Prevention of Pneumococcal Infections in Adults Using Conjugate Vaccines: No Easy Answers

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(See the Major Article by Vadlamudi et al on pages 34–49.)

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In children, the widespread use of protein-polysaccharide conjugate vaccines against pneumococci has led to substantial reductions in the overall incidence of pneumonia, meningitis, and bacteremia due to pneumococci. The currently-available vaccines target either 10 or 13 of the more than 90 different serotypes of pneumococci. The observed reductions in disease incidences result from large reductions in the incidences of infections due to those serotypes targeted by the vaccine, despite smaller increases in the incidences of infections due to non-vaccine serotypes [1]. Pneumococcal conjugate vaccines (PCVs) induce antibodies that both protect against the infections caused by the serotypes included in the vaccines and reduce or eliminate nasopharyngeal colonization by those serotypes. Because healthy, colonized children are the main reservoir for pneumococci in the population, immunizing children with PCVs reduces the exposure of both children and adults to these serotypes. As a result, immunizing children leads to large declines among adults in the incidences of

infections due to those serotypes targeted by the vaccine. However, the frequency of colonization with non-vaccine serotypes increases substantially in the healthy, immunized children who carry and may transmit these bacteria (serotype replacement). Subsequent increases in the incidences of infections due to non-vaccine serotypes may erode some of the benefit of PCV immunization programs, particularly for adults. Critical questions include:

- Why has serotype replacement largely offset the indirect benefits of the vaccine for adults in some populations (eg, in England [2]), while in other populations (eg, in the United States [3]), little serotype replacement has been reported?
- Should adults be directly vaccinated with PCVs, or is vaccinating only children sufficient to protect adults from infections due to vaccine serotypes?
- What is the marginal benefit of introducing PCVs with larger numbers of serotypes?
- Could a different PCV, designed to be administered only to adults, be beneficial?

Most immunization programs had initially introduced the first-generation PCV7, prior to switching to PCV13. This study evaluates the marginal impact of switching from PCV7 to PCV13, rather than the absolute impact of a PCV program (which would entail comparing the epidemiology of pneumococcal infections after the introduction of PCVs to that of a period prior to use of any PCVs). While there are other reviews and meta-analyses on the effects of PCVs [1, 5–7], this review includes up-to-date data on the effects of PCV13 from a wide range of geographical areas. The authors compiled a large and comprehensive dataset on PCV13's effects on IPDs, as well as on other outcomes, and they compare changes in the numbers of cases before and after introduction of PCV13. As expected, they found substantial declines in infections due to vaccine-targeted serotypes and important, but generally more modest, increases in infections due to non-vaccine serotypes.

There is a remarkable amount of heterogeneity in the estimates of effects across studies. This could be due, in part, to the repetitive, multi-year epidemic cycles of infections associated with those diseases caused by a number of different serotypes of pneumococci [8]; to other secular trends; to variations between studies in the numbers of years included before and/or after introduction of PCV13 in the calculation of the rate ratios; to changes in the sensitivity of surveillance; to study differences in methods of surveillance; or

In this issue of *Clinical Infectious Diseases*, Vadlamudi et al [4] review the evidence of the impact that introducing PCV13 into national children's immunization programs had on both invasive pneumococcal disease (IPD) and other outcomes. PCV13 is a second-generation, conjugate vaccine.

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to actual differences between the populations. The heterogeneity could also be due, in part, to the analytic method employed in the meta-analysis (a simple comparison of incidence rates pre- vs post-introduction of PCV13), which does not account for underlying temporal trends and, in some cases, has produced estimates that were different than those of the original studies (eg, Simonsen et al [9]). Moreover, while the analyses controlled for vaccine uptake, they did not distinguish between countries that had used PCV7 for many years prior to the introduction of PCV13 and those in which PCV7 had been introduced shortly before PCV13 replaced it. This could result in important differences in the baseline incidences of infections due to those serotypes included in PCV7, of infections due to the additional serotypes in PCV13, and/or of infections due to the non-vaccine serotypes, all of which would affect the magnitude of the estimated effects. Additional analyses using this dataset could incorporate trends and cycles in the incidence of pneumococcal infections into the meta-regression models, and also could include analyses stratified by the duration of the PCV7 immunization program prior to the introduction of PCV13.

It is important to understand the reasons for the variability in the net effect of PCVs among the populations described in this review. Flasche et al suggested that the amount of serotype replacement in a population can be predicted by the proportion of colonizing pneumococci in children that are vaccine serotypes before the PCV immunization program is begun [10]; if a large niche for potential colonization is opened for non-vaccine serotypes by the elimination of vaccine serotypes, non-vaccine serotypes have the potential to substantially increase in number by expanding to fill that niche. The larger number of infections they consequently would cause would thus have a bigger effect in reducing the net benefit of the PCV immunization program. This biological variability, together with differences in both surveillance

methods and underlying secular trends in the incidences of pneumococcal infections among studies, leads to a complex picture of reported effects of PCV13 and of serotype replacement. Further, systematic investigations, with clarification of these potentially-confounding variables and adjustment for their potential effects, are needed to fully disentangle the reported variation among the studies and to better understand the overall impact of PCV13.

Looking toward the future, having good epidemiological information about increases in the incidences of pneumococcal infections due to non-vaccine serotypes is important to be able to forecast the possible impact of the next generation of PCVs, which may target 15, 20, or more different serotypes. Therefore, continued investment in programs to gather high-quality, serotype-specific surveillance data about both colonization and infection with pneumococci is critical. The analysis of high-quality epidemiological data with appropriate statistical models, combined with information on costs and benefits, can help to determine the marginal benefit of switching to PCVs with ever more serotypes. Such analyses could also be used to develop optimal strategies for immunization programs, such as targeting different age groups or using different PCVs for immunization. For instance, would it be more beneficial (1) to use PCV13 for both adults and children in the United States, as is currently recommended; (2) to administer PCV20 to all recommended age groups; or (3) to continue to administer PCV13 to children but to administer a PCV with either different or more serotypes to adults? While it is widely accepted that PCV immunization programs have successfully reduced the incidence of pneumococcal infections in children, additional research and further analyses of published studies will help to sort through these critical issues and to optimize the strategies for using PCVs to protect adults.

Notes

Disclaimer. Work on this manuscript was performed solely by the 2 authors. The findings

and conclusions of this paper are those of the authors and do not necessarily represent the official position of the National Institutes of Health.

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