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Pneumococcal conjugate vaccine use in adults – Addressing an unmet medical need for non-bacteremic pneumococcal pneumonia

Heather L. Sings

Pfizer Inc, 500 Arcola Road, Collegeville, PA 19426, USA

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ABSTRACT

Streptococcus pneumoniae is a frequent cause of community acquired pneumonia (CAP), with the largest burden of disease attributed to non-bacteremic pneumonia. Due to the high persistent burden of disease, pneumococcal pneumonia, particularly non-bacteremic pneumococcal pneumonia, continues to be a major public health concern. There are currently two pneumococcal vaccines approved for use in adults in the United States (US) and other countries worldwide: a 23-valent pneumococcal simple polysaccharide vaccine (PPV23), and a 13-valent pneumococcal conjugate vaccine (PCV13). The capsular polysaccharides included in PPV23 induce antibodies primarily by a T-cell independent mechanism, thus the immune response is short lived and lacks the ability to elicit an anamnestic response. PCV13, on the other hand, has the bacterial polysaccharides covalently conjugated to an immunogenic carrier protein resulting in the formation of memory B lymphocytes, thus proving long-acting immunologic memory and an anamnestic response. Despite 30 years of use, the question of PPV23 vaccine efficacy, particularly with respect to efficacy for non-bacteremic pneumonia, has been extensively debated and investigated; whereas PCV13 efficacy against vaccine-type pneumococcal CAP, both bacteremic and non-bacteremic, was confirmed in a large randomized controlled trial in older adults. PCV13 was approved under the US Food and Drug Administration's accelerated pathway, which allows for earlier approval of products that provide meaningful benefit over existing treatments – in this case, protection of adults from non-bacteremic pneumococcal pneumonia. Its use is now increasingly recommended globally. This article summarizes the history and use of PPV23 and PCV13 in adults and how vaccination of adults with PCV13 addresses an unmet medical need.

1. Introduction

Streptococcus pneumoniae has long been recognized as an important pathogen. While there are several potential clinical manifestations of pneumococcal disease, the distribution of these presentations varies substantially between populations. For example, in young children, acute otitis media is the most common, while bacteremia (without a known site of infection) is the most common form of invasive disease [1]. In adults, pneumococcal pneumonia constitutes the vast majority of pneumococcal disease [2]. In a systematic literature review and meta-analysis of studies evaluating the etiology of community acquired pneumonia (CAP), it was estimated that approximately 25% of CAP cases are invasive, involving infection of normally sterile sites, and 75% of are non-invasive (i.e. non-bacteremic [2]). In the United States, it is estimated that in adults ≥50 years of age, there are approximately 500,000 annual cases of non-invasive pneumonia and nearly 20,000 related deaths [3,4]. Non-bacteremic pneumococcal pneumonia is thus a major public health concern.

To borrow a title of an editorial by Klugman, when it comes to protection of adults against pneumococcal disease, we have a "Tale of Two Vaccines" [5]. On the one hand, there is a 23-valent

Abbreviations: ABC, Active Bacterial Core surveillance; ACIP, Advisory Committee on Immunization Practices; BAC, bacteremic; CAP, community acquired pneumonia; CDC, Center for Disease Control and Prevention; HR, hazard ratio; KPNC, Kaiser Permanente Northern California; NB, non-bacteremic; pCAP, pneumococcal community acquired pneumonia; VE, vaccine efficacy; CAPAMIS, Effectiveness of Pneumococcal Vaccination Against Community-Acquired Pneumonia, Acute Myocardial Infarction and Stroke; CAPiTA, Community-Acquired Pneumonia immunization Trial in Adults; ELISA, enzyme-linked immunosorbent assay; EMA, European Medicines Agency; EU, European Union; FDA, US Food and Drug Administration; GMT, geometric mean titer; IPD, invasive pneumococcal disease; NVT, non-vaccine type; OPA, opsonophagocytosis assay; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPV23, 23-valent pneumococcal polysaccharide vaccine.; UK, United Kingdom; US, United States.

E-mail address: heather.sings@pfizer.com

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pneumococcal polysaccharide vaccine (PPV23, Merck) which has been licensed and available for more than 30 years for use in persons older than 2 years of age. On the other hand, we have 13-valent pneumococcal conjugate vaccine (PCV13; Prevnar 13/Prevenar 13, Wyeth/Pfizer Vaccines) which was first approved for use in children. There are no confirmatory, randomized, placebo-controlled efficacy studies of PPV23 in the general population of older adults for the prevention of vaccine-type pneumococcal pneumonia, whereas PCV13 efficacy for both vaccine-type bacteremic and non-bacteremic pneumococcal pneumonia in the general population of community dwelling adults was confirmed in a large randomized placebo controlled trial, namely the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA) [6]. As a result, PCV13 has been recommended for use in adults (age-based or risk-based recommendations) in 45 countries. Based on data from immunogenicity studies, in countries where both PCV13 and PPV23 are recommended for adults, it is generally recommended that PCV13 be administered first [7,8].

The use of both vaccines in adults is a subject of some debate [9]. If there is a 23-valent vaccine for adults, and if PCV13 use in children provides indirect protection in adults through herd effect, what is the value of adding PCV13 to an adult national immunization program (NIP)? To answer this, one must acknowledge that, despite high PPV23 vaccine uptake in countries such as the the United States (US) [10] and the United Kingdom (UK) [11], surveillance data have shown no measurable impact on invasive pneumococcal disease (IPD) caused by the serotypes in PPV23. In addition, effectiveness studies of PPV23 for preventing non-bacteremic community-acquired pneumonia (CAP), the most common manifestation of pneumococcal disease in adults [2,12] have been conflicting. There have been approximately 33 observational studies of PPV23 (20 cohort studies [13–32], 11 case-control studies [33–43], 1 case-cohort study [44], and 1 study with self-controlled risk windows [45]) that have reported at least one vaccine effectiveness estimate for CAP, comparing subjects vaccinated with PPV23 to those unvaccinated. In these studies, vaccine effectiveness for CAP has ranged from −143% [32] to 60% [22]. It is therefore not surprising that there have been at least 11 systematic reviews and meta-analyses of PPV23 vaccine effectiveness for CAP (bacteremic and/or non-bacteremic), that have yielded varying results [46–56].

Both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) acknowledged the need for an effective vaccine to prevent pneumococcal disease in adults, as PPV23 efficacy even against IPD appears to wane over a period of 3–5 years and the efficacy of PPV23 against CAP was uncertain [7,11]. In addition, despite PCV13 use in children, there was a remaining burden of disease due to the PCV13 serotypes that made use of PCV13 in adults cost-effective, leading to the recommendation to vaccinate older adults with PCV13 [7]. This article summarizes the history and use of PPV23 and PCV13 in adults and how vaccination of adults with PCV13 addresses an unmet medical need with respect to prevention of non-bacteremic pneumococcal pneumonia.

2. Efficacy studies supporting licensure of pneumococcal polysaccharide vaccine

The first evidence supporting the efficacy of pneumococcal polysaccharide vaccines in the prevention of pneumococcal pneumonia came in 1945, with a 4-valent vaccine [57]. In the 1970's, 6-valent (50 μg each of serotypes 1, 2, 4, 8, 12F, and 25) and 12-valent (50 μg each of serotypes 1, 2, 3, 4, 6A, 8, 9N, 12F, 25, 7F, 18C, and 46) pneumococcal polysaccharide vaccines were developed. The efficacy of the 6-valent and 12-valent vaccines was investigated in two randomized controlled trials conducted in South African male gold miners between 16 and 58 years of age, a population with a high attack rate for pneumococcal pneumonia and bacteremia [58]. In both studies, conducted with the diagnostic technology and scientific rigor of the time, attack rates for vaccine-type pneumococcal pneumonia were observed from 2 weeks through 1 year post-vaccination. Vaccine efficacy was estimated at 76% and 92% for the 6- and 12-valent vaccines for vaccine-type pneumococcal pneumonia, respectively. Subsequently, three similar studies in South African gold miners were performed with a different 6-valent formulation (50 μg each of serotypes 1, 3, 4, 7, 8, and 12) and a 13-valent formulation (50 μg each of serotypes 1, 2, 3, 4, 6, 7, 8, 9, 12, 14, 18, 19, and 25) [59]. In these studies, performed in young adults, the reduction in pneumococcal pneumonia caused by serotypes contained in the vaccines (observed from 2 weeks through 1 year post-vaccination) was 79%. Reduction in serotype-specific pneumococcal bacteremia was 82%.

A 14-valent polysaccharide vaccine (50 μg each of serotypes 1, 2, 3, 4, 6A, 7F, 8, 9N, 12F, 14, 18C, 19F, 23F, and 25) was licensed in the US in 1977, based on the results of the randomized clinical trials of the 6- and 12-valent vaccines in young male African gold miners [58,59]. In the US, the 14-valent vaccine was recommended for use in patients with illnesses such as chronic pulmonary, cardiac, or renal disease. However, there were some reports of the 14-valent vaccine failure and uncertainty about the vaccine's efficacy in some target populations in the US [60–62]. Efficacy studies conducted post-licensure also yielded conflicting results [63–72]. The vaccine was later expanded to include 23 strains (25 μg each of 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) and was licensed for use in adults and children >2 years of age in the US in 1983. PPV23 is recommended for use in older adults in several countries; however it is not widely used in Western Europe [73].

There are no randomized, placebo-controlled efficacy studies of PPV23 in the general population of adults ≥65 years of age. Of the 6 efficacy studies cited in the US prescribing information, none are with the current 23-valent vaccine formulation [58,59,66,69,74,75]. The largest and, considered by some, the most robust study since PPV23 licensure is the Effectiveness of Pneumococcal Vaccination Against Community-Acquired Pneumonia, Acute Myocardial Infarction and Stroke (CAPAMIS) study [21]. This was a population-based, prospective cohort study which evaluated the effectiveness of PPV23 in preventing hospitalization with pneumococcal CAP (pCAP) and all-cause pneumonia. The primary outcomes, CAP diagnoses, statistics, and patient demographics are summarized in Supplementary Table 1.

Approximately 27,204 adults ≥60 years of age in Tarragona, Spain were prospectively followed from 1 December 2008 until 30 November 2011. As shown in Fig. 2, in the total cohort, there was no efficacy for any outcome, even after multivariable adjustment. Of the 4 cases of bacteremic pCAP in vaccinated subjects, 2 (50%) were due to a serotype in PPV23 (9N, 19A), and 6 of the 12 cases in unvaccinated subjects (50%) were due to a serotype in PPV23. Of the 109 non-bacteremic pCAP cases (42 in vaccinated subjects, incidence of 1.46 per 1000 person years; 67 in unvaccinated subjects, incidence of 1.44), 32% had no blood culture preformed, thus it cannot be confirmed that they were non-bacteremic. Of the 566 patients diagnosed with CAP (207 vaccinated subjects, incidence of 7.19; 359 unvaccinated subjects, incidence of 7.71), 58 suffered >1 episode of CAP throughout the 3-year survey period (44 had 2 episodes, 12 had 3 episodes, 1 had 4 episodes, and 1 had 5 episodes). Of these 58 patients, the majority (n = 48; 83%) had received PPV23, either within 5 years before study start (n = 23), or >5 years before study start (n = 25).

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