

VIEWPOINT

Developing Better Pneumococcal Vaccines for Adults

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Although preventing pneumococcal disease in adults—specifically, adults 65 years or older and adults with immunodeficiencies—is a clinical and public health priority in the United States, current vaccines are inadequate. It is estimated that *Streptococcus pneumoniae* causes more than 400 000 hospitalizations and more than 16 000 deaths from pneumonia annually among adults in the United States, costing more than \$1 billion.¹ These numbers are likely to increase substantially in the coming decades.¹ At present, the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention recommends that older adults and adults who are immunocompromised receive a dose of pneumococcal protein-polysaccharide conjugate vaccine (PCV13) followed by a dose of pneumococcal polysaccharide vaccine (PPV23).^{2,3} These vaccines target 13 and 23, respectively, of the more than 90 different pneumococcal serotypes; 12 of the serotypes in PCV13 are also included in PPV23. Use of these vaccines in adults, however, has limited effectiveness. A new, adult-specific conjugate vaccine targeting the serotypes that most commonly cause pneumococcal disease could offer substantially greater protection than PCV13 and PPV23 can.

Limitations of Current Pneumococcal Vaccines

For several reasons, the current vaccines have limited effectiveness on serious pneumococcal infections in older adults^{4,5} and adults who are immunocompromised. First, the frequency of serotypes causing pneumococcal disease in adults does not strongly match the serotypes in PCV13. Second, although PPV23 protects against invasive pneumococcal disease, such as bacteremia and meningitis, there is little evidence that it protects against non-bacteremic pneumococcal pneumonia,⁶ which is more common than invasive pneumococcal disease in adults. In contrast, conjugate vaccines, such as PCV13, provide some protection against non-bacteremic pneumococcal pneumonia.⁷

Third, adults living in communities where the uptake of PCV13 in infants is high are already partially protected against the serotypes in PCV13, reducing the benefit of directly immunizing these adults with the same vaccine. The reason is that children who carry pneumococcus in the nasopharynx are the main source of transmission of the bacteria to adults. As a result, the incidence in adults of pneumococcal disease caused by serotypes in PCV13 declined by half within 4 years of PCV13 being used primarily in children.⁸ At the same time, the reduction in the carriage of serotypes targeted by PCV13 in the upper respiratory tracts of children creates an opportunity for serotypes not targeted by the vaccine to colonize these children; this phe-

nomenon is known as *serotype replacement*. These replacement serotypes can be transmitted and thus become frequent causes of pneumococcal disease in adults.⁹

In 2010, PCV13 was introduced for routine immunization of children in the United States and Denmark. Four years later, approximately 25% of cases of invasive pneumococcal disease in older adults were caused by serotypes covered by PCV13, and 75% of cases were caused by serotypes covered by PPV23.⁸ As discussed, non-bacteremic pneumococcal pneumonia is more common among adults than invasive pneumococcal disease and can be prevented by only PCV13 (with limited efficacy) and not by PPV23.⁶ Therefore, the number of cases of non-bacteremic pneumonia preventable with the current vaccines is limited.

New Conjugate Vaccine for Adults

A new vaccine exclusively for older adults and those who are immunocompromised is needed. In our view, the most effective and most feasible approach is to develop a conjugate vaccine targeting serotypes that are different from those in PCV13. Such a vaccine could have fewer serotypes and target the serotypes that cause the most pneumococcal disease in adults, now that PCV13 is widely used in children.

Other approaches to developing a new pneumococcal vaccine have important drawbacks. A vaccine that includes additional serotypes (ie, PCV13 and other serotypes) could be administered to both adults and children. However, as with PCV7 (an earlier vaccine that targeted 7 pneumococcal serotypes and is no longer used) and PCV13, adults would indirectly benefit from any new vaccine used in children and thus reduce the benefit of adults receiving the vaccine directly. Moreover, simply adding serotypes to the current conjugate vaccines could make the new vaccine less likely to pass noninferiority tests of antibody response; thus, regulatory approval might be more difficult. Finally, PCVs are already among the most expensive vaccines, priced at approximately \$160 per dose in the private sector, according to the November 1, 2016, price list of the Centers for Disease Control and Prevention.¹⁰ These vaccines are complicated to manufacture, and adding more serotypes would only make them more costly and complex.

An alternative approach is to develop a vaccine against surface proteins that are present in all pneumococcal strains rather than use a vaccine that targets surface polysaccharides that are present in only some strains (as PCV13 and PPV23 do). Although such a vaccine would be ideal for adults because it would protect against all strains, it is not yet close to clinical use. Such a protein-based vaccine would likely face greater regulatory

scrutiny than would a new conjugate vaccine that merely targets a different set of serotypes.

Challenges of Developing a Conjugate Vaccine for Adults

Our proposal to develop a conjugate vaccine for adults that has a different formulation from that of the vaccine used in children has several challenges. The first is choosing which serotypes to include in the vaccine. The serotypes that are most common at present might not be the most common in several years. Both natural variations in incidence and newer conjugate vaccines that might be introduced in children could influence the serotypes that cause pneumococcal disease in adults. A vaccine that is specifically for adults might require periodic updating so that it can respond to changes in the distribution of serotypes. Accurate forecasts of patterns of serotypes causing pneumococcal disease in adults could help inform the selection of serotypes.

The second challenge is convincing regulatory agencies as well as the Advisory Committee on Immunization Practices and other groups that an alternative formulation provides adequate protection for adults, even if it excludes certain pneumococcal serotypes in the current vaccines. By design, an adult-specific vaccine might exclude some serotypes included in either PCV13 or PPV23 in favor of

other serotypes that more commonly cause pneumococcal disease. Selection of serotypes could be based on the total number of pneumococcal cases they would prevent and should not be restricted by which serotypes are in the current formulation of the vaccine (provided the new serotypes are sufficiently immunogenic).

The third challenge is convincing manufacturers that developing a conjugate vaccine for use in only adults could be profitable. Manufacturers benefit from efficiency of scale if a single vaccine is used for all age groups. As long as the same conjugate vaccines are routinely recommended for use in all age groups, manufacturers have few incentives to develop a vaccine specifically for adults.

Conclusion

In summary, PCV13 and PPV23 have limited effectiveness on disease rates. Because of the distinct distribution of serotypes causing pneumococcal disease in adults and the changes in these serotypes associated with the use of pneumococcal vaccines in children, simply creating a new vaccine with additional serotypes and administering it to both children and adults is unlikely to solve this problem. A compelling solution is to develop a conjugate vaccine for exclusive use in adults while continuing to use PCV13 and PPV23 in children.

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