization for all individuals who are in significant risk of invasive pneumococcal disease such as patients with diabetes mellititus, chronic respiratory diseases

(e.g., COPD, asthma, and bronchiectasis), congestive heart failure, chronic renal failure, and chronic liver disease.(20) Table 1 shows current recommendation for administration of PPSV23 and revaccination at 5 years after the first dose for adults aged ≥19 years.

PPSV23 and immunocompromised patients

Despite the proven effectiveness of PPSV23 to reduce invasive and noninvasive pneumococcal diseases in immunocompetent populations, the data suggest this vaccine does not deliver the same benefits to immunocompromised patients.(39-41) A meta-analysis analyzing 64,852 individuals from 18 randomized clinical trials showed PPSV23 might prevent invasive pneumococcal disease in adults, but evidence did not support the efficacy of PPSV23 in patients with significant underlying diseases such as malignancy, end-stage renal disease and acquired immunodeficiency syndrome.(42) Blumberg et al. showed that IgG antibody responses to 5 representative vaccine capsular polysaccharides of PPSV23 in immunocompromised patients with a heart transplant were significantly impaired.(43) Tobudic *et al.* confirmed these findings in renal transplant recipients.(44) A randomized clinical trial in adult patients with stem cell transplants in Canada showed poor immunogenicity to PPSV23 in this population.(45) This poor antibody response to PPSV23 was also seen in patients Human Immunosuppressive Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS). Rodriguez et al. investigated the immunogenicity of PPSV23 in patients with HIV/AIDS, noting that individuals with lower CD4+ T cell counts had a lower antibody levels against capsular polysaccharide.(46) A 5-year lonigitudal study confirmed these results.(47) All of the above studies support the idea that immunocompromised patients have an inferior immunogenic response to PPSV23. Therefore, this vaccine is not an effective preventative tool for invasive pneumococcal disease in this population.

PPSV23 and pediatric patients

PPSV23 has also proven ineffective in the pediatric population, particularly in children under the age of 2 years. (48) This is an important limitation given the prevalence and potential severity of pneumococcal disease in this population. Several explanations exist for the lack of protection provided of PPSV23 in young children. (49) First, the 23 most common serotypes in adult populations covered by the vaccine are not congruent with the most common serotypes in pediatrics. Also, serotypes covered by the PPSV23 commonly found in this population are more likely to be drug resistant. This undermines the effectiveness of the vaccine by failing to induce immunologic memory and facilitate response in the event of exposure. PPSV23 also fails to protect the nasopharyngeal pathway, thus, failing to prevent infections of the mucosa, which leaves young children susceptible to the one of the most common pneumococcal diseases in this population: acute otitis media. Also, pneumococcal diseases are transmissible to others through exposures from the mucosa, which leaves children both unprotected and contagious.(50)

7-valent pneumococcal conjugate vaccine

Given the limitations of PPSV23 particularly in pediatric populations, PCV7 was developed as a means of preventing pneumococcal disease in children by covering the common

serotypes unique to pediatric populations. These serotypes include 4, 6B, 9V, 14, 18C, 19F, and 23F.(51) Invasive pneumococcal disease was reported in an estimated 68,000 individuals annually before PCV7 was introduced in the US in 2000s. Following the use of PCV7 in children, the numbers of invasive pneumococcal disease identified cases were drastically decreased to around 38,000 annually with an overall incidence reduction of 45% after 7 years. (52) However, infection with non PCV7-serotypes still increased in this population. (53) Also, PCV7 was not proven for immunocompromised adults or for use in children with HIV, sickle cell disease or other specific risk groups for invasive pneumococcal disease.(51)

13-valent pneumococcal conjugate vaccine

According to the CDC, more than half of the serotypes isolated in immunocompromised patients with invasive pneumococcal disease were not serotypes included in the PPSV23 coverage profile. The CDC reports that *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F were isolated in half of immunocompromised adults with invasive pneumococcal disease in 2010.(54) Among the total number of invasive pneumococcal disease cases in the immunocompromised, less than a quarter were caused by serotypes 8, 9N, 10A, 11A, 12F, 15B, 17F, 18C, 19A, 20, 22F, and 33F, which are included in PPSV23.(55) This data offered an explanation for the well-proven mixed results of PPSV23 vaccine studies. Also, this report illuminated the need for a vaccine with coverage of *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. As a result, the 13-valent pneumococcal conjugate vaccine was introduced (PCV13). In February 2010, the FDA licensed PCV13 for prevention of invasive pneumococcal disease and otitis media in infants and young children. In December 2011, FDA licensed this vaccine for prevention of pneumonia and invasive pneumococcal disease in adults aged ≥50 years.(55) In the same year, a large randomized, double blind clinical trial study in Europe demonstrated that PCV 13 (manufactured by Pfizer) is a safe and immunogenic vaccine in the adults aged ≥65 years old.(56)

Given the fact that young children (<2 years old) and immunocompromised patients have a poor response to polysaccharide vaccine, pneumococcal antigens are conjugated to a nontoxic diphtheria carrier protein to improve immunogenicity and inducing T-cells response.(57) For this reason, PCV7 was commonly used in this population instead of PPSV23. PCV13 that is an updated version of PCV7, which improved antibody response with longer coverage against invasive pneumococcal disease in immunocompetent and immunocompromised persons.(58) PCV13 (Prevnar 13, Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer, Inc.) was approved by the FDA for adult based on immunogenicity studies. (59) PCV13 is a safe and effective strategy to prevent invasive pneumococcal disease and induces higher immune response as compared to PPSV23 in pneumococcal vaccine-naive adults.(60) The cost analysis of PVC13 immunization showed that one dose of PCV13 is more cost effective than PPSV23 in immunocompromised persons.(61, 62) While PCV13 covers numerous serotypes that are prevalent in immunocompromised individuals, other non-covered serotypes remain a serious concern in this group of patients. (63)

Recommendations for PCV13

ACIP published new recommendations for PCV13 on 2012.(55) These recommendations include the use of PCV13 in adults 19 years old and older with an underlying immunocompromised disorder. The Infectious Diseases Society of America (IDSA) recently recommended PCV13 vaccination for immunocompromised patients.(64)

PCV13 for patients with pulmonary diseases

Chronic pulmonary diseases are a group of chronic diseases that affect the airways and lung parenchyma. Asthma, bronchiectasis, chronic obstructive lung disease, interstitial lung disease, sarcoidosis, pulmonary hypertension and *cor pulmonale* are some of the most common chronic pulmonary diseases. All patients with chronic pulmonary diseases should receive PCV13 if they meet any of the risk factors listed in table 3.

Concurrent Sickle cell disease or other hemoglobinopathies

The incidence of invasive pneumococcal disease in sickle cell disease cases is higher as compared to normal healthy population.(65) Pneumococcal immunization with PPSV23 and PCV13 have reduced the incidence of invasive pneumococcal disease in patients with sickle cell disease.(66) Lungs may be affected in patients with sickle cell disease and other forms of hemoglobinopathies. Acute chest syndrome, pulmonary hypertension, airway disease, and interstitial lung disease are common respiratory complications in these patients.(67) Pulmonary underlying diseases such as pulmonary hypertension may not meet the indication for PCV13, but physicians should consider PCV13 for patients with pulmonary hypertension associated with hemoglobinopathies.

Primary immunodeficiency disorders

More than 150 distinct syndromes have been categorized as primary immunodeficiency.(68) Patients with primary immunodeficiency may experience a broad range of pulmonary complications.(69) Bronchiectasis, obstructive airway disease, and interstitial lung disease are common pulmonary complications in patients with primary immunodeficiency.(70, 71) Invasive pneumococcal disease is particularly common in patients with most forms of primary immunodeficiency.(72) For example, patients with any humoral, cellular, complement deficiencies and phagocytic disorder types excluding chronic granulomatous disease are considered high-risk groups for invasive pneumococcal disease.(73) Interestingly, research has shown that patients with chronic granulomatous disease, even with neutropenia, are an exception and rarely develop invasive pneumococcal disease.(72, 74) Although there is no clinical trial to show PCV13 may improve immune response in these individuals, conjugated protein may enhance immunity response with involving T cell lymphocytes.

HIV/AIDS patients with pulmonary complications

Pulmonary hypertension is a rare but serious complication of HIV infection. However, given the number of patients who live with chronic HIV infection globally (approximately 30 million), HIV associated pulmonary hypertension will become an important issue in the

coming years.(75, 76) Pulmonary malignancies (77), interstitial lung disease (78), obstructive airway disease and emphysema (79), and bronchiectasis (80) are other pulmonary disorders which are frequently seen in HIV infected population. Immunogenicity and safety of conjugated pneumococcal vaccine have been demonstrated.(81) All pulmonary patients with HIV/AIDS should receive PCV13 and PPSV23 per recommendation.

Immunosuppressive therapy

invasive pneumococcal disease is a serious infection in patients with hematologic and solid malignancies. For example, a population-based retrospective study in Canada showed an increased risk for invasive pneumococcal disease in patients with lung cancer (Odds ratio = 13.4).(82) Leukemia is the most common malignancy in children, which increases the risk for invasive pneumococcal disease 10 fold as compared to children in the general population.(83) PCV13 alone covers 84% of the serotypes that were isolated from invasive pneumococcal disease patients with a hematologic malignancy in a French study. French researchers found when PPSV23 was added, 92% of serotypes were covered. (84) Patients on steroid or immunomodulating drugs (e.g., methotrexate, anti-tumor necrosis factor (TNF) inhibitors) have higher risk for invasive pneumococcal disease and poorer response to vaccines.(85, 86) Although there is little information about sarcoidosis and invasive pneumococcal disease, we recommend PCV13 in all patients on steroid and nonsteroidal treatment. Nonsteroidal therapy for sarcoidosis has been discussed elsewhere.(87)

Vaccination protocol *per* ACIP recommendation (55)

Pneumococcal vaccine-naive persons

Patients who have never been vaccinated with pneumococcal vaccine should receive a single dose of PCV13 first, followed by a dose of PPSV23 at least 8 weeks later. For patients with any of the above listed indications, a follow up dose of PPSV23 is recommended five years following initial vaccination (Table 1 and 3). For patients who do not meet criteria to receive a second dose of PPSV23 per medical indications listed on Tables 1 and 3 should still receive this dose if they were first vaccinated before the age of 65. Please note that the follow up vaccine of PPSV23 is not due in these patients until more than 5 years have elapsed since first immunization with PPSV23.

Previous vaccination with PPSV23

Among patients who have previously received PPSV23, those who meet indication criteria for PCV13 immunization should receive a single dose of PCV13 at least a year after receiving the last dose of PPSV23. In those who meet criteria for repeating PPSV23, the vaccine should be given 8 weeks after receiving PCV13.

Interaction with other vaccines

In healthy adults, it was shown that the concomitant administration of PCV13 and trivalent inactivated influenza vaccine might diminish the antibody response to PCV13.(88) Therefore, it would be recommended to administer these vaccines in different visits.

This review concludes that patients with chronic pulmonary diseases who take steroids or immunomodulating therapy (e.g., methotrexate, anti-TNF inhibitors), having concurrent sickle cell disease or other hemoglobinopathies, primary immunodeficiency disorders, human immunodeficiency virus infection / acquired immunodeficiency syndrome (HIV/AIDS), nephrotic syndrome, and hematologic or solid malignancies should be vaccinated with both 13-valent pneumococcal conjugate vaccine and the pneumococcal polysaccharide vaccine 23-valent.

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Reference List

1. Prevention CfDCa. [Accessed March 6, 2014] Clinical Features: Pneumococcal Disease. Available at: http://www.cdc.gov/pneumococcal/clinicians/clinical-features.html
2. CDC. [Accessed April 3, 2014] Deaths: Preliminary Data for 2011. 2012. Avaiable at http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_06.pdf
3. Fedson DS, Scott JA. The burden of pneumococcal disease among adults in developed and developing countries: what is and is not known. Vaccine. 1999; 17(Suppl 1):S11–8. [PubMed: 10471174]
4. Yu H, Rubin J, Dunning S, et al. Clinical and economic burden of community-acquired pneumonia in the Medicare fee-for-service population. Journal of the American Geriatrics Society. 2012; 60(11):2137–43. [PubMed: 23110409]
5. Henrichsen J. Six newly recognized types of Streptococcus pneumoniae. Journal of clinical microbiology. 1995; 33(10):2759–62. [PubMed: 8567920]
6. Sleeman K, Knox K, George R, et al. Invasive pneumococcal disease in England and Wales: vaccination implications. The Journal of infectious diseases. 2001; 183(2):239–46. [PubMed: 11120930]
7. Nuorti JP, Whitney CG, Centers for Disease C, Prevention. Prevention of pneumococcal disease among infants and children – use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine – recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recommendations and reports: Morbidity and mortality weekly report Recommendations and reports / Centers for Dis. 2010; 59(RR-11):1–18.
8. Le Meur JB, Lefebvre B, Proulx JF, et al. Impact of pneumococcal vaccines use on invasive pneumococcal disease in Nunavik (Quebec) from 1997 to 2010. International journal of circumpolar health. 2014; 73:22691. [PubMed: 24455492]
9. Hausdorff WP, Bryant J, Kloek C, et al. The contribution of specific pneumococcal serogroups to different disease manifestations: implications for conjugate vaccine formulation and use, part II. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2000; 30(1):122–40. [PubMed: 10619741]
10. Tan TQ, Mason EO Jr. Wald ER, et al. Clinical characteristics of children with complicated pneumonia caused by Streptococcus pneumoniae. Pediatrics. 2002; 110(1 Pt 1):1–6. [PubMed: 12093940]
11. Johnson HL, Deloria-Knoll M, Levine OS, et al. Systematic evaluation of serotypes causing invasive pneumococcal disease among children under five: the pneumococcal global serotype project. PLoS medicine. 2010; 7(10)
12. Aliberti S, Mantero M, Mirsaeidi M, Blasi F. Role of vaccination in preventing pneumococcal disease in adults. Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2014
13. Janssens JP, Krause KH. Pneumonia in the very old. The Lancet infectious diseases. 2004; 4(2): 112–24. [PubMed: 14871636]

14. Austrian R, Gold J. Pneumococcal Bacteremia with Especial Reference to Bacteremic Pneumococcal Pneumonia. Annals of internal medicine. 1964; 60:759–76. [PubMed: 14156606]
15. CDC. Active Bacterial Core surveillance report, Emerging Infections Program Network, Streptococcus pneumoniae, 2010. US Department of Health and Human Services, CDC; Atlanta, GA: 2011. http://www.cdc.gov/abcs/reports-findings/survreports/spneu10-orig.html [Accessed April 3, 2014]
16. Smith DF, Boss EF. Racial/ethnic and socioeconomic disparities in the prevalence and treatment of otitis media in children in the United States. The Laryngoscope. 2010; 120(11):2306–12. [PubMed: 20939071]
17. Block SL. Causative pathogens, antibiotic resistance and therapeutic considerations in acute otitis media. The Pediatric infectious disease journal. 1997; 16(4):449–56. [PubMed: 9109158]
18. Thigpen MC, Whitney CG, Messonnier NE, et al. Bacterial meningitis in the United States, 1998-2007. N Engl J Med. 2011; 364(21):2016–25. [PubMed: 21612470]
19. Robinson KA, Baughman W, Rothrock G, et al. Epidemiology of invasive Streptococcus pneumoniae infections in the United States, 1995-1998: Opportunities for prevention in the conjugate vaccine era. JAMA: the journal of the American Medical Association. 2001; 285(13): 1729–35. [PubMed: 11277827]
20. Centers for Disease C; Prevention, Advisory Committee on Immunization P. Updated recommendations for prevention of invasive pneumococcal disease among adults using the 23-valent pneumococcal polysaccharide vaccine (PPSV23). MMWR Morbidity and mortality weekly report. 2010; 59(34):1102–6. [PubMed: 20814406]
21. Musher DM, Alexandraki I, Graviss EA, et al. Bacteremic and nonbacteremic pneumococcal pneumonia. A prospective study. Medicine. 2000; 79(4):210–21.
22. Plevneshi A, Svoboda T, Armstrong I, et al. Population-based surveillance for invasive pneumococcal disease in homeless adults in Toronto. PloS one. 2009; 4(9):e7255. [PubMed: 19787070]
23. Lujan M, Burgos J, Gallego M, et al. Effects of immunocompromise and comorbidities on pneumococcal serotypes causing invasive respiratory infection in adults: implications for vaccine strategies. Clin Infect Dis. 2013; 57(12):1722–30. [PubMed: 24065334]
24. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2013; 1:CD000422. [PubMed: 23440780]
25. Ramakrishnan M, Moisi JC, Klugman KP, et al. Increased risk of invasive bacterial infections in African people with sickle-cell disease: a systematic review and meta-analysis. Lancet Infect Dis. 2010; 10(5):329–37. [PubMed: 20417415]
26. Vestbo J, Hurd SS, Agusti AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013; 187(4):347–65. [PubMed: 22878278]
27. Mor A, Thomsen RW, Ulrichsen SP, Sorensen HT. Chronic heart failure and risk of hospitalization with pneumonia: a population-based study. European journal of internal medicine. 2013; 24(4): 349–53. [PubMed: 23510659]
28. Wang IK, Lin CL, Lin PC, et al. Effectiveness of influenza vaccination in patients with end-stage renal disease receiving hemodialysis: a population-based study. PloS one. 2013; 8(3):e58317. [PubMed: 23516462]
29. Nuorti JP, Butler JC, Farley MM, et al. Cigarette smoking and invasive pneumococcal disease. Active Bacterial Core Surveillance Team. N Engl J Med. 2000; 342(10):681–9. [PubMed: 10706897]
30. Dominguez A, Izquierdo C, Salleras L, et al. Effectiveness of the pneumococcal polysaccharide vaccine in preventing pneumonia in the elderly. The European respiratory journal. 2010; 36(3): 608–14. [PubMed: 20075048]
31. Ridda I, Macintyre CR, Lindley R, et al. Immunological responses to pneumococcal vaccine in frail older people. Vaccine. 2009; 27(10):1628–36. [PubMed: 19100304]
32. Musher DM, Watson DA, Dominguez EA. Pneumococcal vaccination: work to date and future prospects. The American journal of the medical sciences. 1990; 300(1):45–52. [PubMed: 2196794]

33. Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. The New England journal of medicine. 2003; 348(18):1737–46. [PubMed: 12724479]
34. Malley R, Trzcinski K, Srivastava A, et al. CD4+ T cells mediate antibody-independent acquired immunity to pneumococcal colonization. Proceedings of the National Academy of Sciences of the United States of America. 2005; 102(13):4848–53. [PubMed: 15781870]
35. Administration UFaD. [Accessed April 3, 2014] Protection of adults from invasive pneumococcal disease (IPD) by means of active immunization with currently licensed vaccine PNEUMOVAX 23TM (PPV23). available at: http://www.fda.gov/ohrms/dockets/ac/05/briefing/5-4188b2_4b.pdf
36. Biagini RE, Schlottmann SA, Sammons DL, et al. Method for simultaneous measurement of antibodies to 23 pneumococcal capsular polysaccharides. Clinical and diagnostic laboratory immunology. 2003; 10(5):744–50. [PubMed: 12965898]
37. Nuorti JP, Whitney CG, Centers for Disease C, Prevention. Prevention of pneumococcal disease among infants and children – use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine – recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2010; 59(RR-11):1–18. [PubMed: 21150868]
38. Butler JC, Breiman RF, Campbell JF, et al. Pneumococcal polysaccharide vaccine efficacy. An evaluation of current recommendations. JAMA: the journal of the American Medical Association. 1993; 270(15):1826–31. [PubMed: 8411526]
39. Jackson LA, Janoff EN. Pneumococcal vaccination of elderly adults: new paradigms for protection. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2008; 47(10):1328–38. [PubMed: 18844484]
40. Johnstone J, Eurich DT, Minhas JK, et al. Impact of the pneumococcal vaccine on long-term morbidity and mortality of adults at high risk for pneumonia. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2010; 51(1):15–22. [PubMed: 20504233]
41. Musher DM, Rueda-Jaimes AM, Graviss EA, Rodriguez-Barradas MC. Effect of pneumococcal vaccination: a comparison of vaccination rates in patients with bacteremic and nonbacteremic pneumococcal pneumonia. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2006; 43(8):1004–8. [PubMed: 16983612]
42. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. The Cochrane database of systematic reviews. 2013; 1:CD000422. [PubMed: 23440780]
43. Blumberg EA, Brozena SC, Stutman P, et al. Immunogenicity of pneumococcal vaccine in heart transplant recipients. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2001; 32(2):307–10. [PubMed: 11170924]
44. Tobudic S, Plunger V, Sunder-Plassmann G, et al. Randomized, single blind, controlled trial to evaluate the prime-boost strategy for pneumococcal vaccination in renal transplant recipients. PloS one. 2012; 7(9):e46133. [PubMed: 23029408]
45. Kumar D, Chen MH, Welsh B, et al. A randomized, double-blind trial of pneumococcal vaccination in adult allogeneic stem cell transplant donors and recipients. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2007; 45(12): 1576–82. [PubMed: 18190318]
46. Rodriguez-Barradas MC, Musher DM, Lahart C, et al. Antibody to capsular polysaccharides of Streptococcus pneumoniae after vaccination of human immunodeficiency virus-infected subjects with 23-valent pneumococcal vaccine. The Journal of infectious diseases. 1992; 165(3):553–6. [PubMed: 1347058]
47. Hung CC, Chang SY, Su CT, et al. A 5-year longitudinal follow-up study of serological responses to 23-valent pneumococcal polysaccharide vaccination among patients with HIV infection who received highly active antiretroviral therapy. HIV medicine. 2010; 11(1):54–63. [PubMed: 19659943]
48. Prevention CfDCa. [Accessed April 3, 2014] Recommended immunization schedule for persons aged 0 through 18 years – United States. 2014. Avaialble at: http://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-schedule.pdf

49. Richter SS, Heilmann KP, Dohrn CL, et al. Pneumococcal serotypes before and after introduction of conjugate vaccines, United States, 1999-2011(1.). Emerging infectious diseases. 2013; 19(7): 1074–83. [PubMed: 23763847]
50. Grijalva CG, Pelton SI. A second-generation pneumococcal conjugate vaccine for prevention of pneumococcal diseases in children. Current opinion in pediatrics. 2011; 23(1):98–104. [PubMed: 21191300]
51. Food and Drug Administration (FDA) web site. [Accessed April 3, 2014] Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM197 Protein) Prevnar®. Available at: http://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm137038.pdf
52. Pilishvili T, Lexau C, Farley MM, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. J Infect Dis. 2010; 201(1):32–41. [PubMed: 19947881]
53. Mistry RD, Wedin T, Balamuth F, et al. Emergency department epidemiology of pneumococcal bacteremia in children since the institution of widespread PCV7 vaccination. The Journal of emergency medicine. 2013; 45(6):813–20. [PubMed: 23992851]
54. Centers for Disease C, Prevention. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among children aged 6-18 years with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morbidity and mortality weekly report. 2013; 62(25):521–4. [PubMed: 23803961]
55. Centers for Disease C, Prevention. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morbidity and mortality weekly report. 2012; 61(40):816–9. [PubMed: 23051612]
56. Schwarz TF, Flamaing J, Rumke HC, et al. A randomized, double-blind trial to evaluate immunogenicity and safety of 13-valent pneumococcal conjugate vaccine given concomitantly with trivalent influenza vaccine in adults aged >/=65 years. Vaccine. 2011; 29(32):5195–202. [PubMed: 21619909]
57. Centers for Disease C, Prevention. Licensure of a 13-valent pneumococcal conjugate vaccine (PCV13) and recommendations for use among children – Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Morbidity and mortality weekly report. 2010; 59(9):258–61. [PubMed: 20224542]
58. Musher DM. How effective is vaccination in preventing pneumococcal disease? Infectious disease clinics of North America. 2013; 27(1):229–41. [PubMed: 23398877]
59. Food and Drug Administration. FDA expands use of Prevnar 13 vaccine for people ages 50 and older. US Department of Health and Human Services, Food and Drug Administration; Silver Spring, MD: Available at http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm285431.htm?source=govdelivery [Accessed March 28, 2014]
60. Jackson LA, Gurtman A, van Cleeff M, et al. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine compared to a 23-valent pneumococcal polysaccharide vaccine in pneumococcal vaccine-naive adults. Vaccine. 2013; 31(35):3577–84. [PubMed: 23688526]
61. Smith KJ, Nowalk MP, Raymund M, Zimmerman RK. Cost-effectiveness of pneumococcal conjugate vaccination in immunocompromised adults. Vaccine. 2013; 31(37):3950–6. [PubMed: 23806240]
62. Cho BH, Stoecker C, Link-Gelles R, Moore MR. Cost-effectiveness of administering 13-valent pneumococcal conjugate vaccine in addition to 23-valent pneumococcal polysaccharide vaccine to adults with immunocompromising conditions. Vaccine. 2013
63. Lujan M, Burgos J, Gallego M, et al. Effects of Immunocompromise and Comorbidities on Pneumococcal Serotypes Causing Invasive Respiratory Infection in Adults: Implications for Vaccine Strategies. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2013
64. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014; 58(3):e44–100. [PubMed: 24311479]

65. Ellison AM, Ota KV, McGowan KL, Smith-Whitley K. Pneumococcal bacteremia in a vaccinated pediatric sickle cell disease population. The Pediatric infectious disease journal. 2012; 31(5):534–6. [PubMed: 22228232]
66. Patel A, Zuzo A, Imran H, Siddiqui AH. Prevalence of pneumococcal bacteremia in children with sickle cell disease. Pediatric hematology and oncology. 2013; 30(5):432–6. [PubMed: 23570543]
67. Vij R, Machado RF. Pulmonary complications of hemoglobinopathies. Chest. 2010; 138(4):973–83. [PubMed: 20923801]
68. Geha RS, Notarangelo LD, Casanova JL, et al. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. The Journal of allergy and clinical immunology. 2007; 120(4):776–94. [PubMed: 17952897]
69. Buckley RH. Pulmonary complications of primary immunodeficiencies. Paediatric respiratory reviews. 2004; 5(Suppl A):S225–33. [PubMed: 14980276]
70. Turner PJ, Mehr S, Kemp AS. Detection of pulmonary complications in common variable immunodeficiency. Pediatric allergy and immunology: official publication of the European Society of Pediatric Allergy and Immunology. 2011; 22(4):449–50. author reply 51-2. [PubMed: 21535182]
71. Touw CM, van de Ven AA, de Jong PA, et al. Detection of pulmonary complications in common variable immunodeficiency. Pediatric allergy and immunology: official publication of the European Society of Pediatric Allergy and Immunology. 2010; 21(5):793–805. [PubMed: 19912551]
72. Picard C, Puel A, Bustamante J, et al. Primary immunodeficiencies associated with pneumococcal disease. Current opinion in allergy and clinical immunology. 2003; 3(6):451–9. [PubMed: 14612669]
73. Bustamante J, Zhang SY, von Bernuth H, et al. From infectious diseases to primary immunodeficiencies. Immunology and allergy clinics of North America. 2008; 28(2):235–58. vii. [PubMed: 18424331]
74. Winkelstein JA, Marino MC, Johnston RB Jr. et al. Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine. 2000; 79(3):155–69.
75. Barnett CF, Hsue PY. Human immunodeficiency virus-associated pulmonary arterial hypertension. Clinics in chest medicine. 2013; 34(2):283–92. [PubMed: 23702177]
76. Sitbon O, Gressin V, Speich R, et al. Bosentan for the treatment of human immunodeficiency virus-associated pulmonary arterial hypertension. American journal of respiratory and critical care medicine. 2004; 170(11):1212–7. [PubMed: 15317666]
77. Lambert AA, Merlo CA, Kirk GD. Human immunodeficiency virus-associated lung malignancies. Clinics in chest medicine. 2013; 34(2):255–72. [PubMed: 23702175]
78. Graham SM. HIV-related pulmonary disorders: practice issues. Annals of tropical paediatrics. 2007; 27(4):243–52. [PubMed: 18053340]
79. Gingo MR, Morris A, Crothers K. Human immunodeficiency virus-associated obstructive lung diseases. Clinics in chest medicine. 2013; 34(2):273–82. [PubMed: 23702176]
80. Masekela R, Anderson R, Moodley T, et al. HIV-related bronchiectasis in children: an emerging spectre in high tuberculosis burden areas. The international journal of tuberculosis and lung disease: the official journal of the International Uni. 2012; 16(1):114–9.
81. Ho YL, Brandao AP, de Cunto Brandileone MC, Lopes MH. Immunogenicity and safety of pneumococcal conjugate polysaccharide and free polysaccharide vaccines alone or combined in HIV-infected adults in Brazil. Vaccine. 2013; 31(37):4047–53. [PubMed: 23684823]
82. Wong A, Marrie TJ, Garg S, et al. Increased risk of invasive pneumococcal disease in haematological and solid-organ malignancies. Epidemiology and infection. 2010; 138(12):1804–10. [PubMed: 20429967]
83. Meisel R, Toschke AM, Heiligensetzer C, et al. Increased risk for invasive pneumococcal diseases in children with acute lymphoblastic leukaemia. British journal of haematology. 2007; 137(5): 457–60. [PubMed: 17488489]
84. Debbache K, Varon E, Hicheri Y, et al. The epidemiology of invasive Streptococcus pneumoniae infections in onco-haematology and haematopoietic stem cell transplant patients in France. Are the

serotypes covered by the available anti-pneumococcal vaccines? Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2009; 15(9):865–8.

85. Kapetanovic MC, Roseman C, Jonsson G, Truedsson L. Heptavalent pneumococcal conjugate vaccine elicits similar antibody response as standard 23-valent polysaccharide vaccine in adult patients with RA treated with immunomodulating drugs. Clinical rheumatology. 2011; 30(12): 1555–61. [PubMed: 21956234]
86. Visser LG. TNF-alpha Antagonists and Immunization. Current infectious disease reports. 2011; 13(3):243–7. [PubMed: 21455717]
87. Korsten P, Mirsaeidi M, Sweiss NJ. Nonsteroidal therapy of sarcoidosis. Current opinion in pulmonary medicine. 2013; 19(5):516–23. [PubMed: 23884295]
88. Frenck RW Jr. Gurtman A, Rubino J, et al. Randomized, controlled trial of a 13-valent pneumococcal conjugate vaccine administered concomitantly with an influenza vaccine in healthy adults. Clinical and vaccine immunology: CVI. 2012; 19(8):1296–303. [PubMed: 22739693]

Clinical Significance

- Immunocompromised patients have a poor response to pneumococcal polysaccharide vaccine 23-valent (PPSV23).
- 13-valent pneumococcal conjugate vaccine (PCV13) is a safe and effective strategy to prevent invasive pneumococcal disease.
- Patients with chronic pulmonary diseases who take steroids or immunomodulating therapy or having some certain risk factors should be vaccinated with both PCV13 and the PPSV23.

Table 1

Indications for administration of PPSV23 and re-vaccination 5 years after the first dose in adults aged ≥19 years*

Vaccine responder	Underlying medical condition	PPSV23	PPV23 re-vaccination
Good responders	Chronic pulmonary diseases**	⋆	
	Chronic heart disease***	⋆	
	Chronic liver disease	⋆	
	CSF leaks	⋆	
	Cochlear implants	⋆	
	Alcoholism	⋆	
	Diabetes mellitus	⋆	
	Tobacco smoking	⋆	
Poor responder	Sickle cell disease and other hemoglobinopathies	⋆	⋆
	Congenital or acquired asplenia	⋆	⋆
	Primary immunodeficiencies§	⋆	⋆
	Iatrogenic immunodeficiency §§	⋆	⋆
	HIV infection	⋆	⋆
	Hematologic malignancies	⋆	⋆
	Generalized malignancy	⋆	⋆
	Solid organ transplant	⋆	⋆
	Chronic renal failure	⋆	⋆
	Nephrotic syndrome	⋆	⋆

Note: adapted from Advisory Committee on Immunization Practices, United States, 2012 with authors' comments. All adults≥65 years should be revaccinated with PPSV23 without consideration of previous pneumococcal vaccination

** Such as COPD, asthma, bronchiectasis, sarcoidosis

*** including congestive heart failure (CHF) and cardiomyopathies

§ All type of B and T cell lymphocyte deficiencies, complement specially early complements (C1, C2, C3, C4), and phagocyte disorders except chronic granulomatous disease.

§§ any condition that patient takes chronic systemic corticosteroids (such as prednisone 15 mg per day for more than 6 months) or immunosuppressant agents such as methotrexate, or radiation therapy

Table 2

Streptococcus pneumoniae strains that are covered by PPSV23 and PCV13 vaccines

Vaccine name	Serotypes covered by
PPSV23	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F
PCV13	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F
Both PPSV 23 and PCV13	1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F

PPSV23 (23-valent pneumococcal polysaccharide vaccine; Pneumovax23, marketed by Merck & Company, Inc.)

PCV13 (Pneumococcal 13-valent Conjugate Vaccine; Prevnar 13, Manufactured by Wyeth Pharmaceuticals Inc. Marketed by Pfizer Inc.)

Table 3

Indications for 13-valent pneumococcal conjugate vaccine (PCV13) in adults aged ≥19 years

Immune status	Underlying medical condition	PCV13
Immunocompetent	CSF leaks	⋆
	Cochlear implants	⋆
Immunocompromised	Sickle cell disease and other hemoglobinopathies	⋆
	Congenital or acquired asplenia	⋆
	Primary immunodeficiencies*	⋆
	Iatrogenic immunodeficiency**	⋆
	HIV infection	⋆
	Hematologic malignancies	⋆
	Generalized malignancy	⋆
	Solid organ transplant	⋆
	Chronic renal failure	⋆
	Nephrotic syndrome	⋆

Note: adapted from Advisory Committee on Immunization Practices, United States, 2012 with authors' comments

* All type of B and T cell lymphocyte deficiencies, complement specially early complements (C1, C2, C3, C4), and phagocyte disorders except chronic granulomatous disease

** Any condition that patient takes chronic systemic corticosteroids (such as prednisone 15 mg per day for more than 6 months) or immunosuppressant agents such as methotrexate, or radiation therapy