Review: Clinical Trial Outcomes

CLINICAL INVESTIGATION

Pneumococcal vaccination in adults: recent evidence from clinical trials and observational studies

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***Streptococcus pneumoniae*, or pneumococcus, is a common and virulent pathogen that causes a high burden of clinical disease. All demographic groups are affected; however, older adults and the immunosuppressed are at higher risk for infection of normally sterile body spaces, called invasive pneumococcal disease. Vaccination, both with free-polysaccharide and more recently conjugate protein formulations, has led to reductions in invasive pneumococcal disease. These reductions are not uniform, however, as patients with comorbid illness derive less protection from the free-polysaccharide vaccine. At best, the free-polysaccharide vaccine appears only modestly effective in protecting against nonbacteremic pneumococcal pneumonia. Conjugated protein vaccines stimulate a more vigorous immune response in young children and most adults, as measured by opsonophagocytosis assays. This suggests the conjugate vaccine may offer improved immune protection against both invasive disease and pneumonia; however, large randomized trials with clinical end points are still needed. If proven to be protective, replacement of the current free polysaccharide with conjugate vaccines would likely be cost-effective among adults over 65 years of age and those at higher risk.**

Keywords: adults • conjugate • COPD • elderly • opsonophagocytosis • pneumococcus • pneumonia • Pneumovax • polysaccharide • Prevnar • vaccination • vaccine

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Streptococcus pneumoniae, or pneumococcus, is a ubiquitous Gram-positive bacterium that commonly causes human disease, ranging in severity from relatively mild infections, such as otitis media, to severe, life-threatening illness, such as pneumonia, bacteremia and meningitis. Invasive pneumococcal disease (IPD) is defined as isolation of pneumococcus in a normally sterile body fluid or space, such as the blood stream, pleural space, peritoneal space or the CNS. IPD causes major morbidity and mortality worldwide and leads to significant health care expenditures and impaired quality of life [1–4].

Since before the advent of penicillin, vaccination has been utilized as a strategy to prevent pneumococcal disease and became a proven method with the approval of a free-polysaccharide vaccine in 1983. The capsular polysaccharide has been utilized as a vaccine target because it is the major contributor to the virulence of pneumococcus and its capacity to evade host defense. Though observational data suggest that the free-polysaccharide vaccine reduces the incidence of IPD in healthy adults [5–8], the vaccine has some limitations including the fact that children and some adults do not mount adequate antibody responses when inoculated. Capsular polysaccharide vaccines rely on mature B lymphocytes, a T-cell-independent mechanism, to induce an immune response. Young children and certain immunosuppressed adults lack mature B cells and are therefore unable to generate sufficient antibodies for immune memory [9]. The development of protein-conjugate pneumococcal vaccines, which stimulate antibody

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formation through a T-cell dependent response, has partially addressed this issue, particularly for the vaccination of young children. However, both serotype-specific vaccines are limited by the diversity of the pneumococcus. There are more than 90 immunologically distinct serotypes of pneumococcus and currently available vaccines only cover a subset of these. Vaccine development has targeted the most prevalent and deadly serotypes; however, with widespread adoption of vaccination, some less prevalent serotypes that were not targeted in the vaccines have emerged in clinical isolates, a phenomenon known as 'serotype replacement' [10]. While not all pneumococcal serotype isolates have been implicated in causing clinical disease, the emergence of replacement serotypes warrants further observation.

This review will discuss the clinical effectiveness of the two most widely available and used pneumococcal vaccines: the 23-valent polyvalent polysaccharide vaccine (PPSV23; Pneumovax®; Merck & Co., NJ, USA) and the recently approved 13-valent pneumococcal conjugate protein vaccine (PCV13; Prevnar-13®; Pfizer, NY, USA). The focus will center on healthy adults, elderly adults and patients with chronic obstructive pulmonary disease (COPD). Compelling data supporting the utility of conjugate pneumococcal vaccination in reducing IPD and otitis in young children, as well as in reducing IPD in elderly patients through herd immunity have been published elsewhere [11–13].

Vaccine formulation

Free-polysaccharide vaccination as a method to prevent pneumococcal disease was first championed by Robert Austrian and was initially developed and approved in the USA to include 14 serotypes [5]. This was later supplanted in 1983 by a 23-serotype free-polysaccharide vaccine that targeted the serotypes that were most commonly associated with IPD (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) [14]. The vaccine contains 25 µg of free polysaccharide from each serotype, mixed with 0.25% phenol as a preservative and isotonic saline. PPSV23 is currently approved by the US FDA for use in older adults (age >65 years) and younger adults with impaired immune function [15]; however, vaccination strategies continue to be modified by the Centers for Disease Control and Prevention (CDC) as newer data with conjugated vaccines become available (Table 1).

Serotype replacement

Due to impaired immune responses to the free-polysaccharide vaccine in young children and previous successes with conjugated vaccines, such as the conjugate vaccine against *Haemophilus influenza* type B in infants and young children [16], a protein-conjugate vaccine was developed in the late 1990s. This vaccine contained seven serotypes (4, 6B, 9V, 14, 18C, 19F and 23F) conjugated to a nontoxic variant of diphtheria toxin (CRM197), which led to significant immunogenicity to the target serotypes and high clinical efficacy in the reduction of otitis media and IPD [17–19]. Due in large part to this success, as well as the associated reduction in IPD in older adults through reduced colonization of disease-causing serotypes, so-called 'herd immunity', the diphtheria conjugate vaccine was expanded to include 13 serotypes. The added serotypes (1, 3, 5, 7F, 6A and 19A) were chosen based on the observation that IPD incidence caused by serotypes not included in the original conjugate vaccine has been rising, especially in certain populations. In a surveillance study of Alaskan-native children, a population group that is high-risk for IPD, there was a 140% increase in IPD caused by nonvaccine serotypes from 1995 (prevaccine) to 2006 (postvaccine) [20]. Less dramatic but similar increases in infection with nonvaccine serotypes were also noted in native Alaskan adults and non-native children and adults during this time period. Despite a 90% reduction in disease caused by serotypes in PCV7, the overall IPD incidence only dropped by 6%, from 49.1 per 100,000 cases to 46 per 100,000 [20]. This relative stability of incidence rates was largely attributable to nonvaccine replacement serotypes. For example, serotype 19A, which was not included in the initial conjugate vaccine, has emerged as a predominant serotype. Active Bacterial Core data of samples from throughout the USA from 2005 to 2007 show an increased incidence of 19A among isolates, many of which are penicillin-resistant strains [10]. Serotype replacement has been well established in pneumococcal surveillance research and remains an important consideration in clinical care and future vaccine development [21].

Surrogate markers of immunogenicity

Comparative clinical trials comparing the efficacy of free-polysaccharide and conjugate vaccination are problematic for a number of reasons. Firstly, randomized trials utilizing a placebo in the control group may not be ethically feasible, given the effectiveness of free-polysaccharide vaccine against IPD and the fact that it is recommended by the CDC and other public health authorities [22]. Second, with reduced rates of invasive disease and of disease caused by vaccine-related serotypes, as well as the inherent difficulties in making a pathogen-specific diagnosis for pneumonia, the numbers of patients required to show a difference in a comparison trial would be prohibitively large. For these reasons, laboratory-based tests have emerged as attractive surrogates for vaccine efficacy. Serologic measurement of IgG against the pneumococcal antigen using ELISA assays was the first surrogate used,

with antibody levels greater than 0.2–0.35 mg/l thought to offer protection against vaccine-targeted serotypes [23]. However, the ELISA assay does not always predict serotype protection, especially in older adults and immunosuppressed populations [24,25]. This may be due to lack of IgM support [24] or production of polyreactive, but nonspecific, IgG antibodies [25]. As a result, a functional assay that measures the capacity of detected antibody to opsonize and kill pneumococcus has emerged as a potentially more specific surrogate marker. These assays, called opsonophagocytosis assays (OPA) combine subject serum, exogenous complement, and human phagocytes with isolates from targeted pneumococcus serotypes. Following an incubation period, the surviving colonies of pneumococcus are counted for each serotype at various titers of subject serum. Survival of 50% of the colonies at a given titer defines the opsonic threshold for protection [26]. This process has been further streamlined, allowing for efficient throughput with small quantities of subject serum. Current multiplex OPA assays are capable of analyzing numerous serotypes at one time and assimilate the data into easily interpretable read-outs (Figure 1).

OPA data have already been used to compare immunogenicity in subjects using PPSV23 and conjugate vaccines. More recent studies of young adults and the elderly have generally shown significantly higher opsonic titers with conjugates compared with the free-polysaccharide vaccine [27–29]. The opsonic response in solid organ transplant still remains unclear. An immunogenicity trial comparing responses of PPSV23 versus PCV7 in 60 renal transplant patients showed no difference in opsonic titers despite ELISA antibody measurements crossing the 'protective threshold' [30]. This lack of opsonic activity has led to various booster strategies.

Antibody titers and opsonic titers are not routinely measured in clinical practice and are mainly limited to use in clinical trials and vaccine development.

Burden of disease

Vaccination of young children with conjugate vaccine has changed the epidemiology of pneumococcal disease. Prior to routine childhood vaccination with PCV7 (1999–2000), overall invasive pneumococcal disease rates among adults in the USA were 41 cases per 100,000 [31]. Elderly adults were preferentially affected, with incidence rates near 70 cases per 100,000 in those over the age of 85 years. Within 3 years of conjugate vaccination, the incidence of IPD in adults caused by all serotypes had dropped by 28%, with the most dramatic benefits seen in adults over 65 years of age [31]. Another evaluation of Active Bacterial Core data by Whitney *et al.* showed similar reductions in IPD, with an 8% rate reduction in adults aged 40–64 and an 18% reduction in adults over 65 years of age [32].

Table 1. Current Advisory Committee on Immunization Practices vaccination recommendations by risk group.

Illness	PCV13	PPSV23†	PPSV23 boost‡
Immune competent			
Heart disease	–	X	–
Lung disease	–	X	–
Liver disease	–	X	–
Diabetes mellitus	–	X	–
Cerebrospinal fluid leak	X	X	–
Cochlear implants	X	X	–
Alcoholism	–	X	–
Tobacco abuse	–	X	–
Asplenia			
Sickle cell disease/ hemoglobinopathy	X	X	X
Congenital/trauma	X	X	X
Immunocompromised			
Acquired or congenital immunodeficiency	X	X	X
HIV infection	X	X	X
Chronic renal failure	X	X	X
Nephrotic syndrome	X	X	X
Leukemia	X	X	X
Lymphoma	X	X	X
Hodgkin's disease	X	X	X
Generalized malignancy	X	X	X
Iatrogenic immunosuppression	X	X	X
Organ transplant	X	X	X
Multiple myeloma	X	X	X

In addition to those recommended, all elderly patients (age >65 years) should receive PPSV23. If previously vaccinated, they should receive an additional booster at age 65 or 5 years after most recent dose, whichever is later [56].

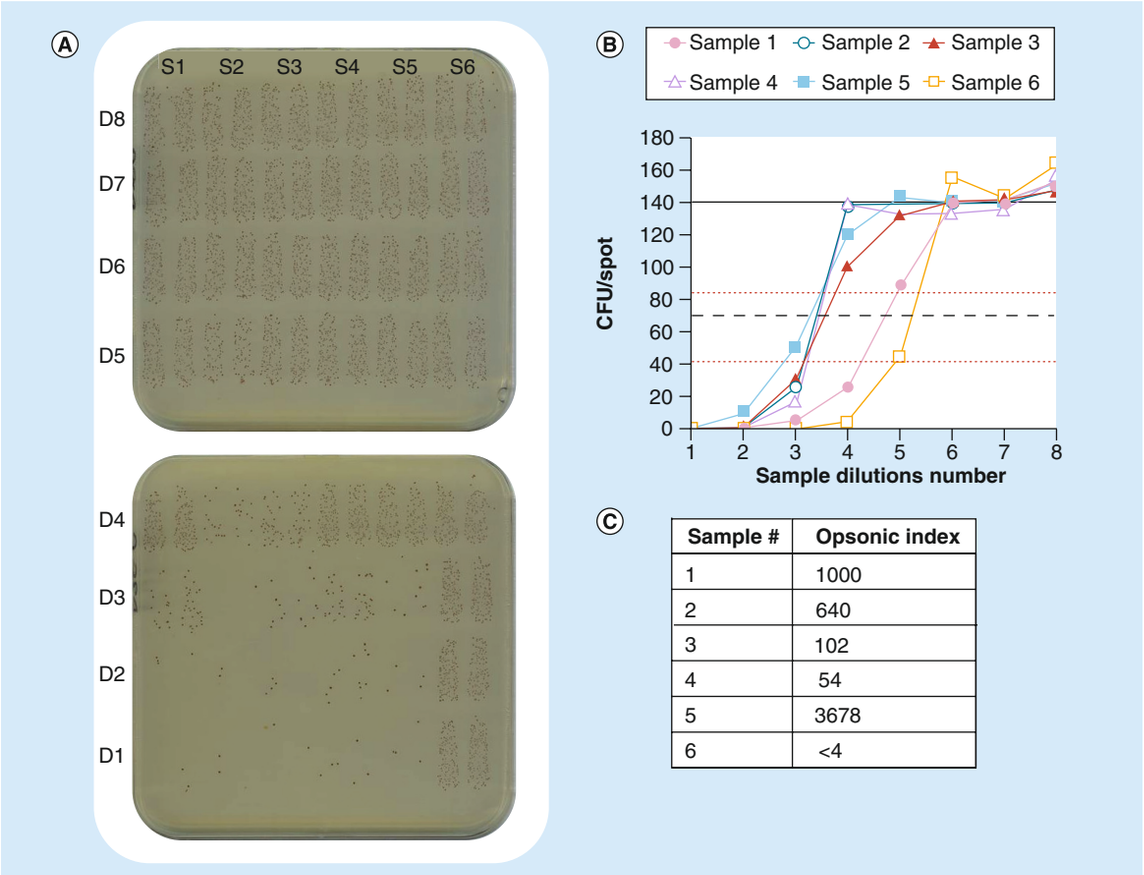
†Patients who require dosing with PCV13, should receive booster vaccination with PPSV23 at least 8 weeks following initial vaccination.

‡An additional PPSV23 booster should be given at 5 years following first PPSV23 dose for all patients with immunocompromised conditions and congenital or functional asplenia.

PCV13: Pneumococcal 13-valent conjugate vaccine; PPSV23: Pneumococcal 23-valent polysaccharide vaccine.

Mortality rates declined as well, albeit not as much as the IPD incidence, leading to increased case-fatality rate [31]. Multivariate analysis showed independent risk factors for mortality included infection with meningitis, disease among immunosuppressed subjects, or infection with serotypes 19F, 23F, 3 and 11A [31].

Conventional microbiologic methods are insensitive for detection of nonbacteremic pneumococcal pneumonia (NBPP), which makes clinical utility of vaccination more difficult to predict. Various studies have attempted to measure the true proportion of *S. pneumoniae* among



Sample #	Opsonic index
1	1000
2	640
3	102
4	54
5	3678
6	<4

Figure 1. Opsonophagocytosis assays microcolony plates with titration curves and opsonic index table. Progressively diluted serum samples from immunized subjects are combined with human phagocytes (HL60 cells), exogenous complement, and serotype-specific isolates of *Streptococcus pneumonia*. **(A)** After an incubation period, the mixture is plated onto yeast agar plates at increasing dilutions of serum/bacteria and allowed to grow overnight. **(B)** Colony growth is measured by microcolony readers and recorded as a data point. These data points are then connected, and an interpolated point is measured along the line that crosses the 50% threshold. **(C)** This point is determined as the opsonic titer for that sample [26].

cases of community-acquired pneumonia (CAP) though these data are variable. A Spanish study obtaining transthoracic needle aspirates along with conventional microbiologic sampling (blood and sputum) in consecutive patients hospitalized with CAP reported an isolation rate of 25% for pneumococcus [33]. Alternatively, a larger prospective cohort study of nearly 1000 patients hospitalized with CAP in the UK reported 40% isolation of pneumococcus [34]. The data for vaccine effectiveness in NBPP remain varied as reported below; however, if incidence reductions are similar to those seen with acute otitis media in children, the incidence of this disease might also be expected to decline.

General clinical efficacy

Excluding immunosuppressive conditions, young and middle-aged adults typically have low risk for pneumococcal infections [24,35]. This is likely related to reduced nasal colonization as children age into adulthood [10]. One exception is among parents of young children, where nasal carriage rates have been reported to be as high as 11% in the USA and higher in developing countries [10]. Despite the lower inherent risk, young and middle-aged adults are still affected by pneumococcal disease, especially NBPP.

Multiple clinical trials have examined the efficacy of free-polysaccharide vaccines in the adult population and have yielded conflicting results particularly in the elderly and those with comorbid medical problems (Table 2). This section will focus on studies involving healthy adults and adults with comorbid illness. Particular attention will be given to the elderly (age >65 years) and patients with chronic pulmonary diseases in later sections.

Table 2. Clinical outcomes for selected trials in pneumococcal vaccines.

Trial design	Population (location)	Outcome	Patients (n)	Treatment events (n)	Control events (n)	Efficacy (%)	Ref.
PPSV							
Meta	Healthy adults (low-income countries)	IPD	5373	2	14	86†	[6]
		Pneumonia	14,562	158	548	46†	
		Mortality	11,958	133	170	21†	
Meta	Chronically ill adults (high-income countries)	IPD	3230	4	2	-56	[6]
		Pneumonia	3071	90	88	3	
		Mortality	2634	233	199	-4	
Meta	Healthy adults (high-income countries)	IPD	26,880	9	44	80†	[4]
		Pneumonia	28,180	587	714	26	
		Mortality	31,017	533	558	16	
Meta	COPD patients	Pneumonia	1372	76	88	28	[35]
		Exacerbations	216	44	32	42	
		Mortality	888	46	44	-7	
RCT	Elderly (Finland)	IPD	26,925	–	–	60	[41]
		Pneumonia	26,925	–	–	-20	
RCT	Elderly (Finland)	NBPP	2837	26	33	15	[42]
		Pneumonia	2837	69	64	-17	
RCT	Nursing home residents (Japan)	NBPP	1006	14	37	64†	[44]
		Pneumonia	1006	63	104	45†	
		Mortality	1006	89	80	-12	
RCT	Bedbound (Japan)	Mortality	294	15	19	23	[45]
RCT	COPD patients	NBPP	596	0	5	–	[50]
		CAP-1st episode	596	25	33	24	
Cohort	Elderly (USA)	IPD	47,385	0.38/1000	0.68/1000	44†	[7]
		Pneumonia	47,385	11.8/1000	10.4/1000	-14†	
		Mortality	47,385	42/1000	50.1/1000	4	
Cohort	Elderly (Spain)	IPD	11,241	0.46/1000	0.95/1,000	40	[8]
		Pneumonia	11,241	1.94/1000	2.30/1000	45†	
		Mortality	11,241	45.1/1000	41.6/1000	3	
Cohort	COPD (Spain)	NBPP	1298	5.26/1000	5.72/1000	24	[51]
		Mortality	1298	81.2/1000	64.4/1000	-20	
PCV							
RCT	COPD (USA)	Exacerbations	181	93	93	‡	[54]
		Pneumonia	181	11	12	–	
		Mortality	181	4	7	–	

All clinical trial data is based on comparison of vaccination versus placebo with the exception of the randomized control trial by Dransfield *et al.*, which measured opsonic titers as a primary outcome and compared PCV7 to PPSV23 [53]. In this study, PPSV23 was given as the control vaccine. Cohort events are listed as incidence rates per 1000 person years.

†Statistically significant.

‡Hazard ratio: 0.91 (efficacy: 9% [trial not powered for clinical end points]).

CAP: Community-acquired pneumonia; COPD: Chronic obstructive pulmonary disease; IPD: Invasive pneumococcal disease; Meta: Meta analysis; NBPP: Nonbacteremic pneumococcal pneumonia; PCV: Pneumococcal conjugate vaccine; PPSV: Free-polysaccharide vaccine (either PPSV14 or PPSV23); RCT: Randomized control trial.

A 2008 update of a meta-analysis, which included 15 randomized control trials, showed a pooled odds ratio for the development of IPD of 0.26 (vaccine efficacy 74%) [6]. However, subgroup analysis revealed that this protection was lost among patients with chronic diseases (odds ratio [OR] for group: 1.56). Healthy adults in both low- and high-income countries showed more definitive efficacy. Within the meta-analysis, only one study examined vaccine efficacy in prevention of IPD in healthy adults of low income countries [36]. Among 5373 participants, there were two cases in the vaccine group and 14 cases in the control, leading to a protective efficacy of 86% (OR for disease: 0.14; 95% CI: 0.03–0.61). Similarly, combined data from four trials totaling 26,880 healthy adults in high-income countries showed protective efficacy of 80% (pooled OR: 0.20; 95% CI: 0.10–0.41).

Free-polysaccharide vaccines also showed protection against all-cause pneumonia; however, these data were less robust. In the meta-analysis, 13 studies were included with a pooled OR for all-cause pneumonia of 0.71 (95% CI: 0.52–0.97). As above, the protection was lost in subgroups that included chronic illnesses [6]. No statistical mortality benefit was seen [6]. Of note, the authors of this meta-analysis concluded there was no evidence to justify use of polysaccharide vaccine in the prevention of pneumonia.

With the introduction of the conjugate protein vaccine in children, the incidence of NBPP in adults appears to be declining, mirroring the reduction in IPD. Based on time series analyses of pneumococcal pneumonia, using data from before and after pneumococcal conjugate vaccine (PCV) usage in children, there has been a 65% reduction in pneumococcal pneumonia with all-cause pneumonia reductions of approximately 40% among children aged under 2 years [37]. Smaller but statistically significant reductions were also noted in younger (aged 18–39 years) and older adults (aged 40–64 years) [37].

Currently, the conjugate protein vaccine is not recommended for routine use in immunocompetent adults. However, given the previously discussed limitations of free-polysaccharide vaccine, as well as the proven benefit of PCV compared with PPSV23 in children, clinical trials are underway to determine PCV effectiveness in healthy adults. Data obtained during Phase I safety trials of PCV13 support the clinical observation of improved vaccine effectiveness; these data demonstrate increased opsonic activity and antibody titers in healthy adults compared with PPSV23 [28]. In addition, data by Jackson *et al.* showed higher immunogenicity among vaccine-naive adults given PCV13 versus PPSV23 for eight out of 12 common serotypes and equivalent immune response for the remaining four, based on opsonic titers measured at 1 month postvaccination [38]. Furthermore, booster immunizations of adults (aged 50–64 years of age) at 3 or 4 years resulted in statistically higher opsonic titers for a majority of serotypes compared with single dosing with PCV13 or PPSV23 [39]. Conversely, there was a diminished response noted in opsonic titers among patients with booster immunizations using PPSV23. As stated above, opsonic assays have served as a surrogate for efficacy; however, a randomized trial addressing pneumococcal pneumonia prevention with PCV13 is ongoing in The Netherlands [40].

Pneumococcal vaccination & the elderly

The elderly are uniquely at risk for pneumococcal disease and have higher mortality once infected. There have been several observational studies as well as controlled trials evaluating vaccine effectiveness in this population.

In an American cohort study by Jackson *et al.*, the largest study to date, more than 47,000 elderly persons (65 years or older) were followed for development of CAP, IPD (as defined by pneumococcal bacteremia) and mortality [7]. Among 1428 diseased cohort members, vaccination with PPSV23 had no effect on risk of CAP hospitalization (HR among vaccinated: 1.14), or mortality (HR among vaccinated: 0.96) after multivariate analyses. The risk for pneumococcal bacteremia was reduced (HR among vaccinated: 0.56), in line with other IPD data.

Another large cohort of 11,241 patients in Catalonia, Spain, was followed from 2002 to 2005 for similar end points as the study by Jackson [8]. Vaccination with PPSV23 was 45% effective at prevention of pneumococcal pneumonia (HR: 0.55); however, this became nonsignificant when assessing only NBPP (HR: 0.61 [0.35–1.06]).

Several randomized trials have been undertaken to evaluate efficacy of PPSV23 among the elderly population using clinical end points. Two large trials from Finland evaluated the coadministration of free-polysaccharide pneumococcal and influenza vaccines [41,42]. One trial, from 1999, included 26,925 participants and again suggested prevention of pneumococcal bacteremia (effectiveness: +60%) but no change in NBPP (effectiveness: -20%) [41]. Notably, this study was not truly randomized, as patients were able to choose dual vaccination or not. An earlier Finnish trial randomized 2837 patients to dual vaccination versus control (influenza alone) and noted no protection from NBPP, with a nonsignificant efficacy of 15% (-43–50%) [42]. Efficacy for prevention of NBPP (59% [6–82%]) was demonstrated among the subgroup of subjects with cardiopulmonary disease, alcoholism, those who were institutionalized and those older than 70 years of age.

Nursing home patients are exposed to a different microbial environment, including pneumonias caused by noncommunity-acquired organisms. Nonetheless, this group of patients also remains at high risk for

pneumococcal disease by virtue of age as well as comorbid conditions [43]. A randomized trial of PPSV23 versus placebo administered to approximately 1000 nursing home patients in Japan showed reduced incidence of pneumococcal pneumonia at 2-year follow up [44]. NBPP was diagnosed in 2.8% of vaccinated versus 7.3% nonvaccinated patients (relative risk: 63.8%; absolute risk reduction: 4.5%). There was no IPD among the 500 vaccinated patients. Of note, all-cause mortality was no different between groups. In addition, diagnostic criteria for NBPP included isolation of pneumococcus from nonsterile sites such as sputum and urinary antigen, which may have in part reflected colonization, especially among nursing home patients. Prevention of hospitalized pneumonia may persist even amongst very old and bedridden patients [45].

Outcome data for conjugate vaccination remains limited in the elderly, especially with respect to pneumonia. As stated earlier, since the introduction of PCV7 the rates of IPD have declined across all age groups, likely from herd immunity. There are no randomized trials assessing direct conjugate vaccine efficacy in adults over 65 years of age. However, OPA studies have demonstrated varied results, ranging from suggestive of superior protection after conjugate vaccination among healthy older adults [29,38–40], to limited immunogenicity in very frail individuals [46].

Pneumococcal vaccination & chronic pulmonary disease

COPD is the fourth leading cause of death worldwide, with increasing prevalence. The total healthcare burden is difficult to quantify; however, it comprises approximately 6% of total healthcare costs in the European Union [47]. US healthcare costs approach US$50 billion [101]. A majority of these expenses are the result of hospital admissions for acute exacerbations of COPD. The incidence and severity of CAP is also higher in this population with higher mortality risk at 90 days [48].

There have been several clinical studies evaluating the clinical effectiveness of pneumococcal vaccination among patients with COPD with mixed results. The largest randomized control trial to date was conducted in Spain from late 1999 to 2004 and administered PPSV23. Among the intervention group, the incidence of NBPP was zero of 298 patients compared with five out of the 298 in the control group; however, risk reduction and efficacy could not be assessed because of the lack of cases in the control group [49]. This study was limited by small numbers of clinical isolates that revealed a pathogen (23/88 cases). When comparing all cases of CAP, a *post hoc* analysis revealed that vaccine effectiveness was 76% among younger patients (<65 years of age) and improved among young patients with severe airflow obstruction (91% effective number needed-to-treat three). Utility was diminished and not significantly effective in older patients with mild disease [49].

In an observational cohort of more than 1200 elderly adults (65 years of age or older) with chronic respiratory illness comparing 701 previously vaccinated with 597 nonvaccinated, there was a trend toward lower incidence of NBPP in the vaccinated group (5.26 episodes/1000 patient years vs 5.72/1000 patient years); however, this was not statistically significant [50]. Again, the isolation rates of pneumococcus from culture was low (20/137 cases). Notably, the vaccinated cohort had a higher rate of 'immunocompromised hosts' compared with the controls, which may have led to an underestimation of effectiveness [50].

A 2010 update of a meta-analysis reviewing vaccine utility in COPD patients included six trials in which pneumonia was a primary end point [35]. All included trials utilized polyvalent, nonconjugate vaccines (PPSV14 or PPSV23). The Spanish study was the largest contributor to the pooled analysis, providing more than 50% of the weight [49]. Pooled OR for development of pneumonia was 0.72; however this did not achieve significance. Among trials included, only one study, of which the data was available from abstract only, showed a significant reduction in odds for pneumonia (OR: 0.39; 95% CI: 0.21–0.75) [51]. Similarly, there was no statistical difference between vaccinated and controls for mortality and acute exacerbations of COPD [35].

Serologic responsiveness of COPD patients to protein-conjugate vaccination has also been examined. In a recently updated trial of 181 patients with COPD, opsonic titers were compared after vaccination with PCV7 versus PPSV23. Secondary end points of exacerbation risk, pneumonia development and mortality were also measured. In this study, opsonic assays showed greater immunogenicity against targeted serotypes using conjugate vaccines as compared with free polysaccharide vaccine [52,53]. As documented elsewhere, the immune response waned over time, but remained statistically higher in four out of the seven serotypes at 2 years. Assessment of clinical end points showed no difference between groups in mortality, exacerbation risk or development of pneumonia; however, the study was not powered to detect a difference in these end points [53].

Cost–effectiveness of vaccination

As presented above, the evidence for prevention of invasive pneumococcal disease via conjugate vaccines appears to be solid in infants, young children and adults, through both direct and indirect mechanisms. However, the utility of conjugates for the prevention of pneumococcal and all-cause pneumonia in adults appears to be less clear. Despite this, primary prevention with vaccination (both PPSV23 and PCV13) provides

an attractive option, as pneumococcal infections often lead to severe clinical illness and prolonged treatments, often requiring hospitalization.

A recent cost–effectiveness analysis by Smith *et al.* suggested a cost–benefit to substituting PCV13 for PPSV23 in the current guideline recommendations [54]. The analysis followed hypothetical cohorts of 50 year olds, subdivided into various groups based on comorbidity, for the development of IPD and inpatient NBPP. Using published estimates for IPD and the costs of the various interventions, as well as setting the rate of CAP caused by pneumococcus at 30%, PCV13 prevented between 2867 (low estimate) and 7217 (high estimate) cases of NBPP compared with PPSV23, which was assumed to prevent no pneumococcal pneumonia episodes. Due to the proven benefit of PPSV23 in IPD prevention, the incremental benefit of PCV13 over PPSV23 was less in terms of cost–effectiveness.

Using these estimates, PCV13 would be judged by many to be cost-effective, with an incremental cost–effectiveness ratio of $28,900/quality-adjusted life year (QALY) relative to no vaccine [54]. PPSV23 was also effective, but less robust ($34,600/QALY) relative to no vaccine. Based on expert committee recommendations, the analysis estimated vaccine effectiveness at prevention for NBPP to be incrementally less than for IPD based on age: 18% lower at 50 years of age, 25% lower at 65 years of age and 30% lower in immunosuppressed individuals. However, if the efficacy of PCV13 at NBPP prevention was overstated, its cost–effectiveness was lost. For example, if vaccine effectiveness for NBPP fell to 40% of the IPD baseline, then cost–effectiveness ratio values changed to $131,000/QALY relative to no vaccine. The group also did not include outpatient pneumococcal pneumonia in the design, which may have important cost implications, especially in younger patients.

Guidelines & future perspective

Based on the data above as well as newer trial data among HIV patients demonstrating clinical efficacy, the Advisory Committee on Immunization Practices of the CDC has recently changed vaccination recommendations [55]. Those patients at high risk for invasive pneumococcal disease and with immunocompromising conditions (Table 1) should now be vaccinated with PCV13 and boosted at least 8 weeks later with PPSV23. However, given the paucity of data among immunocompetent adults, the protective effects of herd immunity, as well as broader serotype coverage, PPSV23 is still recommended in patients with chronic heart, lung and liver disease, and in smokers and alcoholics.

Unfortunately, vaccination of any type (conjugate or free polysaccharide) remains underutilized. A recent survey of physicians and patients in 13 western European countries showed low recognition of IPD as a disease state among physicians, especially primary care providers. Vaccine adherence tended to improve in those countries that made age-based recommendations (as opposed to risk-based) and provided incentive programs for vaccination [56].

Finally, noncapsular protein antigens remain potential targets for vaccine development. Immunity against these antigens, which are typically uniformly seen throughout all pneumococcal species, would potentially avoid the problems of serotype shift and would theoretically provide more uniform and complete protection. Mouse models have demonstrated pneumococcal protection using two such targets (choline binding protein A and pneumococcal surface protein A). Pneumolysin, another noncapsular antigen, has recently been incorporated into a vaccine and is currently in a Phase I clinical trial [57].

Conclusion

In short, pneumococcus continues to be a problematic pathogen. Vaccines targeting the pneumococcal polysaccharide, either free or bound covalently to protein, are effective at preventing the most serious infections. Conjugation of the vaccine to an immunogenic protein increases potency and provides better protection in young children, which in turn reduces invasive disease globally. The utility of both vaccine formulations in prevention of pneumococcal pneumonia is still controversial, especially in older adults and patients with chronic diseases. Regardless, all elderly adults and immunocompetent patients with comorbid illness should be vaccinated with free-polysaccharide vaccine at a minimum. By nonclinical, laboratory-based measurements, PCV13 is more immunogenic in this group; however, confirmatory clinical trial data are lacking and currently under investigation. If proven reliable in preventing pneumococcal pneumonia, PCV13 would likely be cost-effective.

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Executive summary

Vaccine formulation
- Both free-polysaccharide and protein-conjugate pneumococcal vaccines are now approved and have proven effective in preventing invasive pneumococcal disease (IPD).
- Conjugated-protein vaccines stimulate increased immunogenicity in young children and many adults, in part by inducing a T-cell dependent response.

Serotype replacement
- Since the advent of conjugated protein vaccination against pneumococcus, some serotypes that were previously uncommon and not included in the vaccine have emerged in clinical disease isolates.

Surrogate markers of immunogenicity
- Serologic studies, including antibody measurement as well as opsonophagocytosis assays, have become the standard surrogate markers for vaccine efficacy.

Burden of disease
- Childhood vaccination with conjugate protein vaccine has led to reduction in the incidence of IPD in adults, especially in adults over 65 years of age, through herd immunity.
- The population burden of nonbacteremic pneumococcal pneumonia (NBPP) may also be decreasing; however, this is more difficult to quantify.

General clinical efficacy
- The free-polysaccharide vaccine is effective in prevention of IPD among healthy adults.
- Adults with chronic illness may not achieve protection with free-polysaccharide vaccination.
- The conjugate protein vaccine stimulates higher immunogenic responses in many adults and may be more effective in prevention of NBPP; however, trials studying clinical end points are ongoing.

Pneumococcal vaccination & the elderly
- A small number of clinical trials suggest possible benefit for free-polysaccharide vaccine in NBPP prevention among the elderly; however, other trials and large cohort studies have not supported these data.

Pneumococcal vaccination & chronic pulmonary disease
- According to a recent meta-analysis, free-polysaccharide vaccines do not appear to be effective in pneumonia prevention among patients with chronic lung disease.
- Immunogenic responses are higher in chronic obstructive pulmonary disease patients given conjugate protein vaccine as compared with free-polysaccharide vaccine; however, comparison trials have thus far been underpowered for studying clinical end points.

Cost–effectiveness of vaccination
- If proven reliable in preventing pneumococcal pneumonia, routine vaccination of older adults with conjugate protein vaccines would likely be cost-effective.

Reference

Papers of special note have been highlighted as:
- ■ of interest

1 WHO. Pneumococcal conjugate vaccine for childhood immunization – WHO position paper. *Wkly Epidemiol. Rec.* 82, 93–104 (2007).

2 O'Brien KL, Wolfson LJ, Watt JP *et al.* Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates. *Lancet* 374, 893–902 (2009).

3 Huang SS, Johnson KM, Ray GT *et al.* Healthcare utilization and cost of pneumococcal disease in the United States. *Vaccine* 29, 3398–3412 (2011).

4 Whitney CG, Pilishvili T, Farley MM *et al.* Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case–control study. *Lancet* 368, 1495–1502 (2006).

5 Austrian R, Douglas RM, Schiffman G *et al.* Prevention of pneumococcal pneumonia by vaccination. *Trans. Assoc. Am. Physicians* 89, 184–194 (1976).

■ **First clinical trial report documenting effectiveness of free-polysaccharide vaccination against pneumococcus.**

6 Moberly S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. *Cochrane Database Syst. Rev.* 1, CD422 (2008).

■ **Meta-analysis of all randomized trials evaluating free-polysaccharide vaccination in adults; last updated 2008.**

7 Jackson LA, Neuzil KM, Onchee Y *et al.* Effectiveness of pneumococcal polysaccharide vaccine in older adults. *NEJM* 348, 1747–1755 (2003).

8 Vila-Corcoles A, Ochoa-Gondar O, Ansa X *et al.* Protective effects of the 23-valent pneumococcal polysaccharide vaccine in the elderly population: the Evan-65 study. *Clin. Infect. Dis.* 43(7), 860–868 (2006).

9 Giebink GS. The prevention of pneumococcal disease in children. *NEJM* 345(16), 1177–1183 (2001).

10 Song JY, Nahm MH, Moseley MA. Clinical implications of pneumococcal serotypes: invasive disease potential, clinical presentations, and antibiotic resistance. *J. Korean Med. Sci.* 28, 4–15 (2013).

11 Whitney CG, Pilishvili T, Farley MM *et al.* Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study. *Lancet* 368, 1495–1502 (2006).

12 Shinefield HR *et al.* Safety and immunogenicity of heptavalent pneumococcal CRM197 conjugate vaccine in infants and toddlers. *Pediatr. Infect. Dis. J.* 18(9), 757–763 (1999).

13 Grijalva CG, Nuorti JP, Arbogast PG, Martin SW, Edwards KM, Griffin MR. Decline in pneumonia admissions after routine childhood immunization with pneumococcal conjugate vaccine in the USA: a time-series analysis. *Lancet* 369, 1179–1186 (2007).

14 Robbins JB, Austrian R, Lee CJ *et al.* Consideration for formulating the second-generation pneumococcal capsular polysaccharide vaccine with emphasis on the cross-reactive types within groups. *J. Infect. Dis.* 148, 1136–1159 (1983).

15 Pneumovax® 23 (Pneumococcal Vaccine Polyvalent), Package insert. Merck & Co., Inc, NJ, USA.

16 Booy R, Hodgson S, Carpenter L *et al.* Efficacy of haemophilus influenza type B conjugate vaccine PRP-T. *Lancet* 344, 362–366 (1994).

17 Black S, Shinefield H, Ray P *et al.* Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. *Pediatr. Infect. Dis. J.* 19, 187–195 (2000).

18 Fireman B, Black SB, Shinefield HR *et al.* Impact of the pneumococcal conjugate vaccine on otitis media. *Pediatr. Infect. Dis. J.* 22, 10–16 (2003).

19 Taylor S, Marchisio P, Vergison A, Harriague J, Hausdorff WP, Haggard M. Impact of pneumococcal conjugate vaccination on otitis media: a systematic review. *Clin. Infect. Dis.* 54(12), 1765–1773 (2012).

20 Singleton RJ, Hennessy TW, Bulkow LR *et al.* Invasive pneumococcal disease caused by nonvaccine serotypes among Alaska native children with high levels of 7-valent pneumococcal conjugate vaccine coverage. *JAMA* 297, 1784–1792 (2007).

■ **Epidemiologic evidence of serotype replacement among high-risk groups.**

21 Weinberger DM, Malley R, Lipsitch M. Serotype replacement in disease after pneumococcal vaccination. *Lancet* 378(9807), 1962–1973 (2011).

22 Nahm M. Opsonophagocytosis Assays. In: *Pneumococcal vaccines: the impact of conjugate vaccine (1st edition)*. Siber GR, Klugman KP, Makela PH (Eds). Amer Society for Microbiology, Washington, DC, USA (2008).

23 Siber GR, Chang, I, Baker S *et al.* Estimating the protective concentration of anti-pneumococcal capsular polysaccharide antibodies. *Vaccine* 25, 3816–3826 (2007).

24 Park S, Nahm MH. Older adults have a low capacity to opsonize pneumococci due to low IgM antibody response to pneumococcal vaccinations. *Infect. Immun.* 79, 314–320 (2011).

25 Parkkali T, Vakevainen M, Kayhty H, Ruutu T, Ruttu P. Opsonophagocytic activity against *Streptococcus pneumonia* type 19F in allogeneic BMT recipients before and after vaccination with pneumococcal polysaccharide vaccine. *Bone Marrow Transplant.* 27, 207–211 (2001).

26 Burton RL, Nahm MH. Development and validation of a fourfold multiplexed opsonization assay (MOPA4) for pneumococcal antibodies. *Clin. Vaccine Immunol.* 13, 1004–1009 (2006).

27 deRoux A, Schmole-Thoma B, Siber GR *et al.* Comparison of pneumococcal conjugate polysaccharide and free polysaccharide vaccines in elderly adults: conjugate vaccine elicits improved antibacterial immune responses and immunological memory. *Clin. Infect. Dis.* 46, 1015–1023 (2008).

28 Scott DA, Kornjathy SF, Hu BT *et al.* Phase 1 trial of a 13-valent pneumococcal conjugate vaccine in healthy adults. *Vaccine* 25, 6164–6166 (2007).

29 Jackson LA, Neuzil KM, Nahm MH *et al.* Immunogenicity of varying dosages of 7-valent pneumococcal polysaccharide-protein conjugate vaccine in seniors previously vaccinated with 23-valent pneumococcal polysaccharide vaccine. *Vaccine* 25, 4029–4037 (2007).

30 Kumar D, Rotstein C, Miyata G, Arlen D, Humar A. Randomized, double-blind, controlled trial of pneumococcal vaccination in renal transplant recipients. *J. Infect. Dis.* 187(10), 1639–1645 (2003).

31 Lexau CA, Lynfield R, Danila R *et al.* Changing epidemiology of invasive pneumococcal disease among older adults in the era of pediatric pneumococcal conjugate vaccine. *JAMA* 294, 2043–2051 (2005).

32 Whitney CG, Farley MM, Hadler J *et al.* Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *NEJM* 348, 1737–1746 (2003).

■ **Review of active bacterial core surveillance data showing reduction in invasive pneumococcal disease after childhood vaccination with pneumococcal conjugate vaccine (PCV).**

33 Ruiz-Gonzalez A, Falguera M, Nogues A, Rubio-Caballero M. Is *Streptococcus pneumonia* the leading cause of pneumonia of unknown etiology? A microbiologic study of lung aspirates in consecutive patients with community acquired pneumonia. *Am. J. Med.* 106(4), 385–390 (1999).

34 Bewick T, Sheppard C, Greenwood S *et al.* Serotype prevalence in adults hospitalized with pneumococcal non-invasive community-acquired pneumonia. *Thorax* 67, 540–545 (2012).

35 Walters JA, Smith S, Poole P, Granger RH, Wood-Baker R. Injectable vaccines for preventing pneumococcal infection in patients with chronic obstructive pulmonary disease. *Cochrane Database of Syst. Rev.*11 CD0011390 (2010).

■ **Meta-analysis of trials determining pneumococcal vaccine efficacy in adults with chronic respiratory illness.**

36 Riley ID, Andrews M, Howard R *et al.* Immunization with polyvalent pneumococcal vaccine; reduction of adult respiratory mortality in a New Guinea Highlands community. *Lancet* 1(8026), 1338–1341 (1977).

37 Grijalva C. Recognizing pneumonia burden through prevention. *Vaccine* 27(Suppl. 3), C6–C8 (2009).

38 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-naïve adults. *Vaccine* 31(35), 3577–3584 (2013).

39 Jackson LA, Gurtman A, van Cleef M *et al.* Influence of initial vaccination with 13-valent pneumococcal conjugate vaccine or 23-valent pneumococcal polysaccharide vaccine on anti-pneumococcal responses following subsequent pneumococcal vaccination in adults 50 years and older. *Vaccine* 31(35), 3594–3602 (2013).

40 Hak E, Grobbee DE, Sanders EA *et al.* Rationale and design of CAPITA: a RCT of 13-valent conjugated pneumococcal vaccine efficacy among older adults. *Neth. J. Med.* 66(9), 378–383 (2008).

41 Honkanen PO, Keistinen T, Miettinen L *et al.* Incremental effectiveness of pneumococcal vaccine on simultaneously administered influenza vaccine in preventing pneumonia and pneumococcal pneumonia among persons aged 65 years or older. *Vaccine* 17 (20), 2493–2500 (1999).

42 Koivula, I, Sten M, Leinonen M, Makela PH. Clinical efficacy of pneumococcal vaccine in the elderly: a randomized, single-blind population-based trial. *Am. J. Med.* 103, 281–290 (1997).

43 No authors listed. Prevention of pneumococcal disease: recommendations of the committee on immunization practices (ACIP). *MMWR Recomm. Rep.* 46, 1–24 (1997).

44 Maruyama T, Taguchi O, Niederman MS *et al.* Efficacy of 23-valent pneumococcal vaccine in preventing pneumonia and improving survival in nursing home residents: double-blind, randomized and placebo controlled trial. *BMJ* 340, c1004 (2010).

45 Chiba H, Ohrui T, Matsui T, Fukushima T, Sasaki H. Benefits of pneumococcal vaccination for bedridden patients. *J. Am. Geriatr. Soc.* 52(8), 1410 (2004).

46 Ridda I, Macintyre CR, Lindley R *et al.* Immunological responses to pneumococcal vaccine in frail older people. *Vaccine* 27(10), 1628–1636 (2009).

47 European Respiratory Society. *European Lung White Book*. European Respiratory Society Journals, Ltd, Huddersfield, UK (2003).

48 Restrepo MI, Mortenson EM, Pugh JA, Anzueto A. COPD is associated with increased mortality in patients with community-acquired pneumonia. *Eur. Respir. J.* 28, 346–351 (2006)

49 Alfageme I, Vazquez R, Reyes N *et al.* Clinical efficacy of anti-pneumococcal vaccination in patients with COPD. *Thorax* 61, 189–195 (2006).

■ **Largest clinical trial to date evaluating clinical effectiveness of free-polysaccharide vaccine in adults with chronic obstructive pulmonary disease; the trial showed clear efficacy in younger patients with severe airflow obstruction.**

50 Ochoa-Gondar O, Vila-Corcoles A, Ansa X *et al.* Effectiveness of pneumococcal vaccination in older adults with chronic respiratory illnesses: results of the EVAN-65 study. *Vaccine* 26 (16), 1955–1962 (2008).

51 Teramoto S, Yamamoto H, Yamaguchi Y *et al.* Clinical efficacy of anti-pneumococcal vaccination in elderly patients with COPD [Abstract]. Presented at: *American Thoracic Society International Conference*. San Francisco, CA, USA, 18–23 May 2007.

52 Dransfield MT, Nahm MH, Han MK *et al.* Superior immune response to protein-conjugate vs. free pneumococcal polysaccharide vaccine in COPD. *Am. J. Respir. Crit. Care Med.* 180(6), 499–505 (2009).

53 Dransfield MT, Harnden S, Burton RL *et al.* Long-term comparative immunogenicity of protein conjugate and free polysaccharide pneumococcal vaccines in chronic obstructive pulmonary disease. *Clin. Infect. Dis.* 55(5), e35–e44 (2012).

■ **Comparative trial of polyvalent polysaccharide vaccine versus PCV in adults with chronic obstructive pulmonary disease, using opsonic titer as primary end point, showed improved immunogenicity but no difference in mortality, pneumonia or time to first exacerbation.**

54 Smith KJ, Wateska AR, Nowalk MP, Raymund M, Nuorti JP, Zimmerman RK. Cost–effectiveness of adult vaccination strategies using pneumococcal conjugate vaccine compared with pneumococcal polysaccharide vaccine. *JAMA* 307(8), 804–812 (2012).

■ **Analysis demonstrating PCV to be cost-effective by quality-adjusted life year measures if protective against nonbacteremic pneumococcal pneumonia.**

55 Bennett NM, Whitney CG, Moore M, Pilishvili T, Dooling KL. 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 Morb. Mortal. Wkly Rep.* 61 (40), 816–819 (2012).

■ **Recently updated Advisory Committee on Immunization Practices recommendations on pneumococcal vaccine strategy.**

56 Lode H, Ludwig E, Kassianos G. Pneumococcal infection – low awareness as a potential barrier to vaccination: results of a European study. *Adv. Ther.* 30(4), 387–405 (2013).

57 Kamtchoua T, Bologa M, Hopfer R *et al.* Safety and immunogenicity of the pneumococcal pneumolysin derivative PlyD1 in a single-antigen protein vaccine candidate in adults. *Vaccine* 31, 327–333 (2013).

■ Website

101 The Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD). www.goldcopd.org