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Preventing non bacteremic pneumococcal pneumonia in older adults

Historical background and considerations for choosing between PCV13 and PPV23

David S Fedson

Sergy Haut, France

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Not long ago, several observers wrote that discussions of whether to vaccinate older adults with 23-valent pneumococcal polysaccharide (PPV23) vaccine or 13-valent pneumococcal conjugate (PCV13) vaccine were "fueled by polarized viewpoints".[1] This is evident in my recent debate with Hollingsworth and Isturiz in this journal.[2-5] If nothing else, this is one point on which we would agree. In their latest contribution to our exchange, Hollingsworth and Isturiz say that the effectiveness of PPV23 in preventing non-bacteremic (or non-invasive) pneumococcal pneumonia (NPP) or all-cause community-acquired pneumonia (CAP) "has not been established".[5] This statement is the foundation for the current discussions of whether PCV13 or PPV23 should be used to vaccinate older adults.

In order to understand which criteria should be used to choose between the 2 vaccines, it will be useful to first review several issues concerning pneumococcal vaccination that arose during the pre-conjugate vaccine era. It was during this period that uncertainty over whether pneumococcal vaccination protects against NPP and CAP in older adults became firmly established. The introduction of 7-valent pneumococcal conjugate vaccine (PCV7) into the US childhood vaccination schedule in 2000 fundamentally changed the nature of this debate because it changed the epidemiology of pneumococcal disease in both children and older adults. Similar epidemiological changes have occurred in other countries that have introduced PCV7 into their childhood vaccination programs. These epidemiological changes should be the primary focus of the current debate.

The debate became more urgent in 2008 when the manufacturer of what had now become a 13-valent conjugate vaccine launched a large randomized controlled trial of PCV13 in the Netherlands.[6] The primary goal of this trial is to settle once and for all the long-standing question of whether pneumococcal vaccination prevents NPP and CAP in older adults. The first results of the CAPiTA trial were recently presented. Moreover, the final results of the CAPAMIS study of PPV23 have also been published. Thus, we now have both epidemiological and vaccine-related evidence to consider in choosing which of the 2 vaccines should be used to vaccinate older adults.

Pneumococcal Polysaccharide Vaccination in the Pre-Conjugate Vaccine Era

The debate over whether to vaccinate older adults with PPV23 remained unresolved in the pre-PCV7 era because those who questioned its value did not think clearly about what we needed to know in order to justify its use. (Unless specified otherwise, "older adults" refers to those ≥65 y of age.) I discussed several reasons for this confusion in a chapter published 10 y ago.[7] Five of these reasons stand out.

Overlap between invasive pneumococcal disease and pneumococcal pneumonia

In the pre-PCV7 era, it was widely known that approximately 90% of invasive pneumococcal disease (IPD) was due to bacteremic pneumococcal pneumonia,[2,7] yet many commentators failed to acknowledge the overlap between IPD and pneumococcal pneumonia. In other words, they failed to distinguish between bacteremic pneumococcal pneumonia and NPP, implying that

Correspondence to: David S Fedson; Email: dfedson@wanadoo.fr
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Related to the following articles that discuss the roles of PCV13 and PPV23 in vaccinating older adults:

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Hollingsworth R, Isturiz R. Pneumococcal vaccination of older adults: Conjugate or polysaccharide? Hum Vaccin Immunother 2013; 10:45-6; PMID:24018552; http://dx.doi.org/10.4161/hv.26330

Fedson DS. Pneumococcal conjugate vaccination for older adults: Reply letter to Hollingsworth et al. Hum Vaccin Immunother 2013; 10:47-51; PMID:24030320; http://dx.doi.org/10.4161/hv.26422

Hollingsworth R, Isturiz R. The stubborn persistence of adult pneumococcal pneumonia as a public health problem. Hum Vaccin Immunother 2014; 10: (Forthcoming); PMID:24553362; http://dx.doi.org/10.4161/hv.27986

IPD and all pneumococcal pneumonia were separate clinical conditions. Only in recent years have some (but not all) commentators become more careful in specifying that NPP and IPD (including bacteremic pneumococcal pneumonia) are distinct entities.

Pneumococcal polysaccharide vaccine prevents pneumococcal pneumonia in young adults

In his classic randomized controlled trial (RCT) of an experimental 13-valent pneumococcal polysaccharide vaccine conducted in young South African gold miners, Robert Austrian showed the PPV was 82.3% effective in preventing vaccine-type (VT) bacteremic pneumococcal pneumonia, 78.5% effective in preventing all cases of putative VT pneumococcal pneumonia (most cases were diagnosed by sputum cultures alone), and 53% effective in preventing radiographically-diagnosed pneumonia, regardless of microbiological findings.[8] These results were confirmed in several other clinical trials studies conducted in the 1970s.[7] Thus, there was no reason to doubt that PPV prevents both bacteremic and non bacteremic pneumococcal pneumonia in young adults.

Several studies conducted during this period showed that serological responses to PPV in older adults were similar to those in young adults.[7] For this reason, it was assumed that PPV would be similarly protective against bacteremic and non bacteremic pneumococcal pneumonia in older as well as young adults. Nonetheless, in the absence of direct RCT confirmation, understandable doubts were raised about its effectiveness against pneumococcal pneumonia in this age group. Reflecting this doubt, Hollingsworth and Isturiz state that the "effectiveness of polysaccharide pneumococcal vaccines for the prevention of non-invasive pneumococcal pneumonia or all-cause community acquired pneumonia has not been established".[5] Like others who have ignored Austrian's findings, they too fail to distinguish between younger and older adults.

Many systematic reviews and meta-analyses of prospective clinical trials of PPV vaccination of older adults have reinforced the uncertainty over whether PPV23 prevents pneumococcal pneumonia. For this reason, in 2004 I published a review of these studies (ref. 9; discussed in refs. 4 and 7). I used the statistical approach of Detsky and Sackett to calculate how many subjects would be needed in a clinical trial to rule out a false-negative result.[10] I showed that none of the individual prospective clinical trials and none of their meta-analyses included a sufficient number of person-years of observation to rule out a false-negative result. Thus, it was inaccurate and misleading for anyone to conclude from these studies that PPV23 did not reduce hospitalizations and deaths due to NPP and CAP in older adults[9]; the numbers simply weren't there.

I had hoped that my report would put an end to what had clearly become a series of fruitless exercises (as discussed earlier in ref. 4), but this did not stop Huss et al.[11] and Moberley et al.[12] from publishing their studies. Hollingsworth and Isturiz justified including these meta-analyses in their earlier article[3] because they were "two of the most recent studies and their methodology is sound".[5] Sound methodology is beside the point. Like earlier meta-analyses, these more recent studies were destined to be inconclusive and uninformative; they told us nothing we didn't already know. Unfortunately, they helped sustain the uncertainty about the effectiveness of PPV23.

Compound probabilities and the aggregate effectiveness of PPV23

Because PPV23 contains 23 distinct serotype antigens, its effectiveness must be viewed as a compound probability; i.e., the product of the effectiveness of each of the individual serotypes to which a person is at risk of being infected.[7] For example, if a person is at risk of developing IPD due to 5 pneumococcal serotypes, and the individual effectiveness of each pneumococcal serotype antigen is 90%, the aggregate effectiveness of PPV23 would be 59% ($0.9^5 = 0.59$). Not surprisingly, most observational studies have shown that the aggregate effectiveness of PPV23 in preventing IPD in older adults is approximately 50–70%.[7] Hollingsworth and Isturiz cite the recent case-control study of Andrews et al. in the UK that showed PPV23 effectiveness in preventing IPD in older adults fell from 48% within 2 y of vaccination to 15% after 5 y.[13] These findings are almost the same as those reported by Shapiro et al. more than 20 y ago.[14]

The cost-effectiveness of PPV23

In the 1980s, cost-effectiveness studies in the US had shown that PPV23 vaccination to prevent pneumococcal pneumonia in older adults was cost-effective. Observational studies had already shown that PPV23 was effective in preventing IPD,[7,14] but there was persistent uncertainty about whether it was also effective in preventing all cases of pneumococcal pneumonia in this age group. For this reason, a cost-effectiveness study was undertaken in the US in the 1990s to determine whether PPV23 would be cost-effective in preventing IPD alone. The results showed that over a 5-y period, giving one dose of PPV23 was so cost-effective it was cost saving.[15] Thus, in the pre-conjugate vaccine era this meant that for purposes of both public policy and clinical practice, PPV23 vaccination of older adults was fully justified, and it was not necessary to know whether vaccination prevented NPP. The US cost-effectiveness findings were later extended to 10 Western European countries (refs. 2 and 7; see Fig. 3 in ref. 2), and during the period 2001–2010, PPV23 vaccination increased in some of these countries (ref. 16; see Fig. 3 in ref. 16).

Revaccination with PPV23

The parallel decline over time in serum antibody levels and clinical protection following PPV 23 vaccination was recognized in the 1990s.[7,14] These findings suggested a need for periodic revaccination. In the US, the Advisory Committee on Immunization Practices (ACIP) initially recommended only one dose of PPV23 to be given at age 65 y. For a few years the ACIP recommended that revaccination 5 y later be considered, but later backed off: one dose at age 65 y is the current recommendation.[17] (If PPV23 has been given ≥5 y before age 65 y, a second dose can be given at 65 y.) In the US, the most current (2012) estimate for PPV23 vaccination coverage among older adults is 59.9%, and this estimate includes "ever" vaccinated, not just those vaccinated within the past 5 y.[18]

Many observers have noted the lack of evidence that PPV23 vaccination has reduced the incidence of IPD among older adults. In the US, population estimates in 2010 showed that only 31% of the 40.3 million Americans ≥65 y of age were 65–69 y old.[19] Thus there currently is no ACIP recommendation to revaccinate the almost 70% of older adults who are ≥70 y of age, yet this is the

group in which hospitalizations and deaths from pneumococcal infection increase dramatically. The ACIP's failure to recommend revaccination for persons ≥70 y of age might help explain why PPV23 has not reduced the occurrence of IPD in older adults.

The ACIP recommendation for PPV23 is in striking contrast to its recommendation that people of all ages should receive a Td booster every 10 y.[17] In 2012, it was estimated that 55.1% of older adults had been vaccinated against tetanus within the past 10 y and another 8.0% had received a Td booster containing pertussis vaccine within the past 7 y.[18] The Vaccine Preventable Diseases Program at the Centers for Disease Control and Prevention (CDC) has reported that during the 8-y period from 2001–2008, there were only 233 cases of tetanus in the US.[20] Of these cases, 71 (30%) occurred in persons ≥65 y of age; an average of approximately 9 cases per year and an incidence of <0.3 cases/100 000 persons ≥60 y of age. Among 31 fatal cases, 25 occurred in persons ≥60 y, an average of about 3 fatal cases in older adults each year. Case fatality rates for both tetanus and IPD in older adults are approximately 30%, yet the incidence and mortality burden of IPD in this age group is several orders of magnitude greater than that for tetanus. It is obvious that ACIP recommendations for PPV23 and tetanus boosters are inconsistent, illogical, and bear no relationship to the 2 diseases these vaccines are trying to prevent. Nonetheless, the ACIP has not considered the obvious need to periodically revaccinate older adults, and it is rarely discussed.

Hollingsworth and Isturiz "contend that if the positive or negative effects of pneumococcal polysaccharide vaccines (PPSVs) were clear cut, we would not still be debating after nearly 30 y of worldwide use".[5] Yet, as noted above, by the late 1990s a solid rationale had emerged to fully justify vaccinating (and revaccinating) older adults with PPV23.[2,7,9,15]

PCV7 Vaccination of Children and the Epidemiology of IPD, NPP, and CAP in Older Adults

PCV7 began to be used for childhood vaccination in the US in 2000, and over the next 6 y it was introduced into childhood vaccination programs in many developed and developing countries. As a result, arguments for or against PPV23 vaccination of older adults had to change. This was not because PPV23 was biologically any less effective in preventing pneumococcal disease than it had always been; on the contrary, because of the decline in cases of PCV7-serotype disease, there were now fewer cases of pneumococcal disease to prevent. As a result, PPV23 vaccination undoubtedly became less cost-effective than it had been in the pre-PCV7 era. Yet, this was not much discussed; instead, most commentators continued to focus on whether PPV23 prevents NPP.

PCV7 vaccination of children and IPD in older adults

Vaccinating children with PCV7 reduces nasopharyngeal (NP) carriage of vaccine-type (VT) pneumococci in both vaccinated and non-vaccinated children.[21-23] It is the reduction in NP carriage that is directly responsible for impressive reductions in childhood IPD[22,24,25] and pneumonia.[26,27] The reduction in NP carriage in children has presumably led to a similar reduction in NP carriage in older individuals, and this explains the indirect effects (herd protection) that childhood PCV7 vaccination has brought to adults of all ages. This has been most notable in the dramatic reduction in the incidence of IPD in older adults who live in communities where PCV7 vaccination of children is widespread.[2,24,28-31] In populations where children have received PCV7, monitoring changes in NP carriage in those <5 y of age has been shown to accurately predict changes in childhood IPD.[32] Moreover, a strong correlation has been established between reductions in NP carriage and IPD in older adults at the individual as well as population level.[33]

PCV7 vaccination of children and NPP in older adults

It is widely acknowledged that childhood vaccination with PCV7 has led to a dramatic reduction in the burden of IPD in older adults, but there is still uncertainty as to whether the same effects have been seen for NPP. Like all observers, Hollingsworth and Isturiz recognize the limitations of currently available data on the proportion of all hospitalized cases of community-acquired pneumonia (CAP) that are accounted for by pneumococcal organisms of all serotypes. Nonetheless, based on the studies of Griffin et al.[34] and Sherwin et al.,[35] they say, "whatever the magnitude of the decline in PCV7 serotypes in pneumonia has been, these data suggest that PCV7 serotypes continue to cause a notable amount of pneumonia in adults" (see table in ref. 5). This statement needs to be carefully examined.

Sherwin et al. studied a convenience sample of 710 pneumonia patients ≥50 y of age, almost all of whom were hospitalized.[35] Among 708 cases that were tested, 98 (13.8%) were diagnosed as having pneumococcal pneumonia by 1 or more of 3 tests: (1) a newly developed urinary antigen detection (UAD) test diagnosed 78 (11%) of the pneumonia cases as pneumococcal. (This test detects only PCV13-serotype disease and has a sensitivity of 97% and specificity of 100%, calculated in relation to bacteremic pneumococcal disease[36]); (2) bacterial tests were positive in 14 cases, and in 12 cases with positive blood cultures (615 patients were cultured), the UAD test was positive in 11 (the positive "bacterial" tests in 2 additional patients were not specified); (3) the BinaxNOW test for urinary pneumococcal C-polysaccharide antigen was positive in only 34 of 708 cases tested. This test is known to have poor sensitivity (63% in one recent study[36]), and it was positive in only 15 (44%) of the cases that were also positive by the UAD test.[37] This means the BinaxNOW test was also positive in 19 cases of pneumococcal pneumonia that were not UAD-test positive; i.e., they were cases of non PCV13 disease.

In interpreting the study by Sherwin et al., Hollingsworth and Isturiz emphasize the finding that approximately 25% of the 78 UAD-positive CAP patients (i.e., those with PCV13 serotype pneumonia) had PCV7-serotype disease.[5] Although childhood PCV7 vaccination has led to a dramatic fall in rates of IPD in older adults,[34] in their view the data of Sherwin et al. indicate a "stubborn persistence" of PCV7 pneumonia in this age group. For several reasons, my interpretation of this study (and that of others[37]) is more cautious.

The first reason for caution is that pneumococcal infection accounted for only 13.8% of all pneumonia cases in the study by Sherwin et al.[35] This proportion is considerably lower than the

≥20–30% of all-cause CAP hospitalizations among older adults that are thought to be caused by pneumococcal infection.[7,38] Second, 59.8% of all patients studied were <65 y of age, and the overall mortality rate was only 0.9%, suggesting that most of the pneumonia cases were mild; mortality rates for CAP in older adults are usually ≥5–10%.[7] Third, the proportion of cases with positive UAD tests was 17%, 12%, and 10% in patients who were 50–64, 65–74, and ≥75 y of age, respectively. This indicates that PCV13- (and probably PCV7-) serotype disease was less common in the older age groups known to have higher rates of hospitalization and death from CAP. Finally, 19 (66%) of the 34 BinaxNOW-positive patients with pneumococcal pneumonia were not UAD-positive. In another study, Huijts et al. similarly found that the BinaxNOW test was positive in only 91 (46%) of 198 CAP patients who were UAD-positive, but it was also positive in an additional 44% of cases that were UAD-negative.[36] Although the BinaxNOW test has relatively low sensitivity, it can diagnose additional cases of non-PCV13-serotype disease that are missed by the UAD test (i.e., it has greater specificity for all-serotype pneumococcal disease). Thus, in the study by Sherwin et al., many cases (probably more than 19) of non-PCV13-serotype pneumococcal CAP went undiagnosed.[35] A UAD test that could detect all PPV23 serotypes would make it possible to determine the relative proportions of NPP caused by PCV7, PCV13 and the 10 unique PPV23 serotypes. Unfortunately, no such test has been developed.

PCV7 vaccination of children and all-cause CAP in older adults

The argument for the "stubborn persistence" of PCV7-serotype NPP[5] fails to compare the occurrence of PCV7 NPP with that of non UAD-positive (i.e., non-PCV13) NPP. Moreover, a proper accounting of PCV7-serotype and non-PCV13-serotype pneumococcal disease (both IPD and NPP) should be expressed as population-based rates, not simple percentages. Hollingsworth and Isturiz attempt to make up for this omission by presenting a Table[5] showing the annual incidence of all-cause CAP in the US based on the findings of Griffin et al. for 2007–2009.[34] Using the findings of Sherwin et al.,[35] they estimate that in older adults, the annual incidence of PCV7-serotype CAP was 3%, for all serotypes in PCV13 it was 11%, and for the 6 serotypes unique to PCV13 it was approximately 8% (calculated from data in the table in ref. 5). These estimates are not surprising. As noted in my earlier article[4], "Readers should decide for themselves whether…3.4% … of patients with PCV7 pneumonia represents a "notable" cause of CAP or, for that matter, whether … 10.2% … with PCV13-serotype pneumonia is notable."

A recent study from the UK by Bewick et al. provides a better answer to the question of how much of the burden of all-cause CAP is accounted for by PCV7-serotype pneumococcal disease.[39] The investigators studied 1099 adults with CAP who were hospitalized in Nottingham during a 2-y period beginning in September 2008. This was 2 y after the implementation of universal childhood PCV7 vaccination in the UK. The median age was 71 y and overall 30-d mortality was 10%, similar to CAP experience elsewhere[7] and very different from the patients in the convenience sample studied by Sherwin et al.[35] Of these patients, 920 were tested for pneumococcal infection using blood and sputum cultures, the BinaxNOW test for urinary antigen and a Bio-Plex immunoassay for urinary antigen that has a sensitivity of 79% in detecting 14 pneumococcal serotypes (PCV13 serotypes plus serotype 8). Among all 920 patients tested, pneumococcal CAP was documented in 366 (39.8%): 40 by blood culture (807 cultured); 18 by sputum culture (9 of whom were positive by BinaxNOW or Bio-Plex); and 196 by BinaxNOW, of whom 144 (73.5%) were found to have one of the 14 Bio-Plex serotypes. The major findings of this study are summarized in **Table 1**.

Compared with the findings of Griffin et al. in the US (see table in reference 5), the rates of all-cause CAP in adults 65–74, 75–84 and ≥85 y of age in Nottingham[39] were only 18–24% of those observed in the US.[34] The reasons for this large discrepancy are unclear, although differences in the organization of the health care in the UK and US, together with reliance on clinical data in Nottingham and administrative data in the US might explain some of the discrepancy. In addition, there were substantial differences in the proportions of all-cause CAP that were accounted for by PCV7-serotype pneumonia: in the US, Hollingsworth and Isturiz estimate that PCV7-serotype pneumonia accounted for only 3% of all CAP in older adults, but in the UK, PCV7 serotypes accounted for 6–7% of all such cases. The Nottingham data were obtained just 2–4 y after the introduction of PCV7 childhood vaccination in the UK, and this may explain why PCV7 serotypes in the UK accounted for approximately twice the proportion of all-cause CAP cases compared with the estimate for the US. It is worth noting that although the putative incidence of pneumococcal CAP in the US accounted for by the 6 serotypes unique to PCV13 was approximately 8%, the incidence for all cases of non-PCV7-serotype CAP disease seen in the Nottingham was practically the same (**Table 1**).

The Nottingham investigators have further documented the clinical and epidemiological features of PCV7-serotype pneumonia in older adults.[40] Rodrigo et al. compared patients with PCV7-serotype and non-PCV7-serotype CAP, and found that those with PCV7-serotype CAP were 8.3 y older (median) and had a 2.8-fold increase in stroke, a 3.55-fold increase in dementia and a 4.4-fold increase in 30-d mortality. They suggested several possible explanations for these findings. For example, because patients with stroke and dementia were more isolated, they had less frequent contact with children and this could have led to lower rates of serotype replacement than are seen in PCV7-vaccinated children and their adult contacts. In another study,[41] these investigators showed that although pneumococcal CAP was more common in all adults (not just older adults) who had more frequent contact with children, those in contact with PCV7-vaccinated children were less than half as likely to develop PCV7-serotype CAP compared with those without such contact. This important finding showed that on an individual as well as population level, 'herd protection' associated with childhood conjugate vaccination was not limited to IPD; it extended to NPP as well.

The findings reviewed above strongly suggest that in countries with widespread vaccination of children with PCV7, the burden of PCV7-serotype pneumonia in older adults is very low

Table 1. Annual incidence of hospitalized community-acquired pneumonia (CAP) among older adults in Nottingham[1]

Age group	Annual incidence of CAP/100 000			
(y)	All cases	All pneumococcal[2]	PCV7-serotype[3]	Non-PCV7 serotype[4]
65–74	288	71	17	28
75–84	439	135	26	57
≥85	986	274	71	102
≥65	424	234	53	94

[1]Adapted from Tables 2 and 3 in reference 39. All rates have rounded to the nearest whole number. [2]The rates shown in the column do not reflect the total number of cases of all pneumococcal CAP because not all cases could be detected by the BinaxNOW urinary antigen test. [3]Cases of PCV7-serotype CAP were diagnosed by the Bio-Plex urinary antigen test. [4]The rates shown in the column do not reflect the total numbers of cases of non-PCV7-serotype CAP. These numbers include Bio-Plex-positive cases with serotypes unique to PCV13 and cases with a positive BinaxNOW test but a negative Bio-Plex urinary antigen test. Other cases of non-PCV7-serotype CAP may have escaped detection because of the low sensitivity of BinaxNOW test.

and may account for well under 5% of all hospitalizations for community-acquired pneumonia.

Pneumococcal Vaccination of Older Adults in the PCV13 era: The Immunogenicity of PCV13, the Epidemiology of NPP and CAP and the Cost-Effectiveness of PCV13 Vaccination

Immunogenicity of PCV13 in older adults

Hollingsworth and Isturiz criticize my earlier article[4] for not including the pivotal clinical immunogenicity studies that supported licensure of PCV13 for adults ≥50 y of age.[5] I wrote in response to their article,[3] which did not include these data. The studies they mention have now been published, and the findings show that on several measures, PCV13 demonstrates better immunogenicity when compared with PPV23.[42,43] There may also be a lower risk of hyporesponsiveness with PCV13 compared with PPV23.[44] I take this biological issue as seriously as they do, although neither they nor I knows if it is clinically important.

Whether the immunogenicity findings for PCV13 in older adults are associated with better clinical protection compared with PPV23 is not known, and a direct comparison of the 2 vaccines will probably never be made. Hollingsworth and Isturiz ask us to consider vaccinating older adults with PCV13[3,5] on the basis of immunogenicity studies. They would have us believe "more is better," without first addressing the question, "how much is enough?"—in other words, what levels of serotype-specific IgG or opsonophagocytic antibodies are protective? After 30 y, there are no answers to these questions for PPV23, and no one has yet answered them for PCV7 or PCV13.

PCV7 was licensed and recommended for childhood vaccination not only because it was immunogenic and safe, but also because it was efficacious in preventing childhood IPD. Likewise, PCV13 was licensed for children on the basis of immunogenicity and safety, but licensure was also supported by evidence of the extraordinary clinical and epidemiological impact of PCV7 on childhood pneumococcal disease. Immunogenicity and safety criteria also led to licensure of PCV13 for adults ≥50 y of age. Nonetheless, immunogenicity and safety alone are not enough to justify a recommendation to vaccinate older adults with PCV13; the anticipated epidemiological impact of childhood PCV13 vaccination on older adults must also be considered.

PCV13 vaccination of children and its impact on the epidemiology of IPD, NPP, and CAP in older adults

Following the switch in childhood vaccination from PCV7 to PCV13, encouraging data have been published from several countries showing further declines pneumococcal carriage[45] and in the incidence of IPD and pneumonia in children <5 y of age.[46-48] We can only speculate on what the full impact of PCV13 vaccination will be for children, but it is reasonable to assume that it will be similar to what has been seen with PCV7: the almost complete disappearance of NP carriage, IPD and childhood pneumonia due to PCV13-serotype pneumococci.

It is too early to know with certainty whether the indirect effects of childhood PCV13 vaccination on older adults will be like those seen with PCV7. Demonstrating changes in NP carriage can sometimes be difficult because carriage rates in this age group are normally very low.[49] For NPP, a study from Denmark suggests that only one-third of cases of adult NPP would be potentially preventable by PCV13.[50] It is important to note that this study was conducted in 2011, 3 y after the introduction of PCV7 and less than 1 y after the introduction of PCV13 into Danish childhood vaccination programs. If past experience with PCV7 is any guide, it is reasonable to expect that in future years, an even lower proportion of NPP in Denmark will be due to PCV13 serotypes.

A useful model has been published for the US that forecasts the impact that PCV13 childhood vaccination will have on the overall incidence of IPD in children and adults.[51] This Poisson model is based on national surveillance data for IPD beginning in 1998, the year before PCV7 vaccination was introduced for children, and extending through 2009. The model incorporates known data on serotype replacement and the indirect effects of PCV7 vaccination on IPD in older age groups. It does not require information on NP carriage rates, the invasive potential of individual serotypes, the efficacy of specific serotypes, the duration of protection or the dynamics of transmission.[51] Its predictions have been fine tuned so that they replicate actual experience for IPD documented by earlier PCV7 surveillance data. The model has been used to forecast trends in IPD during the PCV13 period (2010–2020). It assumes that trends for PCV13 will follow the

Table 2. Annual incidence of IPD/100 000 (all serotypes) in young children and older adults in the US following the introduction of childhood PCV7 and PCV13 vaccination[1]

Year	Vaccine	<5 y	≥65 y
1998–1999	no PCV	97.6	59.6
2009	10 y after PCV7	21.8	38.5
2020	10 y after PCV13	9.3	25.0

[1]Adapted from reference 51, Tables 2 and 3. PCV7 was introduced in childhood vaccination in 2000 and replaced by PCV13 in 2010.

same path that was seen for PCV7 during the previous decade. The results of the forecast for children <5 y of age and adults ≥65 y of age are summarized in **Table 2**. In the base case analysis, the decline in the incidence of IPD documented during the PCV7 era was greater than the anticipated decline forecasted for the PCV13 era. This pattern was shown for both children and older adults, and sensitivity analyses incorporating extremes of serotype replacement had very little effect on these results.[51]

This forecast can be used to anticipate US trends in pneumococcal pneumonia in older adults following introduction of childhood PCV13 vaccination. The numbers will not be the same as those shown in **Table 2**, but if we assume that the trend for PCV13-serotype pneumonia will follow the trend for PCV13-serotype IPD,[51] the proportions should be about the same. The forecast estimates that during the period from 2010–2020, the incidence of IPD in older adults will fall by about one third (**Table 2**). This means that about two-thirds of the remaining cases will be non-PCV13-serotype IPD. Experience in the PCV7 era suggests the same pattern will probably be seen for cases of non-PCV13-serotype NPP. We cannot know what proportion of the remaining cases of IPD and NPP in 2020 will be due to the 10 serotypes unique to PPV23, but we can be confident there will still be a substantial burden of non-PCV13-serotype disease, some of which will be due to serotypes unique to PPV23.

Cost-effectiveness of PCV13 vaccination of older adults

The cost-effectiveness of PCV13 vaccination of children is well-established, not only in developed countries but in middle- and low-income countries as well.[52] This may not be true for a strategy that adds PCV13 vaccination of older adults. Hollingsworth and Isturiz state that my conclusions about the cost-effectiveness studies of Weyker et al.[53] and Smith et al.[54] are incorrect, and that these investigators "employed reasonable estimates of expected herd effects from widespread childhood use of PCV13".[5] Perhaps so: at this time no one can be certain. Nonetheless, all of the evidence from the PCV7 era shows that NP carriage of PCV7 serotypes was dramatically reduced, and this led to a dramatic reduction in PCV7-serotype IPD and pneumonia in children. As a result of herd effects, PCV7 vaccination of children also led to similarly dramatic reductions in PCV7-serotype disease in older adults. Given all that is known about conjugate vaccines, it is reasonable to assume the same thing will happen once PCV13 vaccination of children becomes widespread, and any cost-effectiveness study of PCV13 vaccination of older adults must take this into account. As noted earlier,[4] Weyker et al. showed in their sensitivity analysis[53] that "if the indirect effects of PCV13 vaccination of children (lead) to a decrease in PCV13 serotype disease in older adults, no PCV13 vaccination strategy in this age group would be cost effective."

Vaccinating Older Adults to Prevent Pneumococcal Pneumonia the CAPAMIS and CAPiTA Studies

The results of the CAPAMIS study have recently been published[55] and the first results of the CAPiTA study[6] were recently presented.[56] These 2 studies provide new information on whether vaccinating older adults with PPV23 and PCV13 prevents NPP and CAP. Their results are summarized in **Table 3**.

The CAPAMIS study: PPV23 protects against NPP and CAP in older adults

The argument that PPV23 does not protect older adults against NPP and CAP has become less persuasive following recent publication of the final results from the CAPAMIS study.[55] This population-based, prospective cohort study evaluated the effectiveness of PPV23 in preventing hospitalization with pneumococcal CAP and all-cause pneumonia. The study population included 27 204 adults ≥60 y of age living in Tarragona, Spain during the 3-y period from 1 December 2008 to 30 November 2011. All study subjects were registered in 1 of 9 primary health care centers. Patients hospitalized with pneumonia were diagnosed as having pneumococcal CAP by blood and sputum culture and the BinaxNOW urinary antigen test. Demographic data and risk factors were carefully documented in an electronic medical record system, and PPV23 and influenza vaccinations were carefully validated. Unique among observational studies of PPV23, vaccination for each subject was considered a time-varying condition. Cox proportional hazards analysis was undertaken using propensity scores to adjust for potential confounders, and outcomes were evaluated according to person-years of observation since the time of vaccination. The investigators found that PPV23 vaccination more than 5 y before pneumonia hospitalization was not protective, but vaccination within the previous 5 y significantly reduced both non-bacteremic pneumococcal CAP (vaccination effectiveness [VE] = 48%) and all-cause CAP (VE = 25%; **Table 3**).[56] PPV23 vaccination within 5 y also reduced episodes of bacteremic CAP (VE = 62%), but there were few episodes of illness and the adjusted odds ratio was not statistically significant.

The CAPAMIS investigators have shown that the degree of PPV23 protection against pneumococcal pneumonia in older adults is similar to that shown for IPD by Shapiro et al. 20 y ago.[14] More important, they have also shown that PPV23 protects against all-cause pneumonia. Many of the pneumonia hospitalizations in the CAPAMIS study may have been caused by undiagnosed pneumococcal infections because the BinaxNOW test used for diagnosis is not very sensitive. In showing that PPV23 was similarly effective in preventing both bacteremic pneumococcal pneumonia (i.e., IPD) and all-cause pneumonia, the CAPAMIS investigators have confirmed the findings that Robert Austrian obtained in his randomized controlled trial of pneumococcal polysaccharide vaccine 40 y ago.[2,7,8]

Table 3. Comparative effectiveness of PPV23 (CAPAMIS)[1] and efficacy of PCV13 (CAPiTA)[2] vaccination of older adults

	CAPAMIS				CAPiTA		
Method	Retrospective cohort				Randomized controlled trial		
Duration of follow up	3 y				2.5 y		
Serotypes	All serotypes				PCV13 serotypes only		
Study population vaccinated/non vaccinated	8981/12 044				42 240/42 256		
Outcome	Cases Vac/ nonVac	Adj. HR[3]	95% CI[4]	VE[5] (%)	Cases Vac/ non-Vac	VE (%)	95% CI
All pneumococcal CAP	45/39	0.49	0.29 - 0.84	51	49/90	46	21.8 -62.5
Non-bacteremic pneumococcal CAP (NPP)	41/31	0.52	0.29 - 0.92	48	33/60	45	14.2 -65.3
All-cause CAP	206/169	0.75	0.58 - 0.98	25	nd[6]	nd	nd
Bacteremic pneumococcal CAP/IPD	4/8	0.38	0.09 -1.68	62	7/28	75	41.4 -90.8

[1]Adapted from reference 55. [2]Adapted from reference 56; per protocol analysis. [3]Adj. HR indicates adjusted hazard ratio. [4]CI indicates confidence interval. [5]VE indicates vaccination effectiveness and vaccine efficacy. [6]indicates no data

The CAPiTA study: PCV13 protects against NPP and CAP in older adults

The first results of the CAPiTA study were recently presented.[56] This randomized, placebo-controlled trial was conducted in The Netherlands where, because of highly restrictive recommendations, very few people had ever received PPV23.[6] The trial enrolled almost 85 000 older adults (mean age 72.8 y). Enrolment began in September 2008 and ended on January 31, 2010. The PCV13-specific UAD test (described above) was used to confirm first episode hospitalizations for pneumococcal pneumonia, and counts of outcome events ended on August 28, 2013. In the primary per protocol analysis, the efficacy PCV13 vaccination in preventing PCV13-serotype CAP was 46% (**Table 3**). In the secondary analysis, it was 45% efficacious in preventing PCV13-serotype NPP and 75% efficacious in preventing PCV13-serotype IPD (**Table 3**).[56]

In the Netherlands, childhood vaccination with PCV7 began in 2006 and PCV10 was introduced in March 2011.[56] (No PCV13 has yet been used to vaccinate Dutch children.) Thus, the effects of several years of PCV7 childhood vaccination should have been reflected in the results of the CAPiTA trial. According to the data presented recently, there were 14 cases of PCV7-serotype CAP in the vaccinated group and 18 in the placebo group, whereas cases of non-PCV7 CAP in the vaccinated and placebo groups (i.e., cases due to serotypes unique to PCV13) were 35 and 73, respectively (DS Fedson, unpublished observation). These findings suggest that the indirect effects of childhood PCV7 vaccination were already evident during the trial period. Unfortunately, it may not be possible to obtain an estimate of the burden of pneumococcal pneumonia in the CAPiTA study population that was due to non PCV13-serotype infection.

Comparing the CAPAMIS and CAPiTA study results

The findings presented in **Table 3** indicate that within 5 y of vaccinating older adults, PPV23 and PCV13 provide similar protection against NPP. It might be argued that PCV13 is the more suitable vaccine to use because its protection is likely to be long lasting and there is no indication that health officials in any country are interested in undertaking revaccination programs for PPV23 every 5 y. Yet the promise of long lasting protection may be of no advantage if, 5 y after implementing childhood PCV13 vaccination, there is so little PCV13-serotype pneumococcal disease in older adults that vaccinating them with PCV13 is not worthwhile. In my earlier response to Hollingsworth and Isturiz,[4] I noted that even if the results show that PCV13 vaccination has reduced the occurrence of PCV13 serotype disease in older adults, "within a few years the long-term indirect effects of … (PCV13 vaccination of Dutch children) … will probably erode whatever benefits were observed during the CAPITA trial period itself."

The Choice between PCV13 and PPV23 for Older Adults

PCV13 has been shown to be immunogenic and safe when administered to adults ≥50 y of age. Yet immunogenicity and safety data alone do not justify recommending PCV13 vaccination of older adults; there has to be a sufficient burden of PCV13-serotype pneumococcal disease to make vaccination clinically worthwhile and cost-effective. For the many reasons summarized above, and despite the impressive results of the CAPiTA study, no convincing case can be made at this time for vaccinating older adults with PCV13. Immunization advisory groups in the US and the UK appear to share this conclusion.[2,4]

This leaves unanswered the question of whether PPV23 vaccination still has a role to play in preventing pneumococcal disease in older adults, and here the uncertainty is of a different kind. There is no reason to doubt that PPV23 vaccination of older adults prevents IPD[2,7,13,14] and pneumococcal pneumonia,[8,54] but there is no information for this age group on the residual burden of pneumococcal disease that is caused by the 10 serotypes unique to PPV23. Furthermore, no country seems interested

in vigorously implementing a program of PPV23 revaccination every 5 y. Whether doing so in the PCV13 era would be cost-effective is not known, and it is unlikely this question will ever be addressed. Some experts believe it is no longer necessary to administer any pneumococcal vaccine to older adults.[1,57]

Given this uncertainty, if we want to improve protection of older adults against pneumococcal infection, we must look beyond PPV23 and PCV13. As I said earlier,[4] we need to develop "serotype independent, protein-based pneumococcal vaccines and potentially life-saving immunomodulatory treatments of pneumococcal disease. While doing this, (we) should also…celebrate the extraordinary contributions that pneumococcal polysaccharide and conjugate vaccines have brought and continue to bring to human health."

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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