Resistance to antibiotics among bacteria has been described with increasing frequency over the past 2 decades, advice, alarm, and admonishment have been repeatedly voiced by experts in infectious disease and public health. In community-based pediatric medicine, the focus has been on pneumococci because it was the most frequent cause of bacterial respiratory infections, especially acute otitis media (AOM), which is the most commonly treated bacterial infection in children.

The introduction in 2000 of a pneumococcal 7-valent conjugate vaccine (PCV7) in the United States offered considerable promise in curtailing pneumococcal infections in children, with a particularly favorable impact on penicillin- and multidrug-resistant strains.1-3 In the early years following widespread use of PCV7, the incidence of invasive pneumococcal disease decreased by 69%1 to 91%5 and the incidence of AOM decreased by 20%.5 Vaccination with PCV7 also has been shown to reduce the frequency of persistent and recurrent AOM by 24%6 and the frequency of AOM leading to tympanostomy tube insertion by 24% to 39%.7 8 9

For editorial comment see p 1803.

The herd immunity impact of implementation of a national immunization program that recommended PCV7 for all infants and young children also produced a significant reduction in pneumococcal disease in unvaccinated children and adults, including elderly persons.1 4 9 Since the strains of pneumococci included in PCV7 were often resistant to multiple antibiotics, a reduction of infections caused by these strains was anticipated to also relieve the therapeutic challenges of producing favorable outcomes with standard antibiotic treatment.10 12

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Soon after widespread use of PCV7 was achieved, epidemiologists, microbiologists, clinicians, and public health authorities detected signs of impending problems. Beginning in 2003, just 3 years after licensure of PCV7 in the United States, reports began to appear of increasing isolations of non-PCV7 serotypes of pneumococci; the strains were found in the nasopharynx of children with AOM and with invasive disease.\textsuperscript{5,13-17} At first, the non-PCV7 strains were reported to be generally susceptible to antibiotics; in particular, penicillin-resistant strains were relatively uncommon.\textsuperscript{8,22} This quickly changed, such that more recent reports described a rising prevalence of penicillin- and multidrug-resistant pneumococci among non-PCV7 serotypes.\textsuperscript{23-29} Emergence of these non-PCV7 strains appears to have occurred as a consequence of replacement of PCV7 strains, unmasking of non-PCV7 strains, and capsular switching among strains.\textsuperscript{23,25,26,30} In 2007, Singleton et al\textsuperscript{31} reported that serotype 19A organisms had emerged among Alaska native children in 2004-2006 as an important replacement serotype strain causing invasive pneumococcal disease. Fortunately, these serotype 19A strains were not multidrug-resistant.

Our group has been monitoring otopathogens in the United States by performing tympanocentesis in children with AOM, mostly those with AOM treatment failure (AOMTF) and recurrent AOM. In 2004, we described a major shift in the distribution of pathogens that cause AOM and a change in antibiotic susceptibility patterns.\textsuperscript{6} After the introduction of PCV7 immunization of infants and toddlers, we observed a significant decline in AOM caused by pneumococci and an increase in the isolation of penicillin-susceptible organisms.\textsuperscript{6} Concomitantly, a proportionate increase in isolation of nontypeable \textit{Haemophilus influenzae} was seen.\textsuperscript{6} In this report, we describe the frequency of isolation of pneumococci from children with AOM, the capsular serotypes, and the antibiotic susceptibility of strains isolated between September 2003 and June 2006.

**METHODS**

**Patient Population**

The children enrolled in this study were part of a multiyear prospective, longitudinal investigation to characterize \textit{S pneumoniae} that caused AOM in children. Two populations of healthy 6- to 36-month-old children were included in the study: (1) children experiencing their first or second AOM episode in life and (2) children with difficult-to-treat AOM, including those with recurrent AOM and those with AOMTF. Children with any immunocompromise or anatomical defect that would make them prone to otitis were excluded. All children were recruited from our suburban private pediatric clinic. Middle ear fluid samples were obtained by tympanocentesis between September 2003 and June 2004, September 2004 and June 2005, and September 2005 and June 2006, hereafter referred to as 3 respiratory seasons. From each patient we ascertained age, sex, AOM history, recent antibiotic treatment, and PCV7 vaccination status. The study was approved by the University of Rochester Institutional Review Board and written informed consent was obtained from parents or guardians for the study and for all tympanocentesis procedures.

Diagnosis of AOM was made by criteria endorsed by the American Academy of Pediatrics (AAP),\textsuperscript{32} except that in all cases, the presence of a bulging or full tympanic membrane was required. Acute otitis media treatment failure and recurrent AOM were defined by previously described criteria.\textsuperscript{33} Specifically, AOMTF required the persistence of the symptoms and signs of AOM after at least 48 hours of antibiotic therapy or AOM persisting after the completion of an appropriate antibiotic treatment course. Recurrent AOM required 3 episodes of AOM within the previous 12 months. In the current study, all AOMTF patients had been unresponsive to 2 (in some cases, 3) treatment courses with antibiotics, always including amoxicillin or amoxicillin-clavulanate at a dose of 80 to 100 mg/kg/d administered twice daily and 3 injections of ceftriaxone on 3 separate sequential days. Referral for tympanostomy tubes occurred when AOM persisted after tympanocentesis had been performed and failed to respond to an additional course of antibiotic therapy.

**Microbiology**

\textit{Streptococcus pneumoniae} isolates were classified as penicillin-susceptible (minimum inhibitory concentration (MIC) <0.06 µg/mL), penicillin-intermediate-resistant (MIC 0.1-1.0 µg/mL), or penicillin-resistant (MIC ≥2.0 µg/mL) according to Clinical and Laboratory Standards Institute criteria using an ETest (AB Biodisk, Piscataway, New Jersey).\textsuperscript{34} The ETest or micro broth dilution method was also used to determine susceptibility of the pneumococci to other antimicrobials approved by the US Food and Drug Administration (FDA) for treatment of AOM, including amoxicillin, erythromycin, clarithromycin, azithromycin, trimethoprim-sulfamethoxazole, cefaclor, loracarbef, cefprozil, cefuroxime, cefpodoxime, cefixime, cefdinir, cefibuten, and ceftriaxone, as well as the non–FDA-approved agents clindamycin, vancomycin, tetracycline, chloramphenicol, rifampin, telithromycin, ciprofloxacin, and levofloxacin. All microbiology evaluations were performed in the laboratory of 1 of us (M.E.P.) in the Department of Microbiology and Immunology at the University of Rochester in Rochester, New York, and confirmed in the laboratory of Gary Doern, PhD, University of Iowa, Iowa City.

**Serotyping**

Serotyping of \textit{S pneumoniae} was performed by latex agglutination and confirmed by quellung reaction with type-specific capsular antiserum from the

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Statens Serum Institute (Copenhagen, Denmark).

**Multilocus Sequence Typing of S pneumoniae**

Multilocus sequence typing (MLST) used the internal fragments of 7 housekeeping genes, *aroE* (shikimate dehydrogenase), *gdh* (glucose-6-phosphate dehydrogenase), *gki* (glucose kinase), *recP* (transketolase), *spi* (signal peptidase I), *xpt* (xanthine phosphoribosyltransferase), and *ddl* (D-alanine-D-alanine ligase), to characterize the pneumococcal strains. The sequences at each of the 7 loci were then compared with the sequences of all of the known alleles at those loci in the database at the pneumococcal MLST Web site (http://www.mlst.net). New allelic number or new sequence type number was assigned by a curator at the pneumococcal MLST Web site (http://www.mlst.net). The specific serotypes (PCV7 and non-PCV7) of pneumococci isolated in each of the 3 respiratory seasons are shown in Table 1. From September 2003–June 2004, 12 of the 16 *S pneumoniae* (75%) that expressed capsular serotypes included in PCV7 were penicillin-nonsusceptible *S pneumoniae* (penicillin-resistant *S pneumoniae* and penicillin-intermediate-resistant *S pneumoniae*); the proportion of strains expressing PCV7 serotypes that were penicillin nonsusceptible did not change over the 3-year study time frame. In contrast, the proportion of non-PCV7 strains of *S pneumoniae* that were penicillin nonsusceptible did change over time, from 3 of 12 (25%) in 2003–2004 to 13 of 14 (93%) in 2005–2006 (P < .001) (Table 2).

Among the 12 pneumococcal isolates with serotypes not included in PCV7 in the 2003–2004 respiratory season, 2 (17%) were a serotype 19A strain that was multidrug-resistant. In the 2004–2005 respiratory season, 2 of 8 (25%) and in the 2005–2006 respiratory season, 5 of 14 (36%) pneumococcal isolates proved to be the same multidrug-resistant serotype 19A strain. We performed MLST on these 9 serotype 19A pneumococcal strains and all appeared to be the same clone with an unreported sequence type now assigned MLST number 2722. The strain is closely related to MLST 156, seen in *S pneumoniae*–expressing serotypes 9/9V/9F, 11, 14, and 19F.

By MIC₉₀ testing, this serotype 19A strain demonstrated resistance to penicillin, 8 µg/mL; amoxicillin, 8 µg/mL; trimethoprim, >32 µg/mL; erythromycin, >32 µg/mL; clarithromycin, >32 µg/mL; azithromycin, >32 µg/mL; clindamycin, >64 µg/mL; tetracycline, >16 µg/mL.

### RESULTS

During the study time frame, 1816 children were seen for AOM; 375 had a first or second AOM episode, recurrent AOM, or AOMTF. Fifty tympanocenteses were performed in 48 children: 48 for the first episode of AOM, then 2 children had a second tympanocentesis for a second episode of AOM. Of 203 children with AOMTF or recurrent AOM, 162 had a tympanocentesis and 41 did not. Tympanocentesis was not performed because parents declined consent or logistical barriers precluded performing the procedure in the clinic. Among the 212 tympanocenteses procedures, an otopathogen grew in 162. Non-PCV7 pneumococci were isolated for each respiratory season and the percentage for that season.

### Statistical Analysis

Differences in groups were analyzed with the χ² test or test of proportions, and P < .05 (2-tailed) was considered significant. Analyses were performed using Primer of Biostatistics, version 4.0 (McGraw-Hill, Columbus, Ohio).

### Table 1. Cases of Pneumococcal Acute Otitis Media by Serotype and Respiratory Season Among Rochester, New York, Children

<table>
<thead>
<tr>
<th>Year</th>
<th>PCV7 Serotypea</th>
<th>Non-PCV7 Serotypea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>No. of Cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total (%)b</td>
</tr>
<tr>
<td>2003–2004</td>
<td>1 4 9 15 16</td>
<td>3 1 2 2 2 1 1 1 1 14</td>
</tr>
<tr>
<td>2004–2005</td>
<td>1 1 2 4</td>
<td>1 2 1 2 1 1 8</td>
</tr>
<tr>
<td>2005–2006</td>
<td>1 5 6 1</td>
<td>1 1 5 1 1 1 1 1 1 14</td>
</tr>
</tbody>
</table>

Abbreviation: PCV7, pneumococcal conjugate vaccine containing 7 serotypes. The decrease in isolation of PCV7 serotypes and increase in non-PCV7 serotypes over time are both significant at P < .001. Total number of *Streptococcus pneumoniae* isolates for each respiratory season and the percentage for that season.
The AOM infections caused by the S pneumoniae 19A serotype organisms continued to cause symptoms and signs of AOM until aggressive therapy was provided (either surgery or levofloxacin). Table 3 describes the 9 children from whom we isolated pneumococci expressing the serotype 19A strain and their treatment outcomes. Two cases came from the group of children undergoing a tympanocentesis for their first episode of AOM (both were in day care) and 7 cases were children with AOMTF, recurrent AOM, or both. None of the 4 cases from the 2003-2004 or 2004-2005 respiratory seasons were treated with effective antibiotics because we did not perform antibiotic susceptibility testing (or serotyping) contemporaneously as we did in 2005-2006. Those 4 cases (cases 1, 3, 4, and 5) are remarkable because all 4 had continued drainage from their tympanocentesis site after additional antibiotic therapy, all were therefore referred to an otolaryngologist for tympanostomy tube insertion, and all continued with drainage from their tubes for 1 to 4 weeks despite use of antibiotic otic drops. In our clinic, about 2% of children with AOM overall and about 10% of children with AOM who underwent tympanocentesis for recurrent AOM or AOMTF are referred to surgery. All 5 children treated with levofloxacin in 2005-2006 (cases 2, 6, 7, 8, and 9) recovered fully.

**COMMENT**

This is the first study to our knowledge to describe a highly antibiotic-resistant pneumococcal strain that is not targeted by PCV7 as an otopathogen among immunized children in Rochester, New York. Indeed, among the 59 pneumococcal isolates in our study, 9 (15.3%) were a single clone serotype 19A strain that was resistant to all FDA-approved antibiotics for AOM in children. The infections caused by this strain continued to produce symptoms and signs of AOM until aggressive therapy was provided (either surgery or levofloxacin, an antibiotic unapproved for children). While the studied children represent a relatively small subset of all children in our practice, the proportion of S pneumoniae that expressed non-PCV7 serotypes and were PRSP or PISP increased significantly (P < .001) from 2003-2004 to 2005-2006.

**Table 2. Penicillin Susceptibility Among Streptococcus pneumoniae Isolates**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV7 PRSP</td>
<td>10 (63)</td>
<td>2 (50)</td>
<td>2 (40)</td>
<td>14 (50)</td>
</tr>
<tr>
<td>PISP PRSP</td>
<td>2 (13)</td>
<td>1 (25)</td>
<td>2 (40)</td>
<td>5 (20)</td>
</tr>
<tr>
<td>PISP PSSP</td>
<td>4 (25)</td>
<td>1 (25)</td>
<td>1 (20)</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Non-PCV7 PRSP</td>
<td>2 (17)b</td>
<td>2 (25)b</td>
<td>5 (26)b</td>
<td>9 (32)</td>
</tr>
<tr>
<td>PISP PRSP</td>
<td>1 (8)</td>
<td>2 (25)</td>
<td>8 (57)</td>
<td>11 (32)</td>
</tr>
<tr>
<td>PISP PSSP</td>
<td>9 (75)</td>
<td>4 (50)</td>
<td>1 (7)</td>
<td>14 (41)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>12 (43)</strong></td>
<td><strong>4 (33)</strong></td>
<td><strong>7 (37)</strong></td>
<td><strong>23 (39)</strong></td>
</tr>
</tbody>
</table>

**Table 3. Nine Cases of AOM Caused By a Multidrug-Resistant Streptococcus pneumoniae Serotype 19A ST 2722 Strain**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>First episode/AOMFT/recurrent AOM</td>
<td>First episode of AOM</td>
<td>AOMTF</td>
<td>AOMTF and recurrent AOM</td>
<td>Recurrent AOM</td>
<td>AOMTF and recurrent AOM</td>
<td>Recurrent AOM</td>
<td>AOMTF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at tympanocentesis, mo</td>
<td>6</td>
<td>7</td>
<td>13</td>
<td>11</td>
<td>8</td>
<td>11</td>
<td>12</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>No. of PCV7 doses</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>No. of prior AOM episodes</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Levofloxacin-treated</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tympanostomy tube insertion</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

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tice with AOM, these observations are clearly worrisome, especially since there are no new antibiotics in phase 3 clinical trials for AOM in children. The study suggests that an expanded pneumococcal conjugate vaccine to include additional serotypes may be needed sooner than previously thought, with an outer-membrane protein-based vaccine to follow.

In the meantime, clinicians need to be aware that an *S pneumoniae* strain has emerged in the United States that is multidrug-resistant but susceptible to levofloxacin. 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. Levofloxacin resistance among *S pneumoniae* that causes respiratory infections in adults has already been described.86 Most likely, the serotype 19A isolates described in this report are susceptible to fluoroquinolones because these drugs are infrequently used in children. With use, especially frequent use in children, resistance among *S pneumoniae* to fluoroquinolones will almost certainly develop and spread,90 and there may be safety concerns.91

The AAP recently issued a position statement regarding the use of fluoroquinolones in children91; use of this drug class for AOM was not included in their recommendations. However, the AAP advocated use in circumstances where the risk-benefit assessment indicated that fluoroquinolones appeared to be necessary. Acute otitis media caused by the 19A strain described in this report would be an appropriate infection to treat with a fluoroquinolone. Our approach has been to use levofloxacin only for children in whom we have performed a tympanocentesis and isolated a 19A serotype organism that is susceptible only to that drug.

In 1999, a Centers for Disease Control and Prevention *S pneumoniae* working group advocated selective use of tympanocentesis for children with AOMTF and/or recurrent AOM.62 This recommendation for tympanocentesis was also included in the treatment guidelines issued by the AAP in 2004.32 In the near future, more primary care clinicians may need to become trained to perform tympanocentesis,45 especially if excessive use of fluoroquinolones in children with AOMTF is to be avoided.

The overall benefits of the US national immunization campaign to include PCV7 are clear. Widespread use of PCV7 in the United States has led to dramatic reductions in invasive pneumococcal disease.1-3 A recent retrospective case-series analysis of bacteremia in 3- to 36-month-old children identified a 67% reduction in overall bacteremia and an 84% reduction in pneumococcal bacteremia between 1998 and 2003 in a northern California clinic.44 Poehling et al3 recently described a 17% reduction in frequent AOM in children from Tennessee and a 28% reduction in children from Rochester, New York, comparing the years 2000-2001 and 2001-2002 (after PCV7 was in widespread use). Similarly, a 16% reduction in Tennessee children and a 23% reduction in Rochester children was seen in the frequency of tympanostomy tube placements.

In April 2007, Singleton et al11 reported the occurrence of an increasing proportion of invasive pneumococcal disease among Alaska native children (a high-risk population) caused by serotypes of the organism not included in PCV7. The study used statewide longitudinal, population-based laboratory surveillance data from 1995-2006. They found that the invasive pneumococcal disease rate caused by nonvaccine serotypes increased 140% comparing the years 1995-2000 (pre-PCV7) and 2004-2006 (post-PCV7). Serotype 19A accounted for 28.3% of all invasive pneumococcal disease in Alaskan children in 2004-2006. Also in 2007, Pelton et al45 described increasing isolation of serotype 19A pneumococci from children with invasive pneumococcal disease in a prospective surveillance study in Massachusetts. None of the serotype 19A strains in Alaska were resistant to ceftriaxone; however, 1 clone from the surveillance study in Massachusetts was multidrug-resistant (MLST 320). Children with AOMTF or recurrent AOM and children in daycare receive antibiotics frequently; thus, they experience antibiotic selection pressure. The circumstance of antibiotic selection pressure plus PCV7 vaccination, as in our patients with AOM, probably differs from the pediatric populations studied in Alaska and Massachusetts by the addition of more intense antibiotic selection pressure.

Penicillin resistance and resistance to other antibiotic classes is frequently expressed by 5 of the 7 serotypes contained in PCV7.52-56 Therefore, it was not surprising that the frequency of AOM caused by penicillin-nonsusceptible pneumococcal strains decreased after introduction of PCV7 in the United States.6 However, our results suggest that the proportion of penicillin-nonsusceptible pneumococci may be increasing again because of non-PCV7 serotypes expressing such resistance.

This study has limitations. All of the children were enrolled from a single practice and location and the number of children studied was small. The population of children with their first or second AOM episode, with AOMTF, or with recurrent AOM are not necessarily representative of all first AOM episodes or patients with difficult-to-treat AOM. Our results should be interpreted in light of potential selection bias.

Changes in the pathogen distribution and antibiotic resistance patterns of bacteria that cause AOM will require continuous monitoring, especially as new vaccines become available. Trials of an 11-valent PCV vaccine have been completed recently in Europe.52 Licensure of a 10-valent version of this vaccine outside the United States is moving forward; however, it does not contain a 19A polysaccharide component. Trials are under way in the United States with an expanded...
product that will contain 13 serotypes including 19A.

In summary, since the introduction of the PCV7 vaccine, we observed in our practice a multidrug-resistant strain of S pneumoniae of serotype 19A in 9 children that caused unresolving AOM. Identification of this organism by tympanocentesis and highly selective use of levofloxacin proved successful to treat the infections. The identification of this organism occurred in the context of a proportional increase in isolation of strains of S pneumoniae not included in PCV7 and an increase in penicillin resistance among these non-PCV7 strains.

Author Contributions: Dr Pichichero had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Pichichero, Casey.

Acquisition of data: Pichichero, Casey.

Analysis and interpretation of data: Pichichero, Casey.

Drafting of the manuscript: Pichichero, Casey.

Statistical analysis: Pichichero, Casey.

Obtained funding: Pichichero.

Study supervision: Pichichero.

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Role of the Sponsors: The sponsors had no role in the study design or implementation, interpretation of data, analysis, or manuscript preparation.

Additional Contributions: Multilocus serotyping was performed by Qingfu Xu, DVM, PhD, Department of Microbiology/Immunology, University of Rochester Medical Center. Antibiotic susceptibility testing was performed in the laboratory of Gary Doern, PhD, University of Iowa, as a courtesy to Dr Pichichero; no compensation was provided.

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