COVER STORY

PCV13 vaccination highly effective but complicated by serotype replacement

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The winter holidays bring generations of families together. The season also brings a heightened risk for respiratory infections, such as influenza and pneumococcal disease, as children come in close contact with older relatives.

This risk was reflected in one study published in *Clinical Infectious Diseases* by Weinberger and colleagues, which showed that bacteremic pneumococcal pneumonia peaked in late winter. According to the CDC, the populations at greatest risk for developing these diseases include children aged younger than 2 years and adults aged 65 years and older.

“The reasons that both the young and the old are more susceptible to pneumococcal disease than those in the middle years are several,” **Kathryn M. Edwards, MD,** professor of pediatrics at Vanderbilt University School of Medicine, told *Infectious Diseases in Children*. “First, young children have much higher carriage rates of pneumococcal organisms in the nasopharynx than in older ages, and colonization precedes disease. Additionally, the immune systems in both the young and the old are less robust, with poorer responses to vaccines.”

Pneumococcal disease has been prevented by routine vaccination of young children with a pneumococcal conjugate vaccine (PCV) since 2000. The first vaccine included seven serotypes of pneumococcus (PCV7; Prevnar, Pfizer) — 4, 6B, 9V, 14, 18C, 19F and 23F. In 2010, six additional serotypes were included to create PCV13 (Prevnar13, Pfizer) — 1, 3, 5, 6A, 7F and 19A. All children in the United States should

Kathryn M. Edwards, MD, professor of pediatrics at Vanderbilt University School of Medicine, has studied the microbiologic causes of pneumonia in children. She said the public health impact of pediatric pneumococcal vaccination is profound.

Source: Vanderbilt University School of Medicine

receive PCV13 at ages 2, 4 and 6 months, and a booster dose between 12 and 15 months. Additionally, adults aged 65 years and older should receive PCV13 if they have not yet received it and a dose of a pneumococcal polysaccharide vaccine, or PPSV23 (Pneumovax23, Merck), at least 1 year later.

Although vaccination with PCV13 and PPSV23 can prevent infections due to multiple serotypes of pneumococcus in both children and adults, WHO reports that approximately 90 serotypes of pneumococcus exist. Research suggests that the universal use of PCV provides an opportunity for nonvaccine serotypes to cause an increased proportion of pneumococcal disease in a phenomenon known as serotype replacement.

Infectious Diseases in Children spoke with leading pediatric infectious disease specialists about the effectiveness of pediatric pneumococcal vaccination across numerous age groups and the complications caused by serotype replacement.

An effective vaccine

Before the introduction of PCV7, Streptococcus pneumoniae was a major cause of meningitis, pneumonia and bacteremia among vulnerable populations, including young children, older adults and those with immunodeficiencies. According to Reingold and colleagues, the seven serotypes included in PCV7 caused 80% of invasive pneumococcal disease (IPD) in children. The incidence of IPD caused by those serotypes decreased by 77% just 5 years after the introduction of PCV7.

“Pediatricians have really embraced immunization with PCVs, with good reason,” **William Schaffner, MD,** professor of preventive medicine at Vanderbilt University School of Medicine, told *Infectious Diseases in Children*. “The impact on invasive disease in infants, children and adolescents has been very dramatic and profound.”

The effect of pediatric vaccination has also been profound among older adults.

In a study published in the *Journal of Infectious Diseases*, Pilishvili and colleagues found that the introduction of routine PCV7 vaccination in young children reduced the incidence of disease due to serotypes in the vaccine among adults aged 65 years and older by 92% (95% CI, 89-94) by 2007.

However, by 2010, IPD cases due to nonvaccine serotypes began to erode the reductions in disease in both children and adults, according Pelton and colleagues.

In February 2010, the CDC’s Advisory Committee on Immunization Practices recommended immunization with PCV13. According to **Sheldon L. Kaplan, MD,** professor, executive vice chair and head of the section of infectious diseases in the department of pediatrics at Baylor College of Medicine, pneumococcal disease caused by the additional serotypes in PCV13 has significantly decreased since the vaccine’s introduction.

William Schaffner

“Since licensure and use of the 13-valent vaccine, disease due to 19A and 7F have definitely gone down,” Kaplan told *Infectious Diseases in Children*. “People are still seeing quite a bit of disease due to serotype 3, although some studies are finding a little bit of a decline and others are not seeing much of a decrease at all.”

Although adults have experienced the indirect benefits of pediatric vaccination with PCV13, **Eugene D. Shapiro, MD,** professor of pediatrics and epidemiology and vice chair for research in the department of pediatrics at Yale University and an *Infectious Diseases in Children* Editorial Board member, said it is still recommended that adults aged 65 years and older receive PPSV23, which was introduced in 1977.

PCV13 and polysaccharide vaccines like PPSV23 can reduce the likelihood of disease in the adult population, but the CDC’s AdultVaxView showed that uptake among adults aged 65 years and older is weak, with more than one-

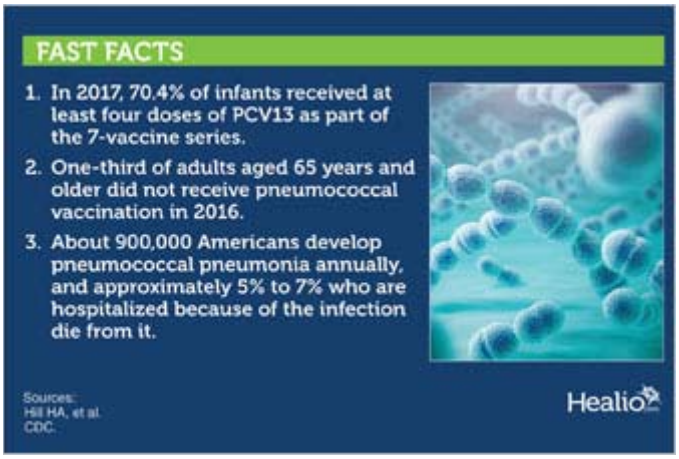
third not receiving pneumococcal vaccination in 2016. Adults aged younger than 65 years with special risk factors, including immunocompromising conditions, are also recommended to be vaccinated with PCV13. This population also reported low rates of pneumococcal vaccination — approximately 75% have never been vaccinated.

Schaffner said part of the reason why vaccine uptake among adults may be low for PCV13 and PPSV23 is because a risk-based system is used to determine whether people aged younger than 65 years should be immunized.

“You have to have a certain condition which makes you eligible to receive one or both vaccines,” he said. “It is a very complicated set of recommendations, and we know that risk-based recommendations are very difficult to implement. This continues to be true for pneumococcal vaccination in adults.”

Kaplan added that internal medicine physicians do not usually stock pneumococcal vaccines in their offices like pediatricians do.

“It is not vaccine refusal as much as vaccination is not convenient,” he said. “Some people think — and it very may well be true — that we really do not need to immunize adults to prevent these 13 serotypes because they are already on the decline due to pediatric vaccination.”



Schaffner added that the burden of reducing rates of pneumococcal disease and improving vaccination rates lies with physicians who care for adults.

“I do not think that we can interfere with hugs and kisses over the holidays,” Schaffner said. “I would think that the emphasis ought to be on doctors who care for adults to make sure that their adult patients are appropriately

vaccinated according to ACIP recommendations. I think that will provide them the best protection against acquiring pneumococci, which might go ahead and produce invasive disease."

'The complexity of pneumococcal epidemiology'

Schaffner said every pneumococcal serotype is "quite individual," and that PCV13 does not protect against colonization or disease from serotypes that are not included in the vaccine.

"From an immunization point of view, there is hardly any cross-protection," Schaffner said. "The notion of serotype replacement is that if you immunize people against a certain number of serotypes and they are protected from those, that may create an ecological niche in the nasopharynx where less common pneumococcal serotypes will begin to take advantage, colonize and start to cause disease."

Eugene D. Shapiro

When PPSV23 was first introduced, Shapiro said serotype replacement was not a regular phenomenon because polysaccharide vaccines do not affect colonization.

"As an example, if you were colonized with serotype 14 and you received a polysaccharide vaccine, nothing would happen," he said. "If you were colonized with serotype 14 and you received the pneumococcal conjugate vaccine, you develop immunity that also extends to colonization. It is not 100% effective, but it is quite likely that the frequency in which people are colonized goes down and can go down substantially. That sort of opens a niche for other serotypes to come in."

Pneumococcal epidemiology can be complex, particularly with serotype replacement. For example, Cohen and colleagues observed that the number of cases of IPD caused by PCV7 serotypes decreased in France by 90% between 2001 and 2012. However, the country saw "important serotype replacement" following PCV7's introduction in 2003, according to researchers. They theorized that the prevalence of nonvaccine serotypes before the vaccine was implemented was "probably a major factor in determining replacement." In addition, relatively low vaccine uptake combined with the lack of a catch-up program may have accelerated serotype replacement, they said. The speedy introduction and uptake of PCV13, however, limited this phenomenon.

“These findings underline the complexity of pneumococcal epidemiology and the importance of high and fast vaccination coverage,” Cohen and colleagues wrote. “The need for long-term surveillance of both IPD and carriage to determine the formulation of extended future PCVs is crucial.”

Serotype replacement may be more common in countries other than the United States. Kaplan theorized that one of the reasons why adults in other countries may not experience the same degree of protection through childhood immunization is differing vaccine schedules.

“In the United Kingdom, they have what is called a two-plus-one schedule, where they give the first two doses plus a booster dose, but they do not give a dose at 6 months,” he said. “They are even considering dropping one of the first two doses. Other countries give the first three doses but do not give a booster dose.”

Kaplan further explained that populations in other countries have varying degrees of exposure to pneumococci. He said it is difficult to pinpoint the exact reason why the effects of serotype replacement may be different in other parts of the world.

Edwards, who is an *Infectious Diseases in Children* Editorial Board member, said that an assessment of serotype prevalence in each country could help researchers better understand how the pneumococcus impacts disease and colonization around the world.

Vaccine strategies

Increasing rates of pneumococcal disease caused by nonvaccine serotypes may be addressed by adjusting the composition of certain vaccines. One possibility would be to add more serotypes that are causing disease to the vaccine. However, Shapiro doubts this would help.

“The problem is that serotype replacement may still happen if we make a new vaccine with more serotypes,” he said. “What some people think we should be doing is giving children PCV13 and giving a different conjugate vaccine to adults. Just by giving PCV13 to children, we are eliminating most disease in adults caused by those 13 serotypes. It seems a waste to give it to adults, but if we could predict which serotypes are most likely to cause replacement disease, we could — in theory — design a vaccine that targets those serotypes. You are always going to be chasing your tail a bit, but presumably, there are some types that are not going to cause disease at all.”

Sheldon L. Kaplan

Schaffner hinted at the difficulties surrounding the development of a vaccine with additional serotypes.

“If we look at the global epidemiology of pneumococcal disease, would we need to identify distinctive regional differences so that one might tailor-make a vaccine for Asia, Africa, Eastern Europe or another location and have them be different?” he asked. “And if the effect in the U.S. is so powerful, should we look at the residual cases of invasive pneumococcal disease in adults and create an adult-specific vaccine designed to target those serotypes? I think that would probably make manufacturers go cross-eyed. It gets very complicated, and it is not entirely clear — at least in the U.S. — that the residual disease in adults would justify the entire expense of creating and having to get an entirely new vaccine licensed in adults.”

Currently, Merck is recruiting participants for two phase 3 studies to examine the safety and efficacy of a PCV containing 15 serotypes (V114). These studies will include participants aged 50 years and older with and without HIV. Previous phase 1 and 2 studies included healthy adults and toddlers.

‘Changing the face of severe disease’

According to a review published in *Influenza and Other Respiratory Diseases* by **Jane C. Deng, MD,** from the University of Michigan, 25% to 30% of pneumonia patients requiring hospitalization and 50% of all autopsies conducted during the 2009 influenza pandemic had an identifiable bacterial superinfection. Edwards said that influenza may trigger bacterial pneumonia and further explained that it is important for physicians to understand the relationship between viral and bacterial infections.

“During influenza season, superimposed bacterial pneumonia with staph and with pneumococcus are seen more commonly,” Edwards said. “One thing we are questioning is if you are infected with a virus and you have pneumococcus in your throat, does that somehow contribute to the enhanced growth of bacteria? Does the fact that a patient has a respiratory infection and they sneeze and cough because of the viral infection make the transmission of pneumococcus greater because they are sneezing? The relationship between viruses and bacteria and how they play off one another is very intriguing, and we are trying to better understand this now.”

A 2015 study published in the *New England Journal of Medicine* — of which Edwards was a co-author — examined the microbiologic causes of pneumonia in 3,803 children. This study demonstrated that 66% of hospitalized children with radiographically confirmed pneumonia had at least one viral pathogen detected, 8% had a bacterial cause identified and 7% had a disease caused by both viral and bacterial pathogens. During a presentation at the annual *Infectious Diseases in Children* Symposium, Editorial Board member **C. Buddy Creech, MD, MPH,** from Vanderbilt University School of Medicine, said that viral pathogens, including human rhinovirus and RSV, “rule the roost” with pneumonia.

Laboratory evidence from several investigations suggested that people may become more susceptible to bacterial infections, including those caused by S. pneumoniae, between 4 to 14 days after infection with influenza.

Although Edwards said more studies are needed to better understand the causes of pneumococcal disease, as well as the role of serotype replacement in shaping its complex epidemiology, she stressed “how enormously important” PCV vaccines have been and asked physicians not to lose sight of their public health impact.

“We do not see Haemophilus influenzae meningitis, and we do not see much pneumococcal meningitis anymore,” she said. “The impact of these potent conjugate vaccines has really been remarkable in terms of changing the face of severe disease in children.” – *by Katherine Bortz*

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