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REVIEW

Effectiveness and practical uses of 23-valent pneumococcal polysaccharide vaccine in healthy and special populations

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ABSTRACT

Streptococcus pneumonia (S. pneumoniae) is responsible for significant morbidity and mortality throughout the world. The 23-valent pneumococcal polysaccharide vaccines (PPV23) have been widely used for many years, but challenges are remaining in some respects, especially for its effectiveness among high-risk populations and older adults. This review aims to summarize recent clinical trials and studies of PPV23 vaccination among healthy people ≥ 2 years of age and those with high-risk conditions such as pregnant women, individuals with immunocompromising diseases and other chronic conditions, and provide health officials in China and other developing countries a comprehensive understanding of the current vaccination strategies for PPV23 and for the combined use of PPV23 and pneumococcal conjugate vaccines (PCVs) in adults.

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Introduction

S. pneumoniae is the main cause for the invasive pneumococcal disease (IPD) and community-acquired pneumonia (CAP), causing upper respiratory tract infection, otitis media (primarily in children), pneumonia, bacteremia, sepsis and meningitis. Every year, a large number of patients suffer severely or even die from these diseases. The highest rates of morbidity and mortality are among infants<2 years of age and older adults ≥ 65 years of age, as well as those with high-risk conditions such as pregnant women, individuals with immunocompromising diseases and other chronic conditions.

Currently, there are two licensed pneumococcal vaccines: pneumococcal polysaccharide vaccines (PPVs) and pneumococcal conjugate vaccines (PCVs). The conjugation of pneumococcal polysaccharide to carrier proteins elicits a T-cell dependent immune response, mainly characterized by the differentiation of memory B cells and increased antibody concentrations.[1] With the widely use of these two vaccines, scientists now are considering the combined PCV/PPV regimens, which may open up the possibility of broadening serotype coverage as well as prolonging the duration of vaccine protective effect.

The pathogen and epidemiology of pneumococcal disease

S. pneumoniae is a Gram-positive encapsulated diplococcus, and its polysaccharide capsule is an essential virulence factor. At least 94 serologically distinct pneumococcal serotypes have been identified.[2] The distribution of these serotypes varies significantly between countries and populations.[3] In Europe, the most frequent serotypes are 1, 3, 7F, 14 and 19A,[4,5] while in China, 19F, 23F, 19A, 6B, 14, 6A and 15B are most frequent.[6] A worldwide surveillance program undertaken in 2008 showed that the most common serotypes in children were 19A (28%), 19F (10%) and 14 (9%), whereas in adults the most common serotypes were 19A(13%), 3(7%), 6A (7%) and 7F(7%).[7]

In general, pneumococcal diseases can be classified as either invasive (IPD) or non-invasive pneumococcal disease. The incidence of IPD is bimodal, with one peak in infants<2 years of age and the other in older adults ≥ 65 years of age.[8] The World Health Organization (WHO) reported that in 2015, pneumonia (due to all causes, but *S. pneumoniae* is the most common cause) killed ~920 K children ≤ 5 years of age, accounting for 16% of all deaths in this age group.[9] Pneumonia mortality was especially severe in South Asia and sub-Saharan Africa. In China, approximately 30 K children under 5 years of age die from IPD every year.[10] In the US in 2014, the IPD morbidity and mortality rates for older adults aged 65–74 years were 19.1 cases and 2.41 deaths per 100,000 population, respectively, while in those ≥ 85 years of age, the rates were 42.6 cases and 8.01 deaths per 100,000 population.[11] In developing countries, the incidence rates for IPD are several times higher than they are in industrialized countries, and existing data probably underestimate the true disease burden because of the insufficient diagnostic capacity and extensive antibiotic use.

In addition to affecting young children and older adults, *S. pneumoniae* often attacks persons with high-risk conditions: e.g., human immunodeficiency virus (HIV) infection, pregnant

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women, and patients with cancer, influenza and diabetes. For example, individuals with diabetes may have three- to six-fold increased risk of IPD compared with healthy individuals.[12] For many persons who are immunocompromised, the risks are even greater.

The development of pneumococcal polysaccharide vaccines

S. pneumoniae was first isolated in the US and France in 1880.[13,14] In 1911, the first pneumococcal whole-cell vaccine was tested among young gold miners in South Africa, but despite early claims that it was protective, careful analysis showed it was not efficacious.[14] Later, in 1930, Tillet and Francis discovered that purified pneumococcal polysaccharides could induce specific anti-capsular antibodies in humans. In 1945, Macleod, Heidelberger and colleagues showed that a 4-valent pneumococcal polysaccharide vaccine (PPV4) containing serotypes 1, 2, 5 and 7 was protective against pneumococcal disease caused by the same serotypes.[15] Much later in 1968, 6-valent and 13-valent pneumococcal polysaccharide vaccines were shown to be safe. In a classic randomized controlled trial, Robert Austrian showed that PPV13 reduced the occurrence of vaccine-type bacteremic pneumococcal pneumonia by 82.3%.[14,16] In 1977, the Food and Drug Administration (FDA) licensed a 14-valent PPV (PPV14) from Merck, which contained capsular polysaccharide serotypes 1, 3, 4, 6A, 6B, 7F, 8, 9N, 12F, 14, 18C, 19F, 20 and 23F. In 1983, the FDA licensed Merck's PPV23, which contained 10 additional serotypes (2, 5, 9V, 10A, 11A, 15B, 17F, 19A, 22F and 33F, but not 6A). This vaccine covered 65% to 91% of the isolates from adult IPD cases worldwide. Soon thereafter, Wyeth-Lederle and Sanofi Pasteur developed their own PPV23 vaccines (Table 1).

Currently, PPV23 is licensed in more than 75 countries worldwide for those aged ≥ 2 years. In China and other low- and middle-income countries, PPV23 development has been slow. In 2006, a PPV23 developed by the Chengdu Institute of Biological Products (CNBG) was approved by China Food and Drug Administration (CFDA). Two PPV23 vaccines developed by Beijing Minhai and Walvax Biotechnology were evaluated in phase III immunogenicity trials, and have received approval from the CFDA. Three additional Chinese manufacturers (Beijing Zhifei lvzhu Biopharmaceutical, Sinovac Biotech and Lanzhou Institute of Biological Products) are conducting clinical research on PPV23 vaccines.[17]

Effectiveness of PPV23 in children and adults

An enzyme-linked immunosorbent assay (ELISA) is the most commonly used method at present for the routine estimation of specific immunoglobulin G (IgG) response to pneumococcal vaccines in humans. Also, the concept of 'correlate of protection' is raised in order to further predict the effectiveness of vaccines and is related to the clinical endpoint events after vaccination. So far, the minimum protective concentration of 0.35 ug/ml has been established by WHO for evaluating the efficacy of PCVs in infants.[18] Unfortunately, this value was not applicable for adults.

Table 1. 23-valent pneumococcal polysaccharide vaccine approval year, countries and companies.

Approval year	Country	Company
1983	U.S.A	Merck / Lederle Laboratories / Wyeth
1987	France	SANOFI PASTEUR S.A.
2006	China	Chengdu Institute of Biological Products Co., Ltd

In children ≤ 2 years of age, antibody responses elicited by PPV23 are generally poor, and vaccination has been shown in most studies not to be protective. Consequently, PCVs are now widely used in this age group. After PCVs were introduced into childhood vaccination in the US, 1.5 fewer all-cause pneumonia hospitalizations were observed per 1000 children ≤2 years of age.[19] A Spanish study also found a large reduction (76%) in IPD incidence in PCV-vaccinated children, but there was also a 78% reduction in IPD in unvaccinated children.[20] These findings showed that PCVs benefit children through both their direct and indirect (herd) effects. PCV-related indirect protection also benefits those ≥ 2 years of age, leading to reductions in the occurrence of both IPD and non bacteremic pneumococcal pneumonia.

For persons ≥ 2 years of age, numerous studies have shown that PPV23 is effective in preventing IPD. Recent studies from Russia,[21] China[22] and Japan[23] demonstrated that geometric mean antibody titers (GMTs) to all tested serotypes increased dramatically after PPV23 vaccination. High proportions of subjects had ≥2-fold increases in IgG antibodies; for example, rates for serotypes 1, 6B, 14, 19F, and 23F were 92%, 83%, 89%, 81%, 84%, respectively.[21] Opsonophagocytic assay (OPA) GMTs also increased significantly, ranging from 8.2 to 65.4[23]. (See Table 2 for recent clinical trials concerning PPV23 vaccination in healthy populations).

Challenges for using PPV23 in older adults

Although PPV23 has been used for almost 40 years, challenges still remain, especially for older adults. Although individual studies have shown that the efficacy of PPV23 in preventing IPD has ranged from -39% (95% CI<0–78%)[24] to 76% (95%CI 54–88%),[25] there is a consensus that PPV23 is protective in this age group. Because the antibody responses elicited by PPV23 are T cell-independent, serotype-specific IgG and OPA levels decrease over time, thus limiting the duration of protection to ≤5 years.[26-29] With the increase in the elderly population worldwide, revaccination with PPV23 should be considered in order to prolong protection against pneumococcal disease. Currently, both the ACIP and Japanese Association for Infectious Diseases recommend PPV23 revaccination at least 5 years after most recent dose of PPV23 for adults aged ≥65 years.[30]

In 2015, investigators in Japan conducted a clinical trial to evaluate the immunogenicity and safety of PPV23 revaccination among persons ≥70 years of age.[30] The results showed that PPV23 revaccination was well tolerated. IgG antibody concentrations and OPA titers increased substantially and were comparable to those observed following primary vaccination. However, other studies have shown that repeated doses of PPV23 may induce lower antibody responses following the second dose.[31] Whether this hyporesponsiveness has any clinical significance is unknown. The differences in antibody responses

Table 2. Summary of recent clinical trials regarding PPV23.

Author/Reference	Country	year	vaccine	Study Population	Treatment	Key Findings
Ciprero K et al.[21]	Russia	2016	PNEUMOVAX^{TM} 23 (Merck)	Russian Federation who were either 2 to 49 years of age with increased risk for PD or ≥ 50 years	Single dose of PPV23	High proportion of subjects had ≥2-fold increase in IgG following receipt of PPV23. Rates of which were 92.0%, 83.0%, 89.0%, 81%, 84% for serotypes 1, 6B, 14, 19F, and 23F, respectively
Jong Gyun Ahn et al.[94]	Korea	2015	PPSV23 (Merck)	Pneumococcal vaccine-naïve participants ≥ 65 years of age	Single dose of PPV23	GMTs to all tested serotypes significantly increased after vaccination in both groups (65–74 years and ≥75 years of age)
Masanari Shiramoto et al.[23]	Japan	2015	PPSV23 (Merck)	PPSV23-naïve healthy adults ≥65 years	Single dose of PPV23	OPA GMTs 1 month after vaccination increased significantly with geometric mean fold rise ranging from 8.2 to 65.4 in the PPSV23 group
Yujia Kong et al.[95]	China	2015	PPV23 (Walvax, China) / PNEUMOVAX 23 (Merck)	Healthy participants >2 years of age	Two doses of treatment vaccine or control vaccine	The newly vaccine was well tolerated and immunologically non-inferior to the active control vaccine PNEUMOVAX 23 for all 23 vaccine serotypes in the Chinese population (>2 years of age)
Guifan Li et al.[22]	China	2015	PPV23 (Beijing Minhai Biotechnology) /PPV23(Chengdu Biotechnology)	Healthy subjects aged 2–70 years	Single dose of PPV23	The post-vaccination GMCs of the Minhai PPV23 for types 1, 3,9V, 11A and 33F were significantly higher than Chengdu PPV23. It showed a good immunogenicity and tolerability in 2–70 y old healthy people

Abbreviations: PD = Pneumococcal disease; GMT = Geometric meant titer; OPA = Opsonophagocytic assay; GMC = Geometric mean concentration.

after the first and second doses of PPV23 could simply reflect the aging of study subjects who were older when they were revaccinated.

PPV23 vaccination of older adults has not been shown convincingly to prevent all-cause community-acquired pneumonia (CAP), and its effectiveness in preventing laboratory-confirmed non bacteremic pneumococcal pneumonia (NBPP) has been controversial.[32] For this reason, Dutch investigators undertook a randomized controlled trial among older adults to determine the effectiveness of PCV13 (containing serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C,19A, 19F and 23F) vaccination in preventing laboratory-confirmed, community-acquired NBPP (CAP-iTA). They showed PCV13 vaccination was 45% efficacious in preventing NBPP.[33]. Earlier, Spanish investigators published a retrospective cohort study (CAPAMIS) to determine the effectiveness of PPV23 vaccination in preventing NBPP and CAP in adults ≥ 60 years of age.[34] They found that during the first five years following vaccination, PPV23 was 48% effective in preventing hospitalization with NBPP, and it was also effective in preventing all-cause CAP (vaccination effectiveness[VE] = 25%).[35] Earlier conclusions that PPV23 provided weak protection against all-cause pneumonia were shown to be problematic because of questionable diagnostic methods.[36] In addition, a Cochrane meta-analysis published in 2013 concluded that PPV23 reduced bacteremic pneumococcal pneumonia (BPP), NBPP and IPD by 74%, 54% and 80%, respectively.[37]

Some studies have evaluated the effectiveness of PPV23 vaccination in preventing acute myocardial infarction (AMI)[38,39] and stroke.[40] These studies suggested that PPV23 could lower the risk of AMI and stroke, probably because the inflammatory effects of an acute infection like pneumococcal pneumonia are thought to precipitate acute events like AMI or stroke. However, another retrospective cohort study found no connection between PPV23 and AMI (hazard ratio, 1.09) or stroke (hazard ratio, 1.14).[41] Considered together, these studies indicate that the effectiveness of PPV23 vaccination in preventing acute AMI or stroke is still uncertain.

PPV23 vaccination in adults with high-risk conditions

Conditions such as acquired immunodeficiency syndrome (AIDS), diabetes and pulmonary, cardiovascular, liver and kidney diseases all increase the risk of IPD. For example, people who smoke tobacco or have asthma, chronic heart and lung diseases have a three- to six-fold increased risk of IPD compared with healthy adults.[12,42] Several investigators have studied PPV23 vaccination in these high-risk patients (Table 3).

HIV infection/AIDS

Pneumonia is one of the most serious complications of AIDS. In 2010, the estimated incidence of IPD in HIV-positive adults in the US was 173/100,000, compared with 3/100,000 in HIV-negative adults.[43] Following the introduction of highly active antiretroviral therapy (HAART) in 1996, the incidence of IPD among HIV patients decreased, but morbidity rates were still

35–100-fold higher compared with rates in those who were not HIV-infected.[44,45]

The effectiveness of PPV23 vaccination against IPD in HIV-infected individuals is controversial.[46] A retrospective case-control study in Spain suggested that among HIV-infected individuals, PPV23 vaccination was protective against pneumococcal pneumonia (OR, 0.44; 95% CI, 0.22–0.88).[47] Surprisingly, this study suggested that PPV23 was more protective in HIV-infected individuals with CD4+T cell counts <200 cells/μL than it was in those with CD4+T cell counts $\geq$ 200 cells/μL, but the difference between the two groups was not statistically significant. Earlier, a large randomized clinical trial among HIV patients in Uganda showed that PPV23 did not protect against pneumococcal disease.[48] Compared with the control group, the risk of pneumonia was actually higher in PPV23 recipients than in controls, and this difference persisted for at least six years following vaccination. Paradoxically, higher numbers of PPV23 recipients were still alive after six years, although most of them had CD4+T cell counts between 200 and 500 cells/uL at enrollment, suggesting that higher CD4+T cell counts before vaccination led to a lower risk of disease and death.[48] Prior to the availability of PCV13, the ACIP recommended PPV23 for HIV-infected patients with CD4+T cell counts $\geq$ 200 cells/uL.[49] Now that PCV13 is available, the ACIP recommends that they receive one dose of PCV13, followed by a dose of PPV23.[50]

Chronic obstructive pulmonary disease

Patients with chronic obstructive pulmonary disease (COPD) are at increased risk of pneumococcal infection. Several randomized controlled trials and observational studies have reported on the efficacy and effectiveness of PPV23 vaccination in patients with COPD. These studies (and their limitations) have been discussed in an historical review.[51] In general, the RCTs have been underpowered, although the results of some have suggested a modest degree of protection against pneumonia and acute COPD exacerbations, especially in younger patients. The results of observational studies have been more encouraging, suggesting some degree of protection in older COPD patients, including hospitalization for pneumonia. Some studies also suggest that PPV23 vaccination reduces the medical costs of acute COPD episodes. A recent Russian study showed that combination vaccination of COPD patients with PCV13 and PPV23 was not necessary, at least in the short term; vaccination with either vaccine alone provided satisfactory protection.[52] Future research on pneumococcal vaccination in COPD patients should consider potential confounding by systemic inflammation and their frequent use of systemic corticosteroids.

Influenza and secondary pneumococcal pneumonia

WHO has reported that 7∼20% of influenza patients develop secondary bacterial pneumonia, and mortality rates can be 20∼36%.[53] Several investigators have suggested that pneumococcal vaccination might reduce the occurrence of pneumonia during an influenza pandemic. To address this question, Spanish investigators performed a case-control study among 3996 patients to determine whether PPV23 vaccination reduced influenza-related hospitalizations during the 2009 influenza (H1N1) pandemic (2009–2010) and the following influenza season (2010–2011).[54] Influenza vaccination was 79% effective during the pandemic, whereas the following year, seasonal influenza vaccination was 51% effective. Pneumococcal vaccination was associated with a 41% reduction in influenza-related hospitalizations during the two influenza seasons, but when patients were vaccinated with both PPV23 and influenza vaccines, their combined effectiveness in preventing hospitalization with influenza-related illness (in both years combined) was 81%. Earlier, Christenson et al found that combination vaccination was 37% effective, while influenza vaccination alone

Table 3. Key results of recent studies and recommendations of PPV23 for special population.

References	Target population	Results	Recommendations
Rezai et al.[96]	Asplenic patients with thalassemia major	The pneumococcal IgG levels both increased in two groups (one dose of PCV13 before PPV23 / one dose of PPV23 before PCV13) and PCV13 vaccine before PPV23 can be more effective in asplenic thalassemia major patients	One dose of PPV23 as a booster after single dose of PCV13
Maria et al.[47]	HIV infected individuals	PPV23 showed a significant protective effect against pneumococcal disease	ACIP recommends that they receive one dose of PCV13, followed by a dose of PPV23
Hung et al.[56]	Patients with influenza	Dual vaccination of PPV23 and influenza vaccines would significantly reduce hospital admissions.	Dual vaccination with both PPV23 and influenza vaccines is recommended during influenza vaccination period
Munoz et al.[61]	Pregnant woman	Maternal transferred antibodies showed significantly higher concentrations in infants at birth than elder children and maintained at high levels by 2 months of age	ACIP recommends one dose of PPV23 for pregnant woman
Karlsson et al.[70]	Patients with hematological neoplasms	A single dose of PPV23 was not able to elicit significant high IgG concentrations	PPV23 is recommended by US CDC
Nourti et al.[77]	Cigarette smoking adults	The risk of pneumococcal disease for smokers are 4 times higher compared with non-smokers and 2.5 times higher for second-hand smokers	All cigarette smoking adults, especially those aged over 65 years, receive PPV23

Abbreviations: COPD = Chronic obstructive pulmonary disease; ACIP = Advisory committee on immunization; CD4 = cluster of differentiation 4.

was only 26% effective.[55] Also, during 2007–2008 influenza season, Hung et al. noted a significantly lower incidence of influenza-related hospital admissions in those who received both vaccines.[56] Recently, Korean investigators evaluated the safety and immunogenicity of trivalent inactivated influenza vaccine (IIV3) when given to older adults concomitantly with either PPV23 or PCV13.[57] Combination vaccination was safe, and in both groups, GMTs for all three IIV3 strains increased significantly one month after vaccination. Considered together, these studies indicate that combination vaccination with both PPV23 and influenza vaccines should be encouraged to reduce the risk of pneumococcal pneumonia and related complications during influenza outbreaks. In the Republic of Korea and many other countries, combination vaccination is recommended during each year's influenza vaccination period.[58] Nonetheless, WHO has concluded that in countries where PPV23 is not routinely administered, data are insufficient to recommend introducing PPV23 to reduce the mortality and morbidity caused by influenza.[59]

Pregnant women

Women with high risk conditions should be vaccinated before pregnancy, because physiological changes during pregnancy lead to an elevated risk of IPD.[60] Furthermore, vaccination during pregnancy can also benefit infants. According to the ACIP, six vaccines are recommended for pregnant woman, and PPV23 is one of them.[50] In a clinical trial carried out among 60 healthy pregnant women in their third trimester, one dose of PPV23 was safe and immunogenic.[61] Vaccine-elicited IgG antibody levels remained high up to 7 months after delivery. Maternally-transferred antibody levels were significantly higher in infants at birth than in older children, and were maintained at high levels at 2 months of age. Also, during the first 6 months of life, persistently high levels of vaccine-specific pneumococcal IgA antibodies were found in breast milk. This study suggested that maternal vaccination might be an effective way to prevent pneumococcal disease in early infancy.[61] Similar results were seen in another study in the Philippines: a significant rise in antibody levels was observed after PPV23 vaccination, with an average of 5.4-fold rise for different serotypes.[62] Most of these studies were conducted in Asia and Africa.[63-65] Recently, a report from Brazil that evaluated PPV23 vaccination among pregnant woman concluded that PPV23 immunization during pregnancy had the potential to protect the infants before the scheduled start of PCV vaccination.[66]

Hematological neoplasms

People with hematological neoplasms have a very high risk of pneumonia (503.1 cases/100000 persons), even higher than the risk among HIV/AIDS patients (422.9 cases/100000 persons).[12] In a Canada study, patients with multiple myeloma was found to have a 62.8 times greater risk of IPD compared with the overall adult population.[67] Unfortunately, antibody responses to PPV23 vaccination in these patients are compromised by several factors, including the clinical stage of disease, whether a splenectomy has been performed, the extent of chemotherapy and radiotherapy, and the interval between treatment and vaccination.[68] Patients with Hodgkin disease who were vaccinated before treatment develop antibody responses comparable to those in healthy individuals, but after treatment, antibody responses are reduced.[69] A Swedish study published in 2013 noted that baseline IgG antibody levels were low in patients with multiple myeloma, Waldenstrom's macroglobulinemia and monoclonal gammopathy of undetermined significance, and antibody levels did not rise significantly after PPV23 vaccination.[70]

Patients with chronic lymphocytic leukemia (CLL) are at similarly increased risk of pneumococcal infection. Antibody responses to PPV23 are poor; only 20–25% patients achieve a 2-fold increase in antibody titers above baseline levels.[71-73] One study sought to determine whether multiple doses of granulocyte-macrophage-colony-stimulating factor (GM-CSF) (which stimulates the production of neutrophilic granulocytes and macrophages) would improve antibody responses to PPV23[72]. Adverse reactions were minor in all patients, but antibody responses were still poor. In contrast, a more recent study found that PCV13 vaccination induced good antibody responses in CLL patients; 58.3% had at least 2-fold rise in specific pneumococcal antibody titers.[74] These findings suggest that T cell-independent antigens and IgG2-mediated antibody responses may explain the weak immunogenicity of PPV23 among CLL patients. Because CLL patients are immunocompromised, both PCV13 and PPV23 are recommended for preventing pneumococcal disease.[75] Whether sequential vaccination with these vaccines is clinically efficacious in these patients has not been studied.

Other high-risk conditions

For many years, the ACIP has recommended PPV23 vaccination for immunocompetent older adults with diabetes and other chronic medical conditions, but vaccination coverage has been low.[76]

Several studies suggest the risk of pneumococcal disease is four-fold higher in smokers compared with non-smokers, and 2.5-fold higher among second-hand smokers.[77] In 2008, the ACIP added smoking as an indication for PPV23 for persons 19–64 years of age. The ACIP recommends that all cigarette-smoking adults, especially those ≥65 years of age, should be vaccinated against pneumococcal disease. Those who have received PPV23 should quit smoking, and pneumococcal vaccination should be included in all smoking cessation treatment programs.

Patients with surgical or functional asplenia are at extremely high risk of pneumococcal infection, and PPV23 has been recommended for these patients for many years.[50] A study published in 2009 showed that previous doses of PPV23 compromised PCV7 immunogenicity for vaccine serotypes 9V, 19F and 23F.[78] When PCV13 was given to asplenic patients with a history of ≥ 2 doses of PPV23, the antibody responses to these three serotypes were significantly increased, but they were still lower than those obtained one month after PCV7 vaccination,[79] as shown in the earlier study.[78] These findings suggest that hyporesponsiveness following two or more doses of PPV23 may persist for at least six years, and that longer

intervals between PPV23 and PCV vaccination might lead to higher antibody responses.[79] However, the clinical significance of hyporesponsiveness is still unclear, and this is something that policy makers should consider when formulating recommendations for pneumococcal vaccination of asplenic adults.

Considerations for the future

PPV23 vaccination elicits good antibody responses and encouraging protection in healthy adults. Investigators and health officials in developed countries recognize the importance of pneumococcal vaccination in their populations. However, in these countries, PPV23 coverage rates among older adults and younger adults with high-risk conditions are universally regarded as inadequate.[80] In most low-income and middle-income countries, PPV23 has been in either limited supply or unavailable. Thus, health officials in all countries need to increase awareness of pneumococcal disease and the need for its prevention among both the public and health professions.

In 2016, PCV13 produced by Pfizer was approved for the Chinese market, and it soon replaced PCV7. Following the earlier withdrawal of PCV7 in the US, the pneumococcal vaccination schedule for children ≤2 years of age was modified,[81] and this schedule is being followed in China. During the transition period, if children have not completed a four-dose schedule of PCV7, PCV13 should be given for the remaining doses. If all doses of PCV7 have been given, a booster dose of PCV13 could be given before 6 years of age.[82] Using PPV23 as booster dose after completing a primary series of PCV has the advantage of eliciting a broader range of antibodies than PCV boosting.[83] Children with no history of PPV23 vaccination should receive PPV23 at least 8 weeks after the most recent dose of PCV.[84] Data concerning the safety and immunogenicity of PCV13 among high-risk children are still limited. At present, these children should be considered for PPV23 vaccination after they have completed a primary series of PCV13.[85]

Prior to the availability of PCV13 in China and the US, pneumococcal vaccination recommendations for persons 2–64 years of age called for one or two doses of PPV23 for any person with an underlying high-risk condition. In persons ≥65 years of age, considering their higher incidence rate of IPD and declining antibody titers, one dose of PPV23 was recommended, and revaccination every five years could be considered. Recommendations for adults have changed since PCV13 became available.[86] Currently, the ACIP recommends that older adults first receive one dose of PCV13, followed six months later by one dose of PPV23. This complicated recommendation has been adopted by very few developed countries.

In China, neither PCV13 nor PPV23 has been integrated into the Chinese Expanded Program on Immunization (EPI), so people have to pay for pneumococcal vaccination themselves. Although PCV13 may be more immunogenic in some groups, its serotype coverage is lower than it is for PPV23. Moreover, the cost of PCV13 vaccination is a significant economic burden for ordinary families (as it is in other developing countries). In recent years, several cost-effectiveness studies of PCV13 vaccination of older adults in developed countries have been published.[87-90] In each of these studies, PCV13 has been shown not to be cost-effective if the indirect effects of PCV13 childhood vaccination cause a decrease in the occurrence of pneumococcal disease in older populations, something that is usually evident a few years after the introduction of PCV13 vaccination for children. Although combination vaccination with both PCV13 and PPV23 might elicit better antibody responses in the short term, PPV23 alone is a better choice than PCV13 for preventing IPD among healthy adults. In low-and middle-income countries, where cost issues are important, PPV23 vaccination should be the priority.

With widespread use of PPV23 and more recently PCVs, pneumococcal diseases caused by serotypes included in both vaccines are becoming less common. This has led to an increasing frequency of disease caused by nonvaccine serotypes (serotype replacement).As reported by an 8-year survey in England and wales (2006–2014), most fatal IPD cases are currently not vaccine-preventable.[91] To counteract this, Merck and Beijing Zhifeilvzhu are developing higher valency pneumococcal conjugate vaccines (PCV15) by adding serotypes 22F and 33F. Although PCVs containing a larger number of serotypes might be desirable, their production is technically challenging. Also, since protein carriers are used in several vaccines, simultaneous vaccination with these vaccines might interfere with antibody responses to these vaccines and should be of concern.

Because the prevalence of pneumococcal serotypes varies over time and across regions, it will be important to understand their changing epidemiology. In China, there is limited reliable epidemiological information on the distribution of pneumococcal serotypes. Most of the available data have come from large cities, sample sizes have been small, and there has been a lack of year-to-year continuity in surveillance. More extensive surveillance regarding to pneumococcal serotype distribution, drug resistance and disease incidence needs to be obtained at regular intervals in order to develop vaccines specific for China's needs and to formulate suitable guidance for their use.

Due to the large number of distinct pneumococcal serotypes, investigators have explored the possibility of using as vaccine antigens other carbohydrates and proteins found on the pneumococcal surface.[92] Candidate vaccine antigens include pneumococcal surface protein A (PspA), pneumolysin, fusion pneumococcal pilus proteins and protein antigen combination vaccines.[93] For example, PspA is found on the outer membrane of all pneumococcal isolates and it is involved in determining pneumococcal virulence. Mouse models have shown that vaccination with PspA elicits a protective immune response, and two or three PspA proteins could probably protect against all pneumococcal infections. If a PspA vaccine could be shown to be protective in humans, it would be relatively easy and inexpensive to produce. These features could ensure its widespread use in developing countries, and might compensate for the current shortage of polysaccharide and protein conjugate vaccines in these countries. However, a great deal of work will be required before these new protein-based pneumococcal vaccines are licensed and become widely available.

With several pneumococcal vaccines now (or soon to be) available on the market, Chinese investigators have numerous

opportunities for research on different vaccination strategies, new carrier protein development and high quality epidemiological surveillance. For the general population, these studies will ensure a sound scientific basis for preventing pneumococcal diseases.

Abbreviations

ACIP	Advisory Committee on Immunization
AIDS	acquired immunodeficiency syndrome
BPP	bacteremic pneumococcal pneumonia
CAP	community-acquired pneumonia
CAPAMIS	community-acquired pneumonia, acute myocardial infarction and stroke
CAPiTA	community-acquired pneumonia immunization trial in adults
CD4+	cluster of differentiation 4 positive
CDC	Centers for Disease Control and Prevention
CFDA	China Food and Drug Administration
CLL	chronic lymphocytic leukemia
CNBG	Chengdu Institute of Biological Products
COPD	chronic obstructive pulmonary disease
EPI	Expanded Program on Immunization
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
GMC	geometric mean concentration
GM-CSF	granulocyte-macrophage-colony-stimulating factor
GMT	geometric mean titer
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
IgA	immunoglobulin A
IgG	immunoglobulin G
IIV3	trivalent inactivated influenza vaccine
IPD	invasive pneumococcal disease
NBPP	non bacteremic pneumococcal pneumonia
OPA	opsonophagocytic assay
OR	odds ratio
PCV	polysaccharide conjugate vaccine
PPV	polysaccharide vaccine
UK	United Kingdom
USA	United States of America
VE	vaccination effectiveness
WHO	World Health Organization.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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