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Keeping Pneumonia's Vaccines Effective

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Streptococcus pneumoniae certainly can't be trusted. Rather than live in the soil or on kitchen counters, this microbe makes its home among neighborly bacteria inhabiting the nasopharynx of preschool children. Most of the time, colonies hang around for a while and then harmlessly disappear. Other times, *S. pneumoniae* escapes the safe borders of this tiny neighborhood, travels to the inner ear, lungs, or bloodstream, and sparks a variety of illnesses ranging from otitis media to meningitis and pneumonia. Of these invasive pneumococcal diseases, as they're called, pneumonia is the largest public health threat. The World Health Organization describes pneumonia as the leading cause of death in children worldwide, accounting for nearly two million deaths each year. *S. pneumoniae* is the major bacterial pneumonia pathogen.

S. pneumoniae *won't let vaccine designers off the hook so easily.*

Scientists can tell the serotypes of *S. pneumoniae* apart by the polysaccharides that coat the capsule. To date, more than 90 serotypes have been identified. Not all 90 serotypes cause disease, but those that do differ worldwide.

The only weapons against pneumococcal pneumonia are antibiotics and vaccines. Children under 5 years of age and adults over 65 are most susceptible to pneumonia and need the boost from a vaccine. The PPSV23 is a polysaccharide vaccine recommended for adults over 65 and for younger adults who are smokers and who take immune-suppressing drugs. That vaccine won't work in young children, though, because their immune systems can't make antibodies to the polysaccharide coating on the bacteria's capsule. Making a conjugate vaccine by chemically linking the sugars to a protein makes the complex recognizable to the immune systems of infants and young children. Babies' immune systems recognize the protein, and while their immune systems recognize the protein, the systems recognize the polysaccharides as well and induce immunity to both.

"Conjugate vaccines changed the infectious disease world; they totally change the body's immune response," says Edwin L. Anderson, M.D., a vaccine expert at Saint Louis University in St. Louis, Missouri. "If you conjugate the polysaccharide to a protein carrier, then a body's response is a T cell response, meaning it's cell-mediated immunity and with a long-term response, because T cells have a memory."

In 2000, Wyeth (now Pfizer) introduced a conjugate vaccine against the seven most virulent and prevalent serotypes: 4, 6B, 9V, 14, 18C, 19F, and 23F. In the United States, 80% of pneumococcal disease in children 5 years of age is caused by those seven serotypes. Over the past decade, pneumococcal disease caused by serotypes covered in PCV 7 has dropped. Since children are the ones that carry *S. pneumoniae* in their nasal passages, stopping these serotypes in vaccinated children helps protect people of all ages via herd immunity. In 2010, Pfizer introduced PCV 13, which covers the original seven serotypes and six more. The vaccine is licensed in infants and is currently in phase III testing for use in adults.

It's Complicated

With *S. pneumoniae*, nothing proves simple. Since the introduction of PCV 7, other strains not covered by the vaccine are emerging as problems. The most notorious is 19A, which is now the most prominent pneumococcal serotype in the United States. "It makes sense that we're seeing strains not covered in the vaccine," says Rachel Orsheln, M.D., an infectious disease specialist at Washington University in St. Louis, Missouri. "We knew that 19A was a strain that caused invasive pneumococcal disease, and that strain is drug resistant. We just thought the strains in the vaccine would provide some cross-protection; as it turned out, it didn't."

The hope for cross-protection and the real breakthrough for the pneumonia vaccine came in the 1980s with the development of a conjugate vaccine for *Haemophilus influenzae type b*. Since the introduction of that vaccine, all serotypes (A through F) have disappeared. "That organism startled everyone because that disease has been eradicated in every country where vaccine was introduced and there was no replacement with other serotypes," says Steve Black, M.D., of Cincinnati Children's Hospital Medical Center, in Ohio.

Haemophilus influenzae type b vaccine helped boost confidence among vaccine researchers as to how well a conjugate vaccine could work against pneumococcal diseases. The challenge in designing the first pneumococcal vaccine was choosing the serotypes that cause the majority of disease and then making conjugates for all seven serotypes individually to proteins in such a manner that babies could respond to all seven, says Peter Paradiso, Ph.D., vice president of new business and scientific affairs at Pfizer. "This was a big step going from a vaccine that had one serotype to a vaccine that had seven," he says.

Paradiso and his colleagues hoped that PCV 7 would also confer cross-protection against serotypes that were similar in polysaccharide composition just as the *Haemophilus influenzae type b* vaccine did. However, serotypes of *Haemophilus influenzae type b* are mostly clones of one another and the genome is stable, so stopping one serotype put an end to them all. This is why the vaccine for tetanus toxin has been stable as a vaccine candidate for so many years, explains Black.

S. pneumoniae won't let vaccine designers off the hook so easily. To understand why, think of all bacteria as sitting along a spectrum from organisms that don't undergo any transformation to organisms that do. If you put the pneumococcus on that spectrum, it's much more

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of a change artist than *Haemophilus type b*, explains Black: "You can guess that by the fact that there are so many serotypes and they change over time." Mix in the dynamics of antibiotic use and vaccines and a dynamic epidemiology emerges. *S. pneumoniae* exchanges genetic information from one serotype to the other. After such an exchange, pathogenic serotypes will put on the cloak of less pathogenic serotypes and cause disease. "That's what natural selection is all about. Unlike the dodo bird, which couldn't sprout wings and became extinct, the pneumococcus is not intent on that happening," says Black.

Vaccine developers have to adapt as well. Nearly as soon as the PCV 7 vaccine was unveiled in 2000, Wyeth began working on PCV 13. Now, two companies have pneumococcal vaccines with more than seven serotypes. GlaxoSmithKline has a new vaccine called Synflorix that protects against ten serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F). Pfizer's Prevnar 13 includes the original seven in the first vaccine, plus 1, 3, 5, 6A, 7F, and 19A.

Pfizer's Paradiso says, "We didn't say 'we have seven let's just add six more.' We wanted to make this vaccine more worldwide so we included serotypes1 and 5, which are prevalent in sub-Saharan Africa and can be epidemic. We added 6A and 19A, which brought us up to eleven serotypes. Then, worldwide data indicated that 3 and 7F were important."

Protein Targets and Beyond

Even with the introduction of a 13-valent vaccine, other serotypes will emerge, because that's what serotypes do. Over time, the incidence of serotypes rises and falls in different parts of the world. Black has a graph in a recent commentary published in the *Pediatric Infectious Disease Journal* that tracks the change in serotypes over the last 29 years in Spain. Some serotypes can emerge as new clones and spread in months (Black, 2010). "Given air travel and the way people move around these days, time frame is compressed," says Black.

Factor in the decade spent by pharmaceutical companies developing pneumococcal vaccines and then shepherding them through the regulatory process and the fact that vaccines can only protect against a given number of serotypes, and serotypes like 19A can easily surface. "These vaccines, in my opinion, won't solve the whole issue. Everyone is searching very hard for alternative strategies, including common proteins to all pneumococci. We will have to go to these strategies. Conjugated vaccines will buy us time, but no more," says Elizabeth Sanders, M.D., Ph.D., a clinical scientist in the Netherlands.

Sanders got started in clinical research because she sees so many children in her medical practice with otitis media and respiratory tract infections. She and her colleagues undertook a post hoc analysis of a randomized controlled trial in the Netherlands that aimed to see whether reducing the dose schedule would delay colonization with serotype 19A. Antibiotic use in the Netherlands is relatively low compared to the United States, so Sanders figured her study would prove the rise in 19A could be attributed to PCV 7 and not antibiotics. The study published recently in JAMA showed that infants in the reduced dosage group were more likely to have serotype 19A in their nasopharynx, so PCV 7 pressed for colonization with 19A (van Gils et al., 2010).

For at least the past 10 years, scientists have looked beyond conjugate vaccines and have searched for proteins common to all serotypes. One protein may not be enough, says Paradiso, and may need to be added to a conjugate vaccine. Because *S. pneumoniae* are such change artists, any protein could also change as the genomes change. Thus far, none of the protein vaccines has entered clinical trials.

As scientists deal with organisms that are smarter and smarter in terms of their ability to adapt, scientists need to adapt their approach as well. Black supports a solution that he describes as controversial because it's new. If, for example, serotype 2, which is most common in Bangladesh, suddenly took off worldwide, a pneumonia epidemic could occur because no current vaccine contains that serotype. The chemistry for making a new conjugate may take a bit over 1 year. However, the toxicity testing in animals and the subsequent clinical trials bring the process to 10 years. This time frame could be shortened if vaccine manufacturers could switch out, say, serotype 2 with a serotype that wasn't such a problem at the time and then simply using the vaccine.

Such an effort is already in place for the influenza vaccine, which changes every year in composition but is not viewed as an entirely new vaccine, which 13-valent Prevnar was, says Black. If the influenza vaccine had to undergo regulatory testing every time the vaccine changed, 10 years would be required to roll out a new vaccine that would always be a decade behind. "We're going to have to change our frame of reference in terms of development of regulatory controls to allow for more rapid response to changes, or we'll always be behind the eight ball," says Black.

REFERENCES

Black, S. (2010). The volatile nature of pneumococcal serotype epidemiology potential for misrepresentation. Pediatr. Infect. Dis. J. *29*, 301–303.

van Gils, E.J.M., Veenhoven, R.H., Hak, E., Rodenburg, G.D., Keijzers, W.C.M., Bogaert, D., Trzcinski, K., Bruin, J.P., van Alphen, L., and van der Ende, A. (2010). Pneumococcal conjugate vaccination and nasopharyngeal acquisition of pneumococcal serotype 19A strains. JAMA *304*, 1099–1106.

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