Effect of Short-Course, High-Dose Amoxicillin Therapy on Resistant Pneumococcal Carriage
A Randomized Trial

Stephanie J. Schrag, DPhil
Chabela Peña, MD
Josefin Fernández, MD
Jacqueline Sánchez, MD
Virginia Gómez, MD
Eddy Pérez, MD
Jesús M. Feris, MD
Richard E. Besser, MD

Children commonly carry Streptococcus pneumoniae asymptotically in the nasopharynx. Carriage can lead to pneumococcal disease, which ranges in severity from otitis media and pneumonia to meningitis and bacteremia. Globally, pneumococcal infections result in an estimated 1 million deaths each year among children younger than 5 years.1

Penicillin has traditionally been an effective treatment for pneumococcal infections. In recent years, however, an increasing prevalence of drug-resistant S pneumoniae threatens this effectiveness.2 A number of studies have identified recent antibiotic use as a risk factor for carrying resistant pneumococci3-7 and for invasive infection with resistant pneumococci.8-10

Short-course, high-dose antibiotic therapy has been proposed as an intervention to reduce spread of resistant pneumococci in cases in which antibiotic treatment is necessary.11-13 Shorter courses reduce a patient’s exposure to antibiotic selective pressure and may reduce antibiotic use in the community, which often correlate with incidence of resistance.14,15 Additionally, higher doses may achieve antibiotic concentrations that inhibit nonsusceptible strains for a large proportion of the dosing interval.16 Patient adherence to shorter courses is also expected to be higher.

Despite the potential of short-course, high-dose therapy to limit spread of pneumococcal resistance, most clinical trials evaluating short-duration therapy have focused on clinical efficacy as the primary outcome.

Context Emerging drug resistance threatens the effectiveness of existing therapies for pneumococcal infections. Modifying the dose and duration of antibiotic therapy may limit the spread of resistant pneumococci.

Objective To determine whether short-course, high-dose amoxicillin therapy reduces risk of posttreatment resistant pneumococcal carriage among children with respiratory tract infections.

Design and Setting Randomized trial conducted in an outpatient clinic in Santo Domingo, Dominican Republic, October 1999 through July 2000.

Participants Children aged 6 to 59 months who were receiving antibiotic prescriptions for respiratory tract illness (n = 795).

Interventions Children were randomly assigned to receive 1 of 2 twice-daily regimens of amoxicillin: 90 mg/kg per day for 5 days (n = 398) or 40 mg/kg per day for 10 days (n = 397).

Main Outcome Measures Penicillin-nonsusceptible Streptococcus pneumoniae carriage, assessed in nasopharyngeal specimens collected at days 0, 5, 10, and 28; baseline risk factors for nonsusceptible pneumococcal carriage; and adherence to regimen, compared between the 2 groups.

Results At the day 28 visit, risk of penicillin-nonsusceptible pneumococcal carriage was significantly lower in the short-course, high-dose group (24%) compared with the standard-course group (32%); relative risk (RR), 0.77; 95% confidence interval (CI), 0.60-0.97; P = .03; risk of trimethoprim-sulfamethoxazole nonsusceptibility was also lower in the short-course, high-dose group (RR, 0.77; 95% CI, 0.58-1.03; P = .08).

The protective effect of short-course, high-dose therapy was stronger in households with 3 or more children (RR, 0.72; 95% CI, 0.52-0.98). Adherence to treatment was higher in the short-course, high-dose group (82% vs 74%; P = .02).

Conclusion Short-course, high-dose outpatient antibiotic therapy appears promising as an intervention to minimize the impact of antibiotic use on the spread of drug-resistant pneumococci.
AMOXICILLIN AND RESISTANT PNEUMOCOCCAL CARRIAGE

come17–19 and have not assessed the impact on nasopharyngeal carriage of pneumococci. One retrospective carriage study identified long-duration, low-dose antibiotic treatment as a risk factor for penicillin-nonsusceptible S pneumoniae (PNSP) carriage.20 In contrast, 2 clinical trials comparing a 5-day vs a 10-day regimen of high-dose amoxicillin-clavulanate potassium found that risk of nonsusceptible pneumococcal carriage did not differ between the groups after treatment.17,21 In both studies, however, the number of posttreatment nasopharyngeal carriers was small, limiting the power to detect differences in posttreatment nasopharyngeal carriage; moreover, the final sample point was close to the end of treatment and did not allow time for pneumococcal populations to achieve a new equilibrium.

Here, we report results of a randomized trial directly evaluating whether short-course, high-dose amoxicillin therapy reduces risk of PNSP carriage relative to standard amoxicillin regimens among children with respiratory tract illness.

METHODS

Population

Children attending the outpatient clinic at the Clínica Infantil Dr Robert Reid Cabral, a large public hospital in Santo Domingo, Dominican Republic, were eligible for enrollment. Study nurses recruited participants by asking screening questions to waiting patients; they invited potential candidates to wait for a study physician instead of the standard clinic staff. Participation at this stage of recruitment was more than 98%. Inclusion was limited to children aged 6 to 59 months who were residing in the Santo Domingo metropolitan area, who were determined by a study physician to have a respiratory tract illness requiring antibiotic therapy, and whose parents gave informed consent for participation in the study. No attempt was made to standardize diagnostic criteria because clinical outcome was not a study end point. Children who needed hospitalization or who reported penicillin allergy, antibiotic use within the last 7 days, or contraindications for nasopharyngeal swabs were excluded from the study. Enrollment was conducted from October 1999 through July 2000.

Ethical Review

The study protocol was approved by the Dominican Republic National Bioethics Committee, the Clínica Infantil Dr Robert Reid Cabral, and the Institutional Review Board of the Centers for Disease Control and Prevention, Atlanta, Ga. Informed consent was administered orally and confirmed in writing by parents or guardians of all participants.

Study Design

This was a prospective, randomized single-center trial. Because the primary outcomes were microbiologic, only the microbiologists were blinded to treatment group. Since clinical efficacy of treatment regimens has been established previously and was not an outcome measure, the study was not placebo-controlled.

Randomization was performed in blocks of 50 participants. During enrollment, physicians assigned study numbers in consecutive order, then looked up the treatment group preassigned to the study number. Children were randomly assigned to 1 of 2 treatment groups, receiving either amoxicillin, 40 mg/kg per day (twice daily), for 10 days or amoxicillin, 90 mg/kg per day (twice daily), for 5 days. A 90-mg/kg-per-day course of amoxicillin was recently approved by the US Food and Drug Administration and was recommended by the Drug-resistant Streptococcus pneumoniae Therapeutic Working Group for treatment of acute otitis media in regions where pneumococcal resistance is common.22

On enrollment, we administered a brief questionnaire on demographics and risk factors to participants’ parents or guardians and obtained a nasopharyngeal specimen from each participant using a Dacron swab in the posterior nasopharynx. Swabs were immediately placed into skim milk tryptophan glucose glutamine transport media23 and stored at −20°C. Urine specimens were collected from children enrolled early in the study to confirm parental reports that participants had not taken antibiotics recently.

Follow-up visits were conducted at days 5, 10, and 28 after enrollment. Families who did not return for follow-up visit appointments were contacted, and appointments were rescheduled when possible. We obtained nasopharyngeal specimens at each follow-up visit and administered a brief questionnaire about adherence with the protocol and antibiotic use in the household.

Adherence and Adverse Events

At the day 5 and day 10 visits, the volume of amoxicillin remaining in participants’ medicine bottles was measured. Adherence with treatment regimens was defined as completing 80% to 120% of the prescribed course, estimated from the volume of medicine remaining. We placed an upper limit on adherence because taking too much medicine could obscure the distinction between the treatment regimens.

At the day 5, 10, and 28 visits, parents were asked about adverse events potentially associated with treatment (eg, diarrhea, vomiting, rash), and participants were examined. Parents were also asked to report adverse events that occurred between follow-up visits. Participants with adverse reactions to amoxicillin were prescribed an alternative therapy.

Specimen Processing

Urine. Urine was assayed for antimicrobial activity by placing a sterile filter paper disk containing urine on a lawn of pansusceptible Micrococcus luteus and incubating for 48 hours. Lawns were screened for evidence of zones of inhibition. The presence of a zone was considered indicative of antibiotic use within the last 7 days, based on previous studies using similar methods.24,25

Nasopharyngeal Specimens. Nasopharyngeal specimens inoculated into
skim milk tryptophan glucose glutamine media were vortexed for 2 minutes. Fifty microliters of media was plated onto a blood agar plate supplemented with 5 µg/mL of gentamicin and incubated under 5% carbon dioxide at 35°C to 37°C. After 24 to 36 hours of incubation, pneumococci were identified by α-hemolysis and typical colony morphology and confirmed by optochin susceptibility. Strains with optochin inhibition zones between 9 and 13 mm were further confirmed by bile solubility.

One confirmed pneumococcal isolate per specimen was tested for susceptibility to penicillin, amoxicillin, and trimethoprim-sulfamethoxazole by E-test (Remel, Lenexa, Kan) according to the manufacturer’s instructions using National Committee of Clinical Laboratory Standards (NCCLS) break points for pneumococci.26

**Statistical Analysis**

We evaluated differences between treatment groups in baseline demographics and carriage using the χ² test or the Fisher exact test. Nonparametric distributions of continuous variables were compared using the Kruskal-Wallis test.

Our primary objective was to determine whether posttreatment PNSP carriage differed between the treatment groups. To detect a minimum difference in PNSP carriage between treatment groups of 20 percentage points with an α level of .05 and 80% power, we estimated a sample size of 400 children per treatment group, assuming a baseline prevalence of PNSP carriage of 15%. Because carriage at days 5, 10, and 28 were not independent, we used the general estimating equations method, taking into account the repeated-measures design of the study, to compare the prevalence of PNSP between groups at different points. Binomial regression was performed using the GENMOD procedure in SAS version 8 (SAS Institute Inc, Cary, NC). Participants who missed 1 or 2 follow-up visits were included because this method allowed for an unbalanced design.

Ninety-five percent confidence intervals (CIs) and 2-tailed P values are reported throughout. P values less than .05 were considered statistically significant.

The primary outcome of posttreatment carriage of PNSP was analyzed separately in an intention-to-treat population (including all randomized participants except those who did not return for any follow-up evaluation) and a per-protocol study population (those who adhered to the treatment protocol). Relative risks (RRs) were calculated both by using the entire cohort and by limiting the cohort to those with pneumococcal carriage at a given point.

### RESULTS

#### Population

Of 811 eligible children, 795 (98%) were enrolled. The most common reasons for exclusion among children in the study age range were antibiotic use within the last 7 days or lack of a respiratory tract illness identified as needing antibiotic therapy. Acute respiratory tract infection and otitis media were the most common diagnoses on enrollment (Table 1). Negative urine samples from 105 of the first 108 enrolled participants confirmed guardians’ verbal reports that participants had not taken antibiotics in the last 7 days. Subsequently, because of this high concordance, urine collection was stopped.

After enrollment, 398 children were randomly assigned to the short-course, high-dose group and 397 to the standard-course group. Age, sex, antibiotic use in the last 2 months, number and age(s) of children in the household, and prevalence of pneumococcal carriage and PNSP carriage did not differ between treatment groups at baseline (day 0). Among all children en-

<table>
<thead>
<tr>
<th>Table 1. Baseline Patient Demographic and Microbiologic Characteristics*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment Group</strong></td>
</tr>
<tr>
<td><strong>Demographic</strong></td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
</tr>
<tr>
<td>Acute respiratory tract infection</td>
</tr>
<tr>
<td>Otitis media</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Sinusitis</td>
</tr>
<tr>
<td>Received any microbial agent in last 2 mo</td>
</tr>
<tr>
<td>β-Lactam</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td>No. of children in household, median (IQR)</td>
</tr>
<tr>
<td>Age of other children in household, median (IQR), y</td>
</tr>
</tbody>
</table>

| **Microbiologic**                                     |                                          |
| Colonization with Streptococcus pneumoniae            | 296 (74)                                | 287 (72)                             |
| Resistance to penicillin                              | 15 (4)                                  | 11 (3)                               |
| Intermediate susceptibility to penicillin             | 92 (23)                                 | 92 (23)                              |
| Resistance to amoxicillin                             | 1 (0.3)                                 | 0                                    |
| Intermediate susceptibility to amoxicillin            | 2 (0.5)                                 | 0                                    |
| Resistance to trimethoprim-sulfamethoxazole          | 47 (12)                                 | 45 (11)                              |
| Intermediate susceptibility to trimethoprim-sulfamethoxazole | 29 (7)                                 | 36 (9)                              |

*Data are No. (%) unless otherwise noted. IQR indicates interquartile range. The high-dose, short-course group received amoxicillin, 90 mg/kg per day, for 5 days and the standard group received amoxicillin, 40 mg/kg per day, for 10 days. No variables listed in this table were statistically significant between groups at P<.05.
AMOXICILLIN AND RESISTANT PNEUMOCOCCAL CARRIAGE

Table 2. Risk Factors for PNSP Carriage Among Pneumococcal Carriers at Baseline*  

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>PNSP Carriage (n = 210)</th>
<th>PSSP Carriage (n = 373)</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic use in last 2 mo†</td>
<td>63 (30)</td>
<td>68 (18)</td>
<td>1.5 (1.2-1.8)</td>
<td>.001</td>
</tr>
<tr>
<td>≥3 Children in home</td>
<td>114 (54)</td>
<td>167 (45)</td>
<td>1.3 (1.0-1.6)</td>
<td>.03</td>
</tr>
<tr>
<td>School or day care attendance</td>
<td>26 (12)</td>
<td>29 (8)</td>
<td>1.4 (1.0-1.8)</td>
<td>.07</td>
</tr>
<tr>
<td>Visit to a clinic in last 60 d</td>
<td>133 (63)</td>
<td>219 (59)</td>
<td>1.1 (0.9-1.4)</td>
<td>.27</td>
</tr>
<tr>
<td>Young age (&lt;1.5 y)</td>
<td>115 (55)</td>
<td>195 (52)</td>
<td>1.1 (0.9-1.3)</td>
<td>.56</td>
</tr>
<tr>
<td>Exclusive breastfeeding for ≥1st 6 mo</td>
<td>65 (31)</td>
<td>113 (30)</td>
<td>1.0 (0.8-1.3)</td>
<td>.87</td>
</tr>
<tr>
<td>Tobacco use in home</td>
<td>45 (21)</td>
<td>79 (21)</td>
<td>1.0 (0.8-1.3)</td>
<td>.94</td>
</tr>
</tbody>
</table>

*PNSP indicates penicillin-nonsusceptible Streptococcus pneumoniae; PSSP, penicillin-susceptible S pneumoniae.  
†Antibiotic use in last 7 days was an exclusion criterion.

Figure 1. Flow of Participants Through the Intention-to-Treat Trial

- 811 Eligible Patients
- 16 Not Randomized
- 795 Randomized
  - 398 Randomized to Receive Short-Course, High-Dose Amoxicillin
    - 391 NP Specimens Obtained
  - 379 Completed Day 5 Follow-up
    - 375 NP Specimens Obtained
  - 369 Completed Day 10 Follow-up
    - 364 NP Specimens Obtained
  - 368 Completed Day 28 Follow-up
    - 355 NP Specimens Obtained
  - 371 Completed Day 5 Follow-up
    - 365 NP Specimens Obtained
  - 358 Completed Day 10 Follow-up
    - 359 NP Specimens Obtained
  - 371 Completed Day 28 Follow-up
    - 346 NP Specimens Obtained

NP indicates nasopharyngeal.

rolled, 73% carried S pneumoniae and 26% carried PNSP. Most isolates had intermediate resistance; 129 (61%) of 210 PNSP isolates were also nonsusceptible to trimethoprim-sulfamethoxazole. Less than 1% of all isolates were nonsusceptible to amoxicillin (Table 1). Predictors of PNSP carriage among participants are summarized in Table 2. Recent antibiotic use and living in a household with 3 or more children were significantly associated with PNSP carriage. Day care or school attendance was rare in this population and was not statistically significant (P = .07).

Follow-up Visits

The patient return rate and nasopharyngeal specimen collection rate were more than 85% for all follow-up visits; return rates did not differ between groups (Figure 1). Follow-up visits did not always fall on the targeted day, with the most variation at the day 28 visit (day 5: median, 5 [interquartile range (IQR), 5-6]; day 10: median, 10 [IQR, 10-11]); day 28: median, 28 [IQR, 28-30]).

Pneumococcal Carriage During and After Therapy

The proportion of participants with penicillin-susceptible S pneumoniae (PSSP) and PNSP carriage in each treatment group is shown by follow-up visit in Figure 2. Pneumococcal carriage had declined similarly in both groups by day 5. At day 10, carriage was significantly higher in the short-course, high-dose group compared with the standard-course group, which was still receiving antibiotic therapy; on the day 28 visit, carriage in both groups had increased to more than 50% and did not differ significantly.

During the first 5 days of treatment, the proportion of participants carrying PSSP declined dramatically in both groups and the proportion colonized with PNSP also decreased significantly (Figure 2, Table 3). Among pneumococcal carriers, however, the proportion with PNSP more than doubled from day 0 to day 5. At the day 5 visit, the proportion of children carrying PNSP did not differ significantly between groups.

At the day 28 visit, the risk of PNSP carriage (simple RR; Table 3) was significantly lower in the short-course, high-dose group compared with the standard-course group. Additionally, in contrast with the standard-course group, children in the short-course, high-dose group did not have a higher risk of PNSP carriage at the day 28 visit compared with day 0.

When the analysis was limited to pneumococcal carriers, the risk of PNSP carriage (conditional RR; Table 3) at the day 28 visit was also significantly lower in the short-course, high-dose group compared with the standard-course group. However, both groups had a higher risk of carrying PNSP at the day 28 visit compared with that at day 0.

A per-protocol analysis excluding children who took alternative antibiotic therapy during the study period and limited to children who returned for follow-up visits close to the targeted day and who took 80% to 120% of their prescribed treatment regimen showed results similar to the intention-to-treat analysis.

Among pneumococcal isolates, the minimum concentration of penicillin that inhibited growth of 50% of pneumococcal isolates (MIC50) increased in both groups from 0.03 µg/mL at baseline to a maximum of 1.00 µg/mL at the end of treatment; at the day 28 visit, pneumococcal isolates in the short-course, high-dose group had a lower MIC50 than those in the standard-course group (0.05 µg/mL vs 0.19 µg/mL; Kruskal Wallis


χ² = 3.74; P = .05). Among nonsusceptible isolates, the MIC₅₀ increased from day 0 to day 5 in the short-course, high-dose group from 0.38 µg/mL to 1.0 µg/mL and in the standard-course group from 0.50 µg/mL to 1.0 µg/mL and remained similarly elevated at day 28. Throughout the study, 2% to 3% of children in each treatment group carried strains with high-level penicillin resistance.

**Carriage of Trimethoprim-Sulfamethoxazole–Nonsusceptible Pneumococci**

The proportion of children carrying trimethoprim-sulfamethoxazole–nonsusceptible pneumococci at the day 28 visit was lower in the short-course, high-dose group compared with the standard-course group in the population as a whole (short-course, high-dose group, 62/355 [17%] vs standard-course group, 81/346 [23%]; RR, 0.77; 95% CI, 0.58-1.03; P = .08) and among pneumococcal carriers at the day 28 follow-up visit (62/180 [34%] vs 81/185 [44%], respectively; RR, 0.76; 95% CI, 0.59-0.99; P = .04).

**Impact of Treatment Regimen on Colonization Dynamics**

Table 4 summarizes rates of transition between pneumococcal carriage states (no carriage, PSSP carriage, or PNSP carriage) during and after treatment. From baseline to the day 5 visit, the transition rate from PSSP carriage to no carriage was higher in the short-course, high-dose group (P = .04); during treatment, the rates of transition from PNSP carriage to no carriage and from PSSP carriage to PNSP carriage did not differ between groups.

From baseline to the day 28 visit, the transition rate from PNSP carriage to PSSP carriage was higher among the short-course, high-dose group (P = .046). This rate was similarly elevated from day 5 to day 28 (P = .03) and from day 10 to day 28 (P = .006).

**Figure 2.** Pneumococcal Nasopharyngeal Colonization and Prevalence of Penicillin Nonsusceptibility at Days 0, 5, 10, and 28

<table>
<thead>
<tr>
<th>Day</th>
<th>No Carriage</th>
<th>Susceptible</th>
<th>Nonsusceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-Course, High-Dose Therapy, n = 355 (89%)</td>
<td>49</td>
<td>27</td>
<td>24</td>
</tr>
<tr>
<td>Standard Therapy, n = 346 (87%)</td>
<td>46</td>
<td>22</td>
<td>27</td>
</tr>
</tbody>
</table>

Non-susceptible indicates penicillin-nonsusceptible pneumococci; susceptible, penicillin-susceptible pneumococci. Results of within- and between-group comparisons are shown in Table 3.

**Table 3.** Within- and Between-Group Comparisons of Risk of PNSP Carriage*

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>Simple RR (95% CI)</th>
<th>P Value</th>
<th>Conditional RR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-course, high-dose group vs standard group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 5</td>
<td>0.90 (0.68-1.20)</td>
<td>.48</td>
<td>1.04 (0.90-1.20)</td>
<td>.59</td>
</tr>
<tr>
<td>Day 10</td>
<td>1.16 (0.88-1.53)</td>
<td>.29</td>
<td>0.85 (0.72-1.00)</td>
<td>.05</td>
</tr>
<tr>
<td>Day 28</td>
<td>0.77 (0.60-0.97)</td>
<td>.03</td>
<td>0.78 (0.65-0.95)</td>
<td>.01</td>
</tr>
<tr>
<td>Short-course, high-dose group vs day 0</td>
<td>0.71 (0.58-0.86)</td>
<td>&lt;.001</td>
<td>1.90 (1.60-2.21)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Day 28 vs day 0</td>
<td>0.88 (0.71-1.08)</td>
<td>.23</td>
<td>1.22 (1.02-1.48)</td>
<td>.03</td>
</tr>
<tr>
<td>Standard group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 5 vs day 0</td>
<td>0.82 (0.68-0.99)</td>
<td>.03</td>
<td>1.88 (1.60-2.20)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Day 28 vs day 0</td>
<td>1.20 (1.00-1.44)</td>
<td>.06</td>
<td>1.60 (1.36-1.89)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*The simple relative risk (RR) evaluates the proportion of penicillin-nonsusceptible *Streptococcus pneumoniae* (PNSP) carriers in the entire cohort (individuals with and without PNSP). The conditional RR evaluates the risk conditional on pneumococcal carriage. All RRs, confidence intervals (CIs), and P values were calculated using binomial regression, taking into account the repeated-measures design, as described in the *Methods* section of the text.

©2001 American Medical Association. All rights reserved.
Interaction Between Treatment Regimen and Number of Children per Household

We evaluated whether the number of children per household influenced treatment differences in risk of PNSP carriage by classifying children according to whether they lived in households with 3 or more children. We evaluated a saturated model including all the main effects and interaction terms of treatment, follow-up visits, and children per household. Among households with 3 or more children (n=364), risk of PNSP carriage at the day 28 visit was significantly lower in the short-course, high-dose group relative to the standard group (RR, 0.72; 95% CI, 0.52-0.98). In contrast, among households with fewer than 3 children (n=431), the risk was not significantly different (RR, 0.85; 95% CI, 0.59-1.21).

Adverse Events and Adherence

The frequency of adverse events potentially associated with treatment was low and similar across treatment groups (short-course, high-dose group, 23/397 [6%]; standard-course group, 19/398 [5%]). In both groups, diarrhea was most common (34/42 [88%]) followed by vomiting (8/42 [20%]) and rash (4/42 [10%]). No adverse events required medical treatment.

Adherence to treatment regimens could be evaluated in 655 participants (n=349 in the short-course, high-dose group and n=306 in the standard-course group); 511 (78%) took 80% to 120% of their required medicine and were considered adherent. Among non-adherent participants (n=144), two thirds took more medicine than prescribed and one third took less. Overall, adherence was higher in the short-course, high-dose group (82% vs 74%; P=.02). Among those receiving the standard course, we could evaluate adherence separately for days 0 to 5 and 6 to 10. Adherence was significantly lower during days 6 to 10 (183/321 [57%] vs 274/345 [79%]; P<.001), primarily because of failure to take sufficient medicine during the second half of treatment.

**COMMENT**

Although data on the clinical efficacy of shorter courses and the safety of higher doses are increasing, few studies have evaluated how short-course, high-dose therapies affect carriage of nonsusceptible pneumococci. We found that short-course, high-dose therapy reduced an individual's risk of posttreatment carriage of pneumococci nonsusceptible to penicillin and to trimethoprim-sulfamethoxazole compared with standard therapy. This effect was evident at the day 28 visit (2-3 weeks after treatment termination) and not earlier; we do not have data past that point to determine how long it persists.

Among pneumococcal carriers, the posttreatment risk of PNSP carriage was also lower in the short-course, high-dose group. In both standard and modified regimens, however, risk of PNSP conditional on carriage was higher at the day 28 visit than at baseline. This suggests that although the modified regimen reduced an individual's risk of resistant pneumococcal carriage, both regimens may still increase potential for transmission of resistance to the community by reducing carriage of susceptible pneumococci.

The implications of these results are particularly important for β-lactam therapy because penicillin nonsusceptibility correlates strongly with genetically unrelated resistance profiles. Thus, interventions that reduce risk of PNSP may also reduce risk of carrying strains nonsusceptible to other drug classes, as we observed for trimethoprim-sulfamethoxazole.

Mechanisms explaining the lower risk of posttreatment PNSP carriage in the short-course, high-dose group remain unclear. Increased carriage of nonsusceptible strains in the standard-course group occurred after treatment ended rather than during treatment. Moreover, the difference between treatment groups at day 28 was statistically significant among households with 3 or more children, whereas the effect was weaker in households with fewer children. This suggests that the 10-day course increased the likelihood that other children in the household would acquire PNSP carriage while their sib-

---

**Table 4. Transition Rates Between Pneumococcal Carrier States From Day 0 to Days 5, 10, and 28**

<table>
<thead>
<tr>
<th>Periods</th>
<th>From None to</th>
<th>From Penicillin-Susceptible to</th>
<th>From Penicillin-Nonsusceptible to</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Susceptible</td>
<td>Nonsusceptible</td>
<td>None</td>
</tr>
<tr>
<td>Day 0 to 5</td>
<td>1/92 (1)</td>
<td>5/92 (5)</td>
<td>86/92 (94)</td>
</tr>
<tr>
<td>Short-course,</td>
<td>1/101 (1)</td>
<td>4/101 (4)</td>
<td>96/101 (95)</td>
</tr>
<tr>
<td>high-dose group</td>
<td></td>
<td></td>
<td>125/165 (76)</td>
</tr>
<tr>
<td>Standard group</td>
<td></td>
<td></td>
<td>21/165 (13)</td>
</tr>
<tr>
<td>Day 0 to 10</td>
<td>5/90 (6)</td>
<td>9/90 (10)</td>
<td>76/90 (84)</td>
</tr>
<tr>
<td>Short-course,</td>
<td>4/97 (4)</td>
<td>4/97 (4)</td>
<td>89/97 (92)</td>
</tr>
<tr>
<td>high-dose group</td>
<td></td>
<td></td>
<td>126/164 (77)</td>
</tr>
<tr>
<td>Standard group</td>
<td></td>
<td></td>
<td>23/164 (14)</td>
</tr>
<tr>
<td>Day 0 to 28</td>
<td>19/89 (20)</td>
<td>16/89 (18)</td>
<td>55/89 (62)</td>
</tr>
<tr>
<td>Short-course,</td>
<td>17/97 (17)</td>
<td>19/97 (20)</td>
<td>61/97 (63)</td>
</tr>
<tr>
<td>high-dose group</td>
<td></td>
<td></td>
<td>70/152 (46)</td>
</tr>
</tbody>
</table>

©2001 American Medical Association. All rights reserved.
ling received antibiotic therapy; this, in turn, increased the likelihood that the sibling would acquire a nonsusceptible strain after treatment. Rapid transmission of pneumococci among children in close contact, such as those in day care, children in orphanages, and siblings in a household, has been observed.7,28,29 In this study, we did not collect nasopharyngeal specimens from participants’ siblings and, thus, cannot evaluate this hypothesis directly.

In contrast with pharmacodynamic predictions, we found no evidence that the higher-dose regimen more effectively eradicated PNSP than the standard regimen. The higher transition rate from susceptible carriage on enrollment to no carriage at the day 5 follow-up visit in the short-course, high-dose group suggests instead that the high-dose treatment may have been more effective than the standard course at eliminating susceptible pneumococci. In contrast with the prediction that standard-course therapy provides more time for unmasking and amplification of minority resistant pneumococcal clones that were not detectable at baseline, transition rates from PSSP carriage at baseline to PNSP carriage at days 5 and 10 were not higher in the standard-course regimen. Additionally, inconsistent with the prediction that individuals in longer-course therapy have more time to acquire resistant strains during treatment, we found no evidence that individuals in the standard-course group acquired PNSP at an increased rate during treatment.

Results of this study should be considered within the context of a number of limitations. First, we did not perform molecular or serotype analysis of pneumococcal strains. While such information would shed light on the pneumococcal dynamics within individuals, particularly clarifying whether individuals who carried susceptible or nonsusceptible pneumococci throughout the study truly carried the same strain, it does not affect our evaluation of treatment differences or our clinical conclusions. Additionally, we could assess adherence to treatment regimen only among participants who returned medication bottles; it is possible that participants who returned bottles were more adherent than those who did not. Moreover, the volume of remaining medication may not always have accurately reflected the volume of medication taken; in some cases parents reported giving medication to other children. However, because a per-protocol analysis limited to children who adhered to treatment found similar trends, we do not think these difficulties in measuring adherence biased our comparison of regimens.

Finally, the impact of dose and duration of antibiotic therapy is likely to differ depending on the antibiotic used and the prevalence of pneumococcal carriage and intermediate- and high-level resistance in the community. Thus, generalizations from a single clinical trial to other populations should be made with caution. We anticipate that colonization rates and the prevalence of intermediate- and high-level resistance observed in this population will be similar to that in many developing countries.1,2,3,10-33 Moreover, risk factors for PNSP carriage in our baseline population were similar to those reported for other studies, although day care attendance was not a common exposure among participants. If treatment regimens can be modified to minimize carriage of resistant pneumococci while maintaining clinical efficacy, encouraging such prescribing practices represents a low-cost, feasible intervention to limit spread of resistance in developing countries. Short-course, high-dose therapy, which resulted in both improved adherence and decreased risk of PNSP carriage, appears promising as a complement to other approaches to managing spread of resistant pneumococci such as appropriate antibiotic use campaigns.5,34-36 and introduction of the pneumococcal conjugate vaccine.37,38

Author Affiliations: Division of Bacterial and Mycotic Diseases, National Center for Infectious Diseases (Dr Schrag and Besser), and Epidemic Intelligence Service, Epidemiology Program Office (Dr Schrag), Centers for Disease Control and Prevention, Atlanta, Ga; Departamento de Enfermedades Infecciosas, Clínica Infantil Dr Robert Reid Cabral, Santo Domingo, Dominican Republic (Dr Fernández, Sánchez, Gómez, Pérez, and Feris).

Author Contributions: Study concept and design: Schrag, Feris, Besser. Acquisition of data: Peña, Fernández, Sánchez, Gómez, Pérez. Analysis and interpretation of data: Schrag, Fernández, Pérez, Feris. Drafting of the manuscript: Schrag. Critical revision of the manuscript for important intellectual content: Schrag, Peña, Fernández, Sánchez, Gómez, Pérez, Feris. Obtained funding: Besser.

Administrative, technical, or material support: Schrag, Besser. Study supervision: Schrag, Peña, Fernández, Sánchez, Gómez, Feris, Besser.

Funding/Support: This study was funded by the US Agency for International Development. Amoxicillin was donated by SmithKline Beecham.

Disclaimer: SmithKline Beecham did not contribute to study design, analysis or interpretation; company staff reviewed the manuscript but were not required to approve it.

Acknowledgment: We are grateful to Michelle Adler, MD, Nancy Aquino, Lic, Maria Cuervo, Alexander Dominguez, Richard Hacklum, PhD, Teresa Herrera, RN, Lesley LaClaire, MS, Dominica Martínez, RN, Antonio Mejía, MD, Juan Molina, Mirna Novas, Lic, Melida Perez, Mindy Perilla, MPH, Brian D. Plkaytis, MS, Derlys Ramos, Lic, Dignora Rosario, RN, and Elizabeth Zelle, MStat, for their contributions to the project. We are grateful to Scott Dowell, MD, Marc Lipsitch, DPhil, and Anne Schuchat, MD, for comments on an early version of the manuscript.

REFERENCES


26. National Committee for Clinical Laboratory Standards. MIC Interpretive Standards (µg/mL) for Streptococcus pneumoniae. Villanova, Pa: National Committee for Clinical Laboratory Standards; 2000. Table 2G.


