

# Researchers Raise Alarm Over Resistant AOM Bug

BY KATE JOHNSON  
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A strain of *Streptococcus pneumoniae* that is resistant to all antibiotics approved to treat acute otitis media in children has been identified as an otopathogen.

The multidrug-resistant serotype 19A strain is not included in the pneumococcal 7-valent conjugate vaccine (PCV-7), reported Dr. Michael E. Pichichero and Dr. Janet R. Casey, from the University of Rochester Medical Center and Legacy Pediatrics, a private practice involved in the study (JAMA 2007; 298(15):1772-1778).

Children with the serotype 19A strain "represented a small subset of those in our practice, but the results are worrisome, especially since there are no new antibiotics in the pipeline for ear infections in children," said Dr. Pichichero in a statement.

"While it appears that the overall decrease in invasive pneumococcal disease still outweighs the increase in serotype 19A, it is clear that surveillance needs to continue for this important pathogen, both for strain type and antibiotic resistance," commented Dr. Elizabeth Bancroft, from the Los Angeles County Department of Public Health, in an editorial (JAMA 2007;298:1803-4).

The prospective study included 212

children from the authors' clinic who underwent tympanocentesis for acute otitis media (AOM) during one of three respiratory seasons: September 2003–June 2004, September 2004–June 2005, and September 2005–June 2006. All children had been previously immunized with the PCV-7 vaccine.

From the tympanocentesis procedures, a pathogen was identified in 162 cases: nontypable *Haemophilus influenzae* (n = 94); *S. pneumoniae* (n = 59); and other (n = 9). Serotyping of the 59 *S. pneumoniae* pathogens revealed 9 that belonged to serotype 19A, which is resistant to all antibiotics approved by the Food and Drug Administration for the treatment of AOM in children.

Infections caused by the serotype 19A strain "continued to produce symptoms and signs of AOM until aggressive therapy was provided—either surgery or levofloxacin, an antibiotic unapproved for children," the authors noted.

While the incidence was the same in the first two respiratory seasons, with two cases each in the 2003-2004 and 2004-2005 seasons, it increased to five cases in the 2005-2006 season. None of the first four cases was treated with effective antibiotics "because we did not perform antibiotic susceptibility testing (or serotyping) contemporaneously as we did in 2005-2006," they wrote.

The first four cases were referred to an otolaryngologist for tympanostomy tube insertion, "and all continued with drainage

from their tubes for 1-4 weeks despite use of antibiotic otic drops."

The five cases from the 2005-2006 season all recovered fully after treatment with levofloxacin.

Although the American Academy of Pediatrics' recent position statement regarding the use of fluoroquinolones in children did not include AOM, "acute otitis media caused by the 19A strain described in this report would be an appropriate infection to treat with a fluoroquinolone," wrote the authors.

"Our approach has been to use levofloxacin only for children in whom we have performed tympanocentesis and isolated a 19A serotype organism that is susceptible only to that drug."

But the authors cautioned that "this information is shared with concern that some clinicians and the public will interpret this finding as an indication to begin using levofloxacin or other fluoroquinolones in difficult-to-treat cases of AOM, sinusitis, or other pneumococcal infections. This could lead to disastrous results."

The authors suggested that "an expanded pneumococcal conjugate vaccine to include additional serotypes may be needed sooner than previously thought," noting that U.S. trials are underway of a vaccine containing 13 serotypes, including 19A.

They suggested that "in the near future" more primary care clinicians may need to become trained to perform tympanocentesis in order to avoid the excessive use of fluoroquinolones in children.

"It isn't going to be easy for the rank and file pediatricians to do that," commented Dr. Ellen R. Wald, professor and chair of the department of pediatrics at the University of Wisconsin, Madison, and chair of the section of infectious diseases on the American Board of Pediatrics.

"What this study highlights is that when you have a clinical failure [with AOM] it's probably important in this era to be able to send the patient somewhere where [tympanocentesis] can be done. Although serotyping is not routinely performed, susceptibility testing would identify an organism that required treatment with fluoroquinolones," she said.

This is yet another example of why judicious use of all antibiotics, not just fluoroquinolones, is essential, said Dr. Wald.

"We should really reserve antibiotics for situations in which we're highly suspicious that there's a bacterial infection.

Both Dr. Pichichero and Dr. Carey report that they have received support for otitis media trials from Ortho-McNeil, maker of levofloxacin, and that they have received compensation for consulting, speaking, and conducting clinical trials of antibiotics and vaccines from multiple companies, including Wyeth, which has a 13-valent pneumococcal conjugate vaccine in phase III trials. ■



**The results are worrisome, since there are no new antibiotics in the pipeline for ear infections in children.**

DR. PICHICHERO

# As MDR *S. pneumoniae* 19A Spreads, Penems Show Promise

BY BRUCE K. DIXON  
Chicago Bureau

CHICAGO — The multidrug-resistant *Streptococcus pneumoniae* serotype 19A continues to spread across the United States, according to a study led by Dr. David J. Farrell.

"And we believe that that the emergence of this 19A clone has been driven by the 7-valent pneumococcal conjugate vaccine," Dr. Farrell said in an interview during a poster presentation at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

Dr. Farrell, director of clinical microbiology at G.R. Micro Ltd., a London-based company that does contract research for pharmaceutical companies, and his colleagues collected more than 21,000 *S. pneumoniae* samples from 103 U.S. centers within the 4 years of the global PROTEKT (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin) study.

In all, 562 of the isolates were the multidrug-resistant (MDR) 19A strain, Dr. Farrell said at the meeting, which was sponsored by the American Society for Microbiology.

Between 2002 and 2006, the proportion of isolates that were MDR 19A increased from 1% to 6%. The largest proportion was in the group aged 0-2 years (rising from 4% to 15%), followed by the group aged 3-14 years (1% to nearly 9%). In the group of those aged at least 65 years, MDR 19A accounted for 3% of all isolates in 2005-2006, said Dr. Farrell in an interview.

"So we've got this 19A serotype that's not in the vaccine, it's being driven by the vaccine, and it's becoming more prevalent and spilling over to older children and adults, including the elderly population."

A second study examining antimicrobial resistance patterns among *S. pneumoniae* isolated from children showed that the experimental oral penem antibiotic, faropenem, was the most potent oral  $\beta$ -lactam based on in vitro activity.

During the 2005-2006 respiratory season, *S. pneumoniae* isolates were prospectively collected from 104 participating institutions distributed across the United States as part of the faropenem surveillance (FAMOUS) study. In total, 393 isolates were collected from children aged 6-14 years, 3-5 years, and younger than 2 years.

The isolates were then tested for susceptibility to faropenem, meropenem, amoxicillin/clavulanate, cefdinir, cefuroxime, penicillin, azithromycin, levofloxacin, and trimethoprim/sulfamethoxazole.

Multidrug resistance was defined as resistance to either two or three of these agents, said Ian A. Critchley, Ph.D., the director of microbiology at Replidyne Inc., in Louisville, Colo., which is evaluating faropenem.

Of the 393 *S. pneumoniae* isolates from children younger than age 14 years, half were penicillin susceptible, one-fourth were penicillin intermediate, and another fourth were penicillin resistant, the authors stated.

Faropenem was the most active  $\beta$ -lactam against all pediatric isolates, with a minimum inhibitory concentration required

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DR. FARRELL

to inhibit the growth of 90% of organisms (MIC<sub>90</sub>) of 1 mcg/mL. The MIC<sub>90</sub> of both amoxicillin/clavulanate and cefdinir was 8 mcg/mL.

The least effective agents were penicillin, azithromycin, and trimethoprim/sulfamethoxazole, with percent-susceptible rates of 49, 55, and 57, respectively.

Antimicrobial resistance was generally higher among isolates from children aged younger than 2 years, compared with isolates from those aged 6-14 years, the authors reported.

Penicillin resistance ranged from 15% among isolates from children aged 6-14 years to 31% among isolates from children younger than 2 years.

"Among children under age 2 years, [in whom] there's been wide use of  $\beta$ -lactams and macrolides, we saw that the penem compound holds out very favorably in our in vitro minimum inhibitory concentration (MIC) profile, when compared with amoxicillin/clavulanate and cefdinir," said Dr. Critchley. Among the *S. pneumoniae* resistant to three classes of agents, only 29% were susceptible to amoxicillin/clavulanate, and none of the isolates was susceptible to cefdinir, he said.

In a separate comment, Dr. Stephen I. Pelton said MDR 19A should be suspected in children with persisting signs and symptoms of acute otitis media despite antimicrobial therapy.

"Some of these isolates will be susceptible to high-dose Augmentin or a three-dose regimen of intramuscular ceftriaxone, but others may not," said Dr. Pelton, chief of pediatric infectious disease at Boston Medical Center.

Tympanocentesis with or without tube insertion will offer symptomatic benefit for those with treatment failure or persistent earache, irritability, or other symptoms, Dr. Pelton said in an interview. "The 19A strain was intermediate resistant in 2000, and it is both the [PCV7] vaccine's lack of cross-reactivity and the presence of resistance that has selected for the increase in 19A," he said. ■

