Pneumococcal conjugate vaccination for older adults

Reply letter to Hollingsworth et al.

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Hollingsworth and Isturiz[1] have raised several questions about our earlier review of the use of pneumococcal conjugate (PCV) or polysaccharide (PPV) vaccine for older adults (i.e., ≥65 y of age).[2] They begin by citing two metaanalyses published in 2009 and 2013 that concluded that prevention of pneumococcal pneumonia could not be demonstrated for PPV.[3,4] They overlook my earlier review of five metaanalyses that was published in 2004.[5] This review showed that the study populations in prospective trials of PPV were often not representative of the populations of elderly and high-risk adults for whom PPV is recommended. Furthermore, the five metaanalyses often omitted clinical trials that should have been evaluated, included trials that should have been omitted, and frequently miscounted the numbers of subjects and outcome events in the individual clinical trials. More important, retrospective sample size calculations showed that none of the five metaanalyses included an adequate number of person years of observation to rule out false-negative results. The numbers speak for themselves and cannot be ignored. Simply put, metaanalyses of the PPV clinical trials will never tell us whether the vaccine prevents pneumococcal pneumonia or all-cause pneumonia in elderly and high-risk adults, and consequently they must be regarded as inconclusive and uninformative. Since 2004, only one small prospective clinical trial of PPV has been published (reviewed in ref. 6). Nothing new has been added to our knowledge of PPV efficacy by the more recent metaanalyses.[3,4] Epidemiologists have reminded us that the lack of evidence of PPV efficacy is not evidence of its absence. The conclusions of our earlier review still stand.[5]

We did not consider the pivotal clinical immunogenicity trials that supported licensure of PCV13 for adults ≥50 y of age because the results were not available to us when we wrote our paper. However, we noted an earlier study by Goldblatt and colleagues that compared antibody responses following primary vaccination and revaccination with PPV and PCV7.[7] The investigators analyzed only IgG, not functional (opsonophagocytic) antibodies. They found that "immunogenicity studies have failed to conclusively demonstrate the superiority of (PCV7) over PPV," and concluded "… either vaccine can be administered any time between the sixth and eighth decade, with similar resultant concentrations of IgG" antibodies.[7] The more recent studies cited by Hollingsworth and Isturiz compared both IgG and functional antibody responses to PPV and PCV13. Although these newer results suggest that PCV13 might possess some advantages over PPV, drawing firm conclusions from these studies may be premature; there is no a priori reason to think that PCV13 should be indisputably more immunogenic than PPV in older adults because many earlier studies of PCV7 showed no such superiority.[7-9]

Hyporesponsiveness to a second dose of vaccine, whether PPV or PCV, is one aspect of a broader but still unanswered question: what levels of IgG or functional antibody to each of the 23 serotypes in PPV (or the 13 serotypes in PCV13) indicate clinical protection? We will never get an answer to this question. However, it is important to ask whether immunogenicity criteria alone should play a determining role in deciding whether to recommend and use either PPV or PCV in older adults. After all, "the decision to use conjugate or polysaccharide vaccine in elderly persons is informed by more than just considerations of antibody titers."[7]

PCV7 was added to the US childhood immunization schedule in 2000. Epidemiological studies show that its use has had profound indirect (herd) effects on the occurrence of PCV-type invasive pneumococcal disease (IPD) in older adults (**Fig. 1**).[10-13,a] Although Hollingsworth and Isturiz accept these results, they are reluctant to draw firm conclusions regarding the magnitude of these indirect effects on pneumonia–non-bacteremic pneumococcal pneumonia (NPP), all-cause non-bacteremic pneumonia (NBP), or all-cause pneumonia (bacteremic and non-bacteremic combined). Two of the reports that they cite provide information on what the magnitude of these indirect effects might be.

Simonsen et al. compared hospitalization rates in periods before (1996–1999) and after (2005–2006) the introduction of childhood PCV7 vaccination in the US.[14] In persons ≥65 y of age, the indirect effect of PCV7 vaccination in reducing hospitalization rates for all serotype pneumococcal disease was greater for NPP (54%) than it was for IPD (47%). The reduction in the number of NPP hospitalizations was five times greater than it was for IPD. During the same period, there was a 12% reduction
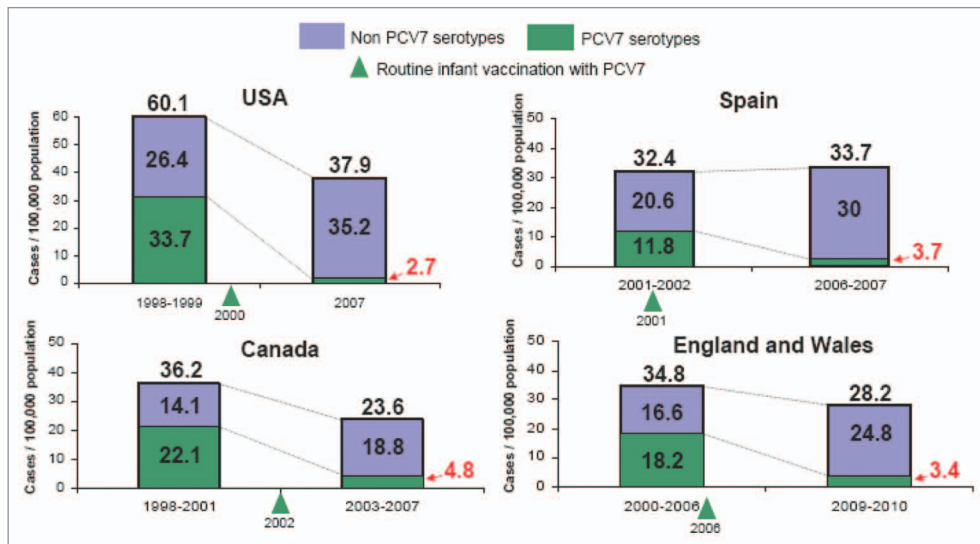
Figure 1. Incidence of invasive pneumococcal disease (IPD) per 100 000 older adults before and after the introduction PCV7 vaccination of children in four countries. Data for adults ≥65 y of age in the US, Spain and England and Wales, and for those 65–64 y of age in Canada. See references 10–13 for details.

in hospitalizations for all-cause pneumonia among older adults, and approximately 30% of these admissions were attributed to pneumococcal infection. In addition, a comparison of ten states that had varying rates of introducing PCV7 showed that higher PCV coverage was associated with greater reductions in hospital mortality for IPD, NPP, and all-cause pneumonia.[14]

A more recent study by Griffin et al. compared the effect of PCV childhood vaccination on hospitalizations for all-cause pneumonia over a longer period: pre-PCV7 (1997–1999) and late PCV7 (2007–2009).[15] During this period, there was an estimated 17.9% reduction in the rate of all-cause pneumonia hospitalizations among persons ≥65 y of age (see Table 1 in ref. 15). Some of this reduction probably reflected secular trends; the median length of hospital stay in this age group also declined during this period.[15] However, rates for PPV and influenza vaccination and for smoking in older adults were stable from 2000 to 2009, whereas the reductions in hospital admissions for in NPP and all-cause pneumonia hospitalizations paralleled those for IPD.[14,15] These reductions were almost certainly due to the indirect effects of PCV7 vaccination of children.

The magnitude of the indirect effects of PCV7 on the burden of IPD, NPP, NBP and all-cause pneumonia in older adults have direct bearing on estimates of the cost-effectiveness of PCV13 vaccination in this age group. Hollingsworth and Isturiz mention two such studies. Weycker et al. evaluated PCV13 cost-effectiveness in preventing hospitalization for IPD and NBP,[16] whereas Smith et al. studied hospitalizations for IPD and NPP.[17] Smith et al. also published an earlier report that provided more details on their methods.[18] Both groups of investigators considered the indirect effects of childhood PCV13 programs in their analyses. For single dose vaccination at 65 y of age, both groups concluded that PCV 13 vaccination would be cost-effective. I believe their conclusions are unreliable.

In their base case analyses, Weycker et al. and Smith et al. assumed that PPV was not effective in preventing any cases of

NBP or NPP.[16-18] In my view and that of others,[8] this was not a reasonable assumption because it ignored studies of the long-term immunogenicity and safety of PPV in older adults[19] and the classic clinical trial in younger adults that showed PPV was similarly efficacious in preventing bacteremic pneumococcal pneumonia and all cases of pneumococcal pneumonia, non-bacteremic as well as bacteremic.[20] Both groups of investigators justified their assumptions that PPV would not prevent NBP or NPP on the basis of misinterpretations of the two metaanalyses mentioned earlier.[3,4] In addition, Weycker et al. stated that their assumption was consistent with other published economic studies (for example, ref. 21), but they overlooked the fact that several of these economic studies analyzed IPD alone precisely because of the continued confusion over whether PPV was clinically effective in preventing NPP in older adults. Despite this self-imposed limitation, these studies found that in the pre-PCV era, PPV was highly cost-effective in preventing IPD alone.[2,6,21]

Weyker et al. based their assumptions for the burden of pneumococcal hospitalizations on data from 2008.[16] Data from the previous year (2007) showed that the seven years following the introduction of PCV7, the rate of PCV7-serotype IPD in older adults had decreased by 92%.[10] This decrease represents the indirect effect of PCV7 shown in the Figure. In 2008, the proportions of IPD serotypes in this age group due to PPV, PCV13, and PCV7 serotypes were 66%, 44%, and ~4%, respectively (see fig. in ref. 22). This means that in 2008 (before the introduction of PCV13 for children in 2010), approximately 40% of IPD serotypes in 2008 were unique to PCV13. (Before the introduction of PCV7 in 2000, 56% of all IPD serotypes in older adults were unique to PCV7[10]). Weyker et al. also assumed that in older persons, the maximum percent reduction in the rates of all serotype IPD due to the indirect effects of PCV13 would be 30.8–32.1%, and the overall percent reduction for NBP would be 6.6–7.1% (see Table 1 in ref. 16). If pneumococcal infections account for ~30% of all hospitalizations for NBP,[14] this

would correspond to an estimated maximum percent reduction of ~20% for NPP.

It is reasonable to assume that following the introduction of PCV13 in the US in 2010, the indirect effects of PCV13 on rates of IPD and NBP among older people will be similar to those seen earlier for PCV7. If so, the indirect effects of PCV13 assumed by Weycker et al. were considerably lower than the indirect effects of PCV7 estimated by Simonsen et al.[14] As discussed above, Simonsen et al. concluded that in the seven-year period following the introduction of PCV7 in the US, hospitalization rates for PVCV7-serotype IPD in older adults fell 92%, rates for all serotype IPD hospitalizations fell 47% (not 30–32%) and rates for NPP hospitalizations fell 54% (not ~20%). According to Weycker et al., "the greatest uncertainty in our model concerns the assumed effectiveness of vaccination with PCV13 against IPD and (especially) all-cause NBP …"[14]. In my opinion, far more uncertainty was introduced into their model by their estimates of the indirect effects of PCV13 in older adults. Weyker et al. assumed that once PCV13 vaccination had been introduced, there would be a much larger number of cases of PCV13 serotype IPD and NBP to prevent than could reasonably be expected to occur. For this reason, their cost-effectiveness estimates for PCV13 should be viewed with great caution.

Smith et al. presented a detailed cost-effectiveness analysis of 15 different PCV13 and PPV vaccination strategies for persons ≥65 y of age[17] (and six different strategies in an earlier paper).[18] They based their analyses for all serotype IPD on annual hospitalization rates per 100 000 persons ≥65 y of age reported in 2007–2008: 25.9 in 65–69 y old adults to 60.1 in those ≥85 y of age, with 40.8 to 48.7% of these cases caused by PCV13 serotypes.[17] During this year, annual hospitalization rates per 100 000 older adults for all-cause pneumonia were 1890–2196, and for NPP they were 547–649.[17] In their papers and the supplementary materials, Smith et al provided extensive information on the assumptions used in their analyses. They also discussed the methods they used to account for the indirect effects of PCV13 childhood vaccination. Unfortunately, they provided no information on the numbers they used to model the expected indirect effects of childhood PCV13 vaccination on the burden of IPD and NPP in older adults. Perhaps this was because an earlier study (conducted over a shorter period of time) had shown that these effects were not significant in adults ≥50 y of age.[17] Nonetheless, in a sensitivity analysis the investigators found that if the indirect effects of PCV13 vaccination of children led to a decrease in PCV13 serotype disease in older adults, no PCV13 vaccination strategy in this age group would be cost-effective (see Appendix I in ref. 17).

Hollingsworth and Isturiz believe that studies of community-acquired pneumonia using a highly specific urinary antigen detection (UAD) test to diagnose PCV13-serotype disease are likely to be "extremely helpful" in determining the magnitude of the indirect effects of PCV13 childhood vaccination on PCV13 serotype NPP in older adults.[1] They cite a study conducted in 2010–2011 that enrolled a convenience sample of 710 patients with radiographically confirmed pneumonia (CAP and healthcare-acquired pneumonia), almost all of whom were hospitalized.[23] Among 322 pneumonia patients ≥65 y of age, only 33 (10.2%) had a positive UAD test for PCV13-serotype disease. Among these 33 cases, 11 were due to PCV7 serotypes and 26 were due to the six additional serotypes in PCV13 (see Table 2 in ref. 23). Hollingsworth and Isturiz believe these findings suggest "PCV7 serotypes remain a notable cause of CAP in US adults 10-12 years post-introduction of PCV."[1] Readers should decide for themselves whether 11/322 (3.4%) of patients with PCV7 pneumonia represents a "notable" cause of CAP or, for that matter, whether 33/322 (10.2%) with PCV13-serotype pneumonia is notable. Clearly, more robust studies are needed to determine the long-term indirect effects of PCV7 and PCV13 vaccination of children on the occurrence of IPD and NPP in older adults.

Investigators in the Netherlands will soon conclude their randomized, placebo-controlled clinical trial (CAPITA) of PCV13 vaccination in 85 000 community-dwelling persons ≥65 y of age.[24] The primary goal of the trial is to determine the efficacy of PCV13 vaccination in preventing first-episode hospitalizations with PCV13 serotype-specific pneumococcal pneumonia. Secondary outcomes are prevention of non-bacteremic PCV13 serotype-specific pneumonia (NPP) and IPD (see reference 24 for specific diagnostic criteria). The study enrolled its first patient in 2008 and the observation period will end in August 2013. Results are expected to be reported one year later.

The sample size calculation for the CAPITA trial was based on the following assumptions: (1) the annual rate for pneumonia hospitalizations in older adults in 2006 would be 10 per 1000, as was seen in the year before the introduction of PCV7 vaccination for Dutch children, (2) 25–30% of all CAP cases would be due to pneumococcal infection, (3) 49% of IPD cases would be caused by PCV13 serotypes and 21% by serotypes unique to PCV13, and (4) the indirect effects of PCV13 in older adults would be similar to those observed following the introduction of PCV7 in the US.[24]

At this time, we cannot know whether the CAPITA trial will yield useful results, but there are reasons for doubt. PCV7 vaccination of Dutch children began in 2006, and given the effectiveness of Dutch immunization programs, high coverage rates were probably achieved within 2–3 y. By the time the CAPITA trial ends, PCV7 will have been used for seven years (2006–2013), a time frame during which there was a dramatic fall in PCV7 serotype pneumococcal disease in older adults in the US.[14,15] A similar decrease should be expected to occur over the same period in the Netherlands. Moreover, PCV10 vaccination of Dutch children began in March 2011. This development, apparently not anticipated by the CAPITA investigators, should amplify the indirect effect of PCV vaccination on the occurrence of pneumococcal disease in older adults. There is a good possibility that the CAPITA trial results will be inconclusive. Even if they show that PCV13 vaccination was efficacious in reducing the occurrence of PCV13 serotype pneumococcal disease, within a few years the long-term indirect effects of PCV10 and the anticipated introduction of PCV13 for Dutch children in 2014 will probably erode whatever benefits were observed during the CAPITA trial period itself.

Hollingsworth and Isturiz present an argument for PCV13 vaccination of older adults that is based primarily on immunogenicity data.[1] However, there will be little reason to use a highly immunogenic vaccine if there is little disease to prevent.[2] Others share this view,[25] and it probably explains why immunization advisory groups in the US and the UK have been unwilling to recommend PCV13 vaccination of older adults. While waiting for more definitive data on which to base PCV13 vaccination policies for older adults, I believe attention should be given to reassessing the burden of pneumococcal disease caused by the ten serotypes unique to PPV, re-evaluating PPV's cost-effectiveness, and revising currently incoherent policies on PPV revaccination. At the same time, investigators and health officials should accelerate the development of serotype independent, protein-based pneumococcal vaccines and potentially life-saving immunomodulatory treatments of pneumococcal disease.[2] While doing this, they should also take time to 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.

End Note

[a]The indirect (herd) effects seen in populations after the introduction of PCV have sometimes been called herd immunity (see references 13, 14, 17, and 18). This is a mistake. Herd immunity is achieved with oral polio vaccination; OPV-vaccinated individuals transfer vaccine virus to unvaccinated individuals who then become actively immunized. No such transfer occurs with PCV. Instead, unvaccinated individuals are protected because they are less frequently exposed to pneumococcal organisms carried in the nasopharyngeal passages of their contacts. These unvaccinated individuals remain fully susceptible to colonization and infection whenever they are exposed to others who are pneumococcal carriers; for example, when they travel to countries where PCV is not used. The indirect effects of PCV are evidence of herd protection, not herd immunity.

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