

# Developing Community-Specific Recommendations for First-Line Treatment of Acute Otitis Media: Is High-Dose Amoxicillin Necessary?

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**ABSTRACT.** *Objectives.* National recommendations are to use high-dose amoxicillin (80–90 mg/kg per day) to treat uncomplicated acute otitis media (AOM) in children who are at high risk for infection with nonsusceptible *Streptococcus pneumoniae* (NSSP). However, high-dose treatment may not be necessary if the local prevalence of NSSP is low. The objective of this study was to estimate the local prevalence of NSSP in children with acute upper respiratory illnesses and to develop community-specific recommendations for first-line empiric treatment of AOM.

*Methods.* We conducted a cross-sectional prevalence study in the offices of 7 community pediatricians in St Louis, Missouri. *S pneumoniae* was isolated from nasopharyngeal swabs collected from children who were younger than 7 years and had AOM, nonspecific upper respiratory infection, cough, acute sinusitis, or pharyngitis. Children were excluded from the study when they had received an antibiotic in the previous 4-week period. Parents and providers completed a brief questionnaire to assess risk factors for carriage of NSSP. On the basis of National Clinical Chemistry Laboratory Standards, isolates with a penicillin minimum inhibitory concentration  $\geq 0.12$   $\mu\text{g/mL}$  were considered to be nonsusceptible to penicillin (NSSP), and isolates with a penicillin minimum inhibitory concentration  $> 2$   $\mu\text{g/mL}$  were categorized as nonsusceptible to standard-dose amoxicillin (35–45 mg/kg per day; NSSP-A).

*Results.* *S pneumoniae* was isolated from the nasopharynx of 85 (40%) of 212 study patients (95% confidence interval [CI]: 33%–47%); 41 (48%) of 85 isolates were NSSP (95% CI: 37%–59%), and 6 (7%) were NSSP-A (95% CI: 1.5%–13%). Among the 212 study patients, the prevalence of NSSP was 19% (95% CI: 14%–25%), and the prevalence of NSSP-A was 3% (95% CI: 0.6%–5%). Carriage of NSSP was increased in child care attendees compared with nonattendees (29% vs 14%; odds ratio: 2.6; 95% CI: 1.3–5.2).

*Conclusions.* In our community, although the prevalence of NSSP among isolates of *S pneumoniae* identified from the nasopharynx of symptomatic children is high (48%), the probability of NSSP-A infection among symptomatic children is  $< 5\%$ . Our data support a recommendation to treat most children who have uncomplicated AOM with standard-dose amoxicillin. Children who attend child care or have recently received an antibiotic may require treatment with high-dose amoxicillin. Other communities may benefit from a similar assessment of

the prevalence of NSSP and NSSP-A. *Pediatrics* 2004;114:342–347; *Streptococcus pneumoniae, acute otitis media, treatment guidelines.*

ABBREVIATIONS. AOM, acute otitis media; NSSP, (penicillin) nonsusceptible *Streptococcus pneumoniae*; ABC, Active Bacterial Core; MIC, minimum inhibitory concentration; URI, (nonspecific) upper respiratory infection; NSSP-A, nonsusceptible *Streptococcus pneumoniae* to standard-dose amoxicillin; CI, confidence interval; OR, odds ratio.

In the United States, antibiotic treatment is recommended for children with acute otitis media (AOM)<sup>1,2</sup> and accounts for 30% of all pediatric outpatient antimicrobial prescriptions.<sup>3</sup> Treatment is targeted primarily at *Streptococcus pneumoniae*, the bacterial pathogen most frequently associated with AOM and the least likely to resolve spontaneously.<sup>4,5</sup> The prevalence of isolates of *S pneumoniae* that are nonsusceptible to penicillin (NSSP) has increased dramatically in the past 20 years.<sup>6–8</sup> Even so, amoxicillin remains the recommended treatment for children with uncomplicated AOM,<sup>1,4</sup> as pneumococcal resistance to penicillin and other  $\beta$ -lactams can be overcome if the concentration of the drug at the site of infection is sufficiently high.<sup>9</sup> Both a consensus panel and the Centers for Disease Control and Prevention recommended that the dose of amoxicillin be increased to 80 to 90 mg/kg per day for children who are believed to have an increased risk of infection with NSSP, including those with recent antibiotic exposure, in child care, or younger than 2 years.<sup>1,4</sup> However, higher doses of amoxicillin may not be needed if the local prevalence of NSSP is low. Community-specific treatment recommendations for first-line treatment of AOM on the basis of the local prevalence of NSSP may limit unnecessary antibiotic use.

Accurate local surveillance data for NSSP are not usually available. Nationally, the prevalence of NSSP is monitored by the Active Bacterial Core (ABC) Surveillance Program using specimens from hospitalized patients.<sup>7,10</sup> Laboratories from 8 states participate in this surveillance system, and case definitions and testing methods are standardized. However, marked geographic variation in prevalence of NSSP has been observed and has persisted over time.<sup>4,10</sup> Missouri does not participate in the ABC Surveillance Program, but the state health department does coordinate a surveillance program for NSSP using voluntary reporting by commercial and hospital lab-

From the \*Division of General Medical Sciences and ‡Department of Pediatrics, Washington University School of Medicine, St Louis, Missouri. Received for publication Aug 28, 2003; accepted Dec 26, 2003. Reprint requests to (J.M.G.) Campus Box 8005, 660 South Euclid Ave, St Louis, MO 63110. E-mail: jgarbutt@im.wustl.edu PEDIATRICS (ISSN 0031 4005). Copyright © 2004 by the American Academy of Pediatrics.

oratories. Nevertheless, variation in laboratory methods and case definitions limit the utility of findings to inform local treatment recommendations. Estimates of NSSP prevalence obtained from specimens submitted to the laboratory at the local children's hospital likely do not reflect the prevalence of NSSP in the community, as specimens are obtained during routine care of children who are hospitalized with invasive disease or with recurrent or chronic infections. However, local prevalence of NSSP can be measured using nasopharyngeal cultures.<sup>11</sup>

Currently, there are no guidelines to translate local prevalence data into recommendations for empiric therapy of AOM.<sup>4,6</sup> Interpretation of *S pneumoniae* antibiotic susceptibility data are confusing, as resistance to penicillin rather than amoxicillin is usually reported. Susceptibility to an antibiotic is measured as the minimum inhibitory concentration (MIC) of the drug required to inhibit bacterial growth. For penicillin, isolates with a penicillin MIC  $\leq 0.06$   $\mu\text{g}/\text{mL}$  are considered to be susceptible to penicillin, those with a penicillin MIC  $\geq 0.12$   $\mu\text{g}/\text{mL}$  and  $\leq 1$   $\mu\text{g}/\text{mL}$  are considered to have intermediate resistance to penicillin, and those with a penicillin MIC  $\geq 2$   $\mu\text{g}/\text{mL}$  are designated as having high-level resistance to penicillin.<sup>12</sup> Until 2000, the recommended MIC cutpoints to indicate susceptibility to both penicillin and amoxicillin were the same. In 2000, the National Clinical Chemistry Laboratory Standards for susceptibility of *S pneumoniae* to amoxicillin were revised such that the MIC cutpoint to define resistance to amoxicillin increased to  $\geq 8.0$   $\mu\text{g}/\text{mL}$  and that for susceptibility to amoxicillin increased to  $\leq 2$   $\mu\text{g}/\text{mL}$ .<sup>12</sup> Thus, all isolates with intermediate penicillin resistance and some with high-level penicillin resistance (those with a penicillin MIC  $\leq 2$   $\mu\text{g}/\text{mL}$ ) are considered susceptible to amoxicillin.<sup>12</sup> For the  $\beta$ -lactam antibiotics, maintaining the serum concentration above the MIC for 40% to 50% of the dosing interval is associated with bacterial cure rates of 80% to 85%.<sup>13,14</sup> Pharmacodynamic studies suggest that standard-dose amoxicillin (35–45 mg/kg per day) will meet this requirement and therefore should eliminate almost all isolates of *S pneumoniae* with a penicillin MIC  $\leq 2$   $\mu\text{g}/\text{mL}$  from the middle ear.<sup>13,14</sup> In addition, clinical studies have demonstrated that

standard-dose amoxicillin results in bacteriologic and/or clinical cure in most children with AOM in whom *S pneumoniae* with intermediate- or high-level penicillin resistance has been isolated at tympanocentesis.<sup>15–17</sup> The objectives of this study were 2-fold: to estimate the local prevalence of NSSP in children with acute upper respiratory illnesses in our community and to develop local recommendations for the first-line empiric treatment of AOM.

## METHODS

### Study Design and Study Population

We conducted a prevalence study in St Louis, Missouri, from March 14 to May 11, 2000, and from February 12 to April 4, 2001. Patients were enrolled at 7 pediatric offices that were selected to provide a demographic cross-section of patients and located throughout the metropolitan area. Specimens were obtained from children who were younger than 7 years and had a new diagnosis of AOM, otitis media with effusion, acute sinusitis, streptococcal pharyngitis, nonspecific upper respiratory infection (URI), or cough illness. The criteria used to establish these diagnoses are summarized in Table 1. Patients were excluded when they had received an antibiotic in the past month or had diabetes, cystic fibrosis, sickle cell disease, a collagen vascular disease, nephrotic syndrome, or cancer or were treated with immunosuppressive drugs (including systemic steroids). Each child was enrolled once only, and siblings of patients already enrolled in the study were excluded. At most sites, patients were enrolled daily during the study period, but at times of increased office activity, not all eligible patients were invited to participate. The study was approved by the Washington University Human Studies Committee, and all parents provided informed consent.

### Measurement

A posterior nasopharyngeal swab was obtained from each child. The swab was plated onto sheep blood agar in the office, and the plate was incubated at room temperature and then transported to the microbiology laboratory at St Louis Children's Hospital within 12 hours. Once in the laboratory, the plate was incubated for 24 to 48 hours at 35°C in 5% CO<sub>2</sub>-enriched atmosphere. *S pneumoniae* was identified on the basis of  $\alpha$  hemolysis and susceptibility to Optochin. Antibiotic susceptibilities were determined using the Kirby-Bauer method and E-strips.<sup>12,18</sup> Susceptibility to penicillin was defined as follows: MIC  $\leq 0.06$   $\mu\text{g}/\text{mL}$ , susceptible; MIC  $\geq 0.12$   $\mu\text{g}/\text{mL}$  and  $\leq 1$   $\mu\text{g}/\text{mL}$ , intermediate resistance; and MIC  $\geq 2$   $\mu\text{g}/\text{mL}$ , high-level resistance.<sup>12</sup> *S pneumoniae* isolates with MIC = 1.5  $\mu\text{g}/\text{mL}$  were grouped together with isolates with MIC = 2  $\mu\text{g}/\text{mL}$  and reported as resistant to penicillin, as recommended by the manufacturer (E-test; AB Biodisk North America Inc, Piscataway, NJ). *S pneumoniae* isolates with intermediate- or high-level penicillin resistance were considered NSSP. Susceptibility to amoxicillin was not tested directly and

TABLE 1. Diagnostic Criteria Used to Identify Study Patients

Diagnosis	Diagnostic Criteria
URI	Nonspecific upper respiratory symptoms <10 d (eg, rhinorrhea, cough)
Acute sinusitis	Prolonged ( $\geq 10$ d) nonspecific upper respiratory symptoms (rhinorrhea [clear or mucopurulent] and cough) without improvement or more rapid onset of more severe upper respiratory symptoms (high fever, facial pain or swelling)
AOM	Otorrhea of middle ear origin or Evidence of middle ear effusion (eg, reduced mobility of TM, air/fluid level) and evidence of local infection (very red TM, bulging TM, ear pain)
OME	Evidence of middle ear effusion without evidence of local infection (eg, reduced mobility of TM, retracted TM, air/fluid level)
Streptococcal pharyngitis Cough illness	Confirmed with either a streptococcal antigen test or culture Cough for <10 d

OME indicates otitis media with effusion; TM, tympanic membrane

instead was defined in terms of penicillin resistance. Isolates with a penicillin MIC  $\leq 2$   $\mu\text{g}/\text{mL}$  were considered to be susceptible to standard-dose amoxicillin (40–45 mg/kg per day), and isolates with a penicillin MIC  $> 2$   $\mu\text{g}/\text{mL}$  were considered to be resistant to standard-dose amoxicillin (NSSP-A). Isolates were also tested for susceptibility to cefotaxime, erythromycin, clindamycin, ofloxacin, trimethoprim-sulfamethoxazole, and vancomycin. For each of these antibiotics, isolates were classified as susceptible or resistant (high-level or intermediate-level).

The parent completed a brief questionnaire that inquired about child care attendance, the number of children at home under the age of 19 years, exposure of any household members to an antibiotic within the previous 4 weeks, and demographic information. The physician completed a 1-page questionnaire that detailed exclusion criteria, comorbidities (eg, asthma, allergic rhinitis), use of the pneumococcal vaccine (polysaccharide or conjugate), duration of symptoms, the diagnosis, and antibiotic treatment given.

### Statistical Analysis

The prevalence of NSSP was calculated among *S pneumoniae* isolates and among patients in the study population. Depending on cell size, the  $\chi^2$  test or Fisher exact test was used to compare proportions in univariate analyses. We used logistic regression to calculate univariate odds ratios (ORs) and to evaluate whether child care attendance and young age were independent predictors of NSSP. To examine the effect of the pneumococcal conjugate vaccine, we restricted the analyses to the second year of the study. As subgroup analyses showed no difference by year of enrollment (data not shown), data from both years were pooled for all other analyses. A probability of  $P < .05$  (2-tailed for all tests) was used to establish statistical significance. All statistical analyses were done using Stata 7.0 (Stata Corp, College Station, TX).

## RESULTS

### Study Patients

A total of 241 patients were enrolled in the study. Among these patients, 29 were excluded from the analyses (3 were enrolled twice, 7 were siblings of study patients, 15 had received an antibiotic within 4 weeks of study enrollment, and 4 did not meet diagnostic criteria for study eligibility). Data about non-participants are not available. Of the 212 children included in the analyses, 118 were enrolled in 2000 and 94 were enrolled in 2001. Patients were drawn from all regions of the St Louis metropolitan area, 54% were younger than 2 years, and 39% attended child care (Table 2). The most frequent diagnoses were URI (33%) and AOM (27%; Table 2). Pneumococcal vaccine was used exclusively in 2001 (the second year of the study), when 44 (47%) of 94 patients received the conjugate vaccine. Of these patients, 5 received 1 dose, 17 received 2 doses, 16 received 3 doses, and 1 received 4 doses (data were unavailable in 5 patients).

### Nasopharyngeal Carriage of *S pneumoniae*

*S pneumoniae* was isolated from the nasopharynx of 85 (40%) of 212 study patients (95% confidence interval [CI]: 33%–47%). Carriage differed significantly by diagnosis ( $P = .007$ ), primarily as no *S pneumoniae* were identified in the 14 patients with streptococcal pharyngitis. For the other diagnoses, carriage rates were 50% (29 of 58) in children with AOM, 48% (11 of 23) for those with otitis media with effusion, 33% (8 of 24) in children with acute sinusitis, and 43% (30 of 70) in those with a URI. Child care attendance was associated with increased carriage of *S pneumoniae* (OR: 2.3; 95% CI: 1.3–4.1). Although carriage of *S pneumoniae* was increased in younger

**TABLE 2.** Characteristics of 212 Children Participating in Nasopharyngeal Prevalence Survey for NSSP

Characteristic	N	%
Demographics		
Age <2 y	115	54
Female gender	94	44
White	103	48
Attends child care	83	39
Medicaid	86	41
Home exposures		
At least 1 other child at home	104	49
Household member had antibiotic in past 4 weeks	35	17
Medical history		
Received at least 1 dose of pneumococcal conjugate vaccine	44/94*	47
Asthma	49	23
Treated with an antibiotic	128	60
Diagnosis		
URI	70	33
AOM	58	27
OME	23	11
Acute sinusitis	24	11
Cough illness	23	11
Streptococcal pharyngitis	14	7

\* Pneumococcal conjugate vaccine was used only in year 2 of the study.

children (Table 3), age younger than 2 years was not a statistically significant risk factor in the univariate analysis (OR: 1.7; 95% CI: 1.0–3.0;  $P = .053$ ). In 2001, receipt of at least 1 dose of the pneumococcal vaccine did not affect carriage of *S pneumoniae* (OR: 1.2; 95% CI: 0.5–2.8).

### Nasopharyngeal Carriage of NSSP

Twenty (24%) isolates had high-level resistance to penicillin, and 21 (25%) had intermediate resistance. The prevalence of NSSP was 48% (95% CI: 37%–59%) in the 85 isolates of *S pneumoniae* and 19% (95% CI: 14%–25%) in the 212 study patients. Carriage of NSSP was increased in child care attendees compared with nonattendees (29% vs 13%;  $P = .006$ ; OR: 2.6; 95% CI: 1.3–5.2) but not in children younger than 2 years compared with older children (23% vs 14%;  $P = .1$ ; OR: 1.8; 95% CI: 0.9–3.7). In the multivariate analysis, child care attendance was an independent predictor of carriage of NSSP (OR: 2.6; 95% CI: 1.3–5.3).

Of the 20 isolates with high-level penicillin resistance, 3 (15%) had a MIC = 1.5  $\mu\text{g}/\text{mL}$ , 11 (55%) had a MIC = 2  $\mu\text{g}/\text{mL}$ , 3 (15%) had a MIC = 3  $\mu\text{g}/\text{mL}$ , 2 (10%) had a MIC = 4  $\mu\text{g}/\text{mL}$ , and 1 had a MIC = 8  $\mu\text{g}/\text{mL}$ . Thus, 6 of 85 isolates were considered to be NSSP-A (penicillin MIC  $> 2$   $\mu\text{g}/\text{mL}$ ). The prevalence of NSSP-A was 7% (95% CI: 1.5%–13%) among *S pneumoniae* isolates and 3% (95% CI: 0.6%–5%) in the 212 study patients. Carriage of NSSP-A was increased in child care attendees (Table 3) but failed to reach statistical significance in the univariate analysis (OR: 8.0; 95% CI: 0.9–69.9;  $P = .06$ ).

### Multidrug-Resistant *S pneumoniae*

Overall, 40 (95%) of 41 NSSP isolates were resistant to at least 1 other antibiotic. Thirty-one (74%) isolates were resistant to trimethoprim-sulfamethoxazole, 29 (71%) were resistant to cefotaxime, 26 (63%) were

**TABLE 3.** Analysis of Risk Factors for Nasopharyngeal Carriage of *S pneumoniae* and NSSP-A in 212 Children With Acute Upper Respiratory Illnesses

Risk Factor	Total, N	Carriage of <i>S pneumoniae</i> in Patients With			Carriage of NSSP-A in Patients With		
		Factor Present, n (%)	Factor Absent, n (%)	P Value*	Factor Present, n (%)	Factor Absent, n (%)	P Value†
Total N	212	85 (40)			6 (3)		
Age <2 y	115	54 (46)	33 (33)	.06	3 (3)	3 (3)	1.0
Attends child care	83	44 (53)	43 (33)	.004	5 (6)	1 (1)	.035
At least 1 other child at home	104	45 (42)	42 (38)	.5	2 (2)	4 (4)	.68
Household member had antibiotic in past 4 weeks	35	10 (28)	76 (43)	.09	0	6 (3)	.59
Received at least 1 dose of conjugated pneumococcal vaccine‡	44/94	19 (42)	18 (36)	.5	0	2 (4)	.50
Asthma	49	19 (38)	68 (42)	.6	0	6 (4)	.34

\* P values are calculated using  $\chi^2$  test.

† P values are calculated using Fisher exact test.

‡ This analysis is restricted to 2001, year 2 of the study.

resistant to erythromycin, 8 (20%) were resistant to clindamycin, and 2 (5%) were resistant to ofloxacin. No isolates showed vancomycin resistance. Fourteen (33%) isolates were resistant to 1 other non- $\beta$ -lactam class of antibiotic, 18 (43%) to 2 additional classes, and 6 (14%) to 3 additional classes. All isolates with high-level resistance to penicillin were resistant to both cefotaxime and trimethoprim-sulfamethoxazole.

Of the 6 NSSP-A isolates, 5 were resistant to erythromycin and 2 were resistant to trimethoprim-sulfamethoxazole, but none were resistant to clindamycin or vancomycin. Two isolates were resistant to 2 additional drug classes (both to trimethoprim-sulfamethoxazole and erythromycin). Of the 44 isolates susceptible to penicillin, 3 (7%) were resistant to erythromycin and 2 (5%) were resistant to clindamycin.

## DISCUSSION

Our findings have an important implication for the treatment of AOM in our community. Although the prevalence of NSSP was almost 50% among study isolates, our data suggest that standard-dose amoxicillin would provide effective treatment for most children in our community who have uncomplicated AOM and require antibiotic treatment. Assuming treatment failure when infection is caused by an isolate of *S pneumoniae* with a MIC  $>2 \mu\text{g}/\text{mL}$ , the probability of treatment failure with standard-dose amoxicillin in the study population was only 3% (95% CI: 0.6%–5%), and we believe that this estimate for the prevalence of NSSP-A is high for several reasons. First, identification of *S pneumoniae* in the nasopharynx does not equate with presence of the bacteria in the middle ear. Although bacterial colonization precedes pneumococcal infections, *S pneumoniae* (including NSSP) can be present in the nasopharynx as a commensal organism.<sup>19</sup> The positive predictive value of a nasopharyngeal swab for the presence of *S pneumoniae* in middle ear fluid is only 22% to 45%,<sup>20,21</sup> suggesting that fewer than half of children with NSSP in their nasopharynx will have NSSP in their middle ear. Second, susceptibility as estimated by the MIC level reflects a pharmacoki-

netic measure of in vitro susceptibility rather than clinical effectiveness. Current penicillin MIC cut-points were developed for patients with meningitis and may not be clinically relevant for children with AOM.<sup>22,23</sup> Finally, ~20% of middle ear infections caused by *S pneumoniae* will resolve spontaneously.<sup>4,5</sup>

Our treatment recommendations are based on the assumption that standard-dose amoxicillin will adequately treat middle ear isolates of *S pneumoniae* with a penicillin MIC  $\leq 2 \mu\text{g}/\text{mL}$ . Pharmacodynamic studies in models to simulate the middle ear,<sup>24</sup> animal models,<sup>25</sup> and patients with AOM<sup>13</sup> suggest that standard-dose amoxicillin (35–45 mg/kg per day) should provide effective treatment for isolates of *S pneumoniae* with a penicillin MIC  $\leq 2 \mu\text{g}/\text{mL}$ . Clinical studies to evaluate the efficacy of standard-dose amoxicillin and amoxicillin/clavulanate (used at the standard dose for amoxicillin) for treatment of AOM have demonstrated bacterial cure at 4 to 6 days and clinical cure at 12 to 14 days for infections associated with isolates with intermediate- and high-level penicillin resistance.<sup>15,17</sup> The patient population in these studies is similar to ours in that only ~10% of isolates categorized as penicillin resistant had a penicillin MIC  $>2 \mu\text{g}/\text{mL}$ . Additional evidence comes from a study designed to evaluate the effect of amoxicillin therapy on carriage of resistant pneumococcal in children with a respiratory tract illness (~30% had AOM).<sup>26</sup> Children were randomized to standard dose (40 mg/kg per day for 10 days) versus high-dose amoxicillin (90 mg/kg per day for 5 days) treatment. Standard-dose amoxicillin effectively eradicated penicillin-resistant *S pneumoniae* from the nasopharynx. We believe that findings from these pharmacodynamic and clinical studies support our assertion that standard-dose amoxicillin will effectively treat isolates of *S pneumoniae* with a penicillin MIC  $\leq 2 \mu\text{g}/\text{mL}$ .

It is easy to misinterpret information about the prevalence of NSSP and overestimate the probability of treatment failure with standard-dose amoxicillin. Prevalence information is most often from laboratory-based surveillance systems that measure the prevalence of NSSP among tested isolates.<sup>4</sup> To use

this information for clinical decision making, the frequency that AOM is caused by *S pneumoniae* must also be considered.<sup>27,28</sup> In contrast, NSSP carriage estimated from a surveillance study such as ours can be used to estimate the likelihood of NSSP infection in the target population. Additional confusion results from reporting the prevalence of NSSP with resistance to penicillin rather than amoxicillin, the clinically relevant drug. Categorizing NSSP strains as having intermediate- and high-level resistance to penicillin does not provide adequate information to determine whether high-dose amoxicillin is required. In our study, all isolates with intermediate resistance and more than two thirds of isolates with high-level resistance to penicillin had a MIC  $\leq 2$   $\mu\text{g}/\text{mL}$  and would likely respond to treatment with standard-dose amoxicillin.<sup>13</sup> We agree with others<sup>4</sup> that clinical decisions would be better informed if the susceptibility of *S pneumoniae* to amoxicillin were tested and reported. Alternatively, penicillin MIC levels could be reported to allow clinicians to estimate the likelihood of infection with NSSP-A as we have done. Providing information in a form that has direct relevance to the clinical decision may reduce the unnecessary use of high-dose amoxicillin and broad-spectrum antibiotics.

Selection bias may limit the generalizability of readily available prevalence estimates of NSSP. In the ABC surveillance system, specimens are obtained from blood and cerebrospinal fluid samples routinely collected from mainly adult patients who are hospitalized with invasive disease.<sup>7,10</sup> Isolates of *S pneumoniae* associated with invasive disease in adults may differ from those associated with noninvasive disease in children,<sup>4,10</sup> and the prevalence of NSSP varies with geography.<sup>10</sup> Indeed, 48% of study isolates were NSSP, compared with 28% of isolates tested through the national ABC surveillance system for the same time period.<sup>29</sup> Our results were similar to a surveillance study that examined data from 6 outpatient laboratories in which almost two thirds of specimens were from children and  $<10\%$  were blood isolates.<sup>22</sup> Among *S pneumoniae* strains, 50% were susceptible to penicillin and 94% were susceptible to amoxicillin.<sup>22</sup> The prevalence of NSSP measured in other local nasopharyngeal surveys ranges from 20% to 90% as a result of variation in the study year, patient population, geographic area, and antibiotic exposure.<sup>11,30–33</sup> Our study has demonstrated that it is relatively easy to measure local prevalence of NSSP and develop community-specific recommendations for empiric treatment of AOM. We believe that this approach may limit unnecessary antibiotic use.

Our findings of increased carriage of NSSP-A in child care attendees supports national recommendations to use high-dose amoxicillin for empiric treatment of AOM in these children. As children with recent exposure to antibiotics were excluded from our study, we are unable to comment on the utility of this factor to guide treatment decisions. In our study, young age ( $<2$  years), a factor previously associated with increased risk for NSSP infection,<sup>4,10,30</sup> failed to identify children with an increased risk for nasopharyngeal carriage of NSSP or NSSP-A.

The explanation may be that we limited the study population to children younger than 7 years to ensure representation of the target population. Alternatively, this finding could reflect a  $\beta$ -error associated with the small sample size.

We did not identify any other predictors of NSSP-A carriage. We were surprised to find no *S pneumoniae* in patients with streptococcal pharyngitis, but antagonism among streptococci has previously been described.<sup>11,33</sup> Receipt of at least 1 dose of pneumococcal conjugate vaccine had no apparent effect on nasopharyngeal carriage of *S pneumoniae* in the study population. However, our ability to see any effect of vaccine use on nasopharyngeal carriage of *S pneumoniae* or NSSP is limited as our study was conducted before widespread use of the conjugate vaccine in the study population. Additional studies are required to quantify better the effect of this vaccine on nasopharyngeal colonization with *S pneumoniae* and on the relationship between colonization and otitis media caused by *S pneumoniae*.

Multidrug resistance of *S pneumoniae* is common. More than 80% of NSSP isolates in our study were resistant to at least 2 other non- $\beta$ -lactam classes of antibiotic. It is interesting to note macrolide resistance in 7% of isolates susceptible to penicillin as well in 63% of NSSP isolates. Macrolide resistance is increasing around the world and is thought to be associated with widespread use of macrolide antibiotics.<sup>35</sup>

There are several limitations to our study. First, our sample size was small and from 1 geographic area, limiting power for subgroup analyses and generalizability to other areas. Unfortunately, we do not have data to characterize potential biases in selection of study sites or study patients. Study sites were selected to ensure that specimens were collected from geographically varied parts of the metropolitan area and demographically diverse patients. Patients were not randomly selected, but all patients included in the analyses were independent. As children who had received an antibiotic in the previous 4 weeks were excluded from the study, our conclusions may not apply to this patient population. Second, nasopharyngeal carriage of NSSP does not confirm that the organism is pathogenic for AOM. Ideally, we would obtain specimens of middle ear fluid to diagnose NSSP infection, but this approach is not currently feasible in community care. As routine antibiotic susceptibility testing at our laboratory did not include testing for amoxicillin, we have used the penicillin MIC cutpoints recommended in national standards to estimate this parameter (MIC  $>2$   $\mu\text{g}/\text{mL}$  for penicillin). Finally, our results will need to be extended in the postvaccine era. Although we found no effect of the pneumococcal conjugate vaccine, recent widespread use in our community may have reduced the incidence of pneumococcal disease and the prevalence of NSSP.<sup>36,37</sup> We plan to repeat this study to address this question and refine our local treatment recommendations.

## CONCLUSION

Among children who live in the St Louis area and have acute upper respiratory infections and have not received an antibiotic in the previous 4 weeks, the probability that infection is caused by *S pneumoniae* that is not susceptible to standard-dose amoxicillin is <5%. Accordingly, we recommend that most children with uncomplicated AOM receive standard-dose amoxicillin (40–45 mg/kg per day) and that high-dose amoxicillin (80–90 mg/kg per day) be reserved for children who attend child care and for those with recent antibiotic exposure.

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