Spread of Multidrug-Resistant *Streptococcus pneumoniae* among Hospitalized Children in Slovakia


A multidrug-resistant serotype 14 strain of *Streptococcus pneumoniae* was isolated from sterile-site specimens and nasopharyngeal secretions from >200 children in Slovakia between 1985 and 1990. Nasopharyngeal culture surveys were done to determine the extent of spread and means of transmission of this strain. The resistant strain was isolated from cultures of 8 (33.0%) of 24 children at hospital A and from 1 (0.8%) of 130 children attending outpatient clinics or day care centers (P < .001). One-quarter of the initially uncolonized children at hospital A acquired the resistant strain during hospitalization. Among hospitalized children, frequent antimicrobial drug use (P < .01), prior hospitalization (P < .005), and length of hospital stay (P < .001) were associated with infection with the resistant strain. These findings support limiting broad-spectrum antimicrobial drug use and nonessential hospitalizations in settings where drug-resistant pneumococci are prevalent. Development of a pneumococcal vaccine that is immunogenic in young children is urgently needed.

*Streptococcus pneumoniae* is the leading bacterial cause of meningitis, pneumonia, otitis media, and sinusitis and a frequent cause of bacteremia. Fifty years after the introduction of penicillin, highly penicillin-resistant strains of *S. pneumoniae* (MIC, ≥2 μg/mL) are emerging in many parts of the world [1–15]. Infections caused by highly penicillin-resistant and multidrug-resistant pneumococci are often difficult to treat [16–18], and effective strategies to limit the spread of such strains have not been identified [19–21].

We recently described the presence of a highly penicillin-resistant (MIC, 4–16 μg/mL) and multidrug-resistant serotype 14 pneumococcal strain causing a high proportion of invasive pneumococcal infections among children in a community in rural Slovakia [22]. The current investigation was initiated to characterize through a prospective study the settings in Slovakia where transmission of the drug-resistant strain occurs and to further define risk factors for its transmission.

**Methods**

**Study population.** Topolcany district, Slovakia has a population of 161,476, including 13,155 children <6 years old (1990 census estimate). Topolcany is divided into three communities, each with one hospital, and one laboratory processes microbiology specimens from all hospitals and outpatient clinics. Community A, the Topolcany community where drug-resistant pneumococci had been isolated just before the study period, has 38,000 persons residing in 38 villages. The 42-bed pediatric ward in hospital A houses children <15 years old and is staffed by 4 physicians and 21 nurses. The ward had 11 inpatient rooms, an examining room, a treatment room, and a small play and eating area connecting to a central corridor. Children are placed in rooms on the basis of similar age and according to available space.

**Case definition of carriers.** We considered a carrier of penicillin-resistant *S. pneumoniae* to be a child or adult from whom an oxacillin-resistant pneumococcal strain (oxacillin disk zone size <20 mm) was isolated from nasopharyngeal secretions during the study period, 17 January to 22 February 1991. *Detection of nasopharyngeal carriers.* Nasopharyngeal culture surveys were conducted in January and February 1991 in community A. On 17 January 1991, we cultured nasopharyngeal secretions from all 24 children who were <6 years old (range, 1–34 months; median, 8) and all 10 who were 6–15 years old (range, 6–13; median, 11) on the pediatric ward at hospital A. Between 17 January and 22 February 1991, we cultured nasopharyngeal secretion samples from all 25 staff on the pediatric ward at hospital A, 73 randomly selected children <6 years old attending all nine outpatient clinics in community A, and all 57 children <6 years old attending six day care centers in community A. We then compared carriage of the resistant strain among children <6 at the hospital, outpatient clinics, and day care centers.

To evaluate the extent of spread of multiply resistant pneumococci over time, we conducted serial culture surveys at hospital A at 3- to 6-day intervals between 29 January and 22 February 1991. We cultured nasopharyngeal secretions at least once from all 60 children <6 years old who were hospitalized >24 h during the study period.

**Investigation of risk factors.** Written, standardized questionnaires providing information on demographics, medical history
and day care center attendance were completed for 3 groups of community A children <6 years old whose nasopharyngeal secretions were cultured: 59 (98%) of 60 hospitalized children, 54 (95%) of 57 children attending day care centers, and all 73 children attending outpatient clinics. Data at hospital A from the 19 children carrying and the 40 children not carrying the resistant strain were compared. Denominators for risk variables sometimes differed because information for these variables was incomplete for a few respondents.

**Laboratory procedures.** Nasopharyngeal secretions, obtained as previously described [10] using sterile calcium alginate–tipped swabs on aluminum shafts, were streaked onto two blood agar plates (one trypticase soy base with 5% sheep blood and one animal protein base with 5% sheep blood; both were prepared in the central laboratory) and incubated at 37°C in a 5% CO₂ atmosphere. Pneumococci were isolated and identified by standard methods [23]. Isolates were screened for penicillin susceptibility using the standard oxacillin disk method [24]. All pneumococcal isolates, whether oxacillin-resistant or oxacillin-susceptible, were tested in the Topo1cany laboratory for agglutination to latex beads coated with antibodies to serotype 14 pneumococcal capsular polysaccharide (prepared in the Respiratory Diseases Laboratory at the Centers for Disease Control and Prevention [CDC]) and sent to CDC. Due to problems with isolate viability during storage and shipment, only 14 (64%) of 22 penicillin-resistant pneumococcal isolates were received in viable condition at CDC. Pneumococcal isolates were serotyped and factored by the appearance of capsular swelling [25] using antisera prepared at CDC, and antimicrobial susceptibility was determined by standard broth microdilution methods using medium with 5% lysed horse blood [26] at CDC.

**Statistical analysis.** Statistical comparisons were made using the Mantel-Haenszel χ² tests [27] and Cornfield’s or Taylor series approximation of 95% confidence intervals (95% CIs) [28]. The Epi Info program [29] was used for statistical comparisons.

**Results**

**Nasopharyngeal carriage studies.** *S. pneumoniae* was isolated from 22 (37%) of 60 children <6 years old, no children 6–14 years old, and 3 (12%) of 25 staff members at hospital A between 17 January and 22 February 1991. Three children <6 years old (5%) carried susceptible strains of *S. pneumoniae*, and 19 (32%) carried oxacillin-resistant strains. Thus, 86% of the pneumococcal isolates from children <6 at hospital A were oxacillin-resistant. One staff member (4%) carried a susceptible strain, and 2 (8%) carried an oxacillin-resistant strain.

Twenty (95%) of 21 oxacillin-resistant isolates agglutinated to latex beads coated with antibodies to serotype 14 pneumococcal capsular polysaccharide; no susceptible isolates agglutinated. All 14 resistant isolates tested at CDC were serotype 14 and had the same antimicrobial susceptibility profile as that of earlier oxacillin-resistant serotype 14 strains from Topo1cany [22] (table 1). All resistant isolates had markedly elevated MICs to penicillin (range, 4–8 μg/mL), cefaclor (>16 μg/mL), erythromycin (>8 μg/mL), tetracycline (>16 μg/mL), and chloramphenicol (range, 8–16 μg/mL). The MIC range for all isolates to ceftriaxone was 0.5–2 μg/mL and to trimethoprim-sulfamethoxazole (TMP-SMZ) was 1/19–2/38 μg/mL. All isolates were susceptible to vancomycin and rifampin. For the purposes of this study, we assumed that all oxacillin-resistant pneumococci isolated in Topo1cany during the study period were the same multidrug-resistant serotype 14 strain.

**Susceptible strains of *S. pneumoniae* were isolated from 4 (3%) of 130 children <6 attending day care centers or outpatient clinics in community A. The resistant strain was isolated from 1 child (0.8%); this child was the brother of a child who had previously been an inpatient at hospital A. By comparison, the resistant strain was isolated from 8 (33%) of 24 children <6 during the initial culture survey at hospital A (odds ratio [OR] = 64.5, 95% CI = 7.3–1467.7, *P* < .001).

**Extent of spread study.** Among 60 children <6 years old at hospital A during the study period, 9 were carrying the resistant strain at the time of initial culture (done on days 3–23 of hospitalization), 10 acquired this strain during the study period after ≥1 negative cultures, 30 had ≥2 consecutive negative cultures, and 11 had 1 negative culture. Thus, the rate of acquisition for the resistant strain during the study was 25% (10/40) among children with initial negative cultures who had serial cultures done.

**Risk factors for carriage at hospital A.** We evaluated risk factors for the 59 children with completed questionnaires (98%) by comparing data for the 19 who carried the resistant strain with data for the 40 who did not. Carriers of the resistant strain were similar in age (mean, 16 months) to noncarriers (mean, 12 months; *P* = .17). There was no difference in sex distribution (13 carriers [68%] and 26 noncarriers [65%] were boys).

Prior admission to hospital A was significantly associated with carriage of the resistant strain: 13 carriers (68%) and 9 noncarriers (23%) had been hospitalized there on one or more occasions during the 12 months preceding current hospitalization (OR = 7.2, 95% CI = 1.8–29.9, *P* < .001). The likelihood of isolating the resistant strain from a child’s nasopharyngeal secretions increased significantly with the length of current stay in hospital A (χ² for linear trend = 11.6, *P* < .001), and no

---

**Table 1. Oxacillin-resistant *Streptococcus pneumoniae* isolates from Topo1cany, Slovakia, showing resistance or decreased susceptibility to various antimicrobial agents.**

<table>
<thead>
<tr>
<th>Agent</th>
<th>MIC (μg/mL)</th>
<th>No. of isolates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>≥2</td>
<td>14 (100)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>≥4</td>
<td>14 (100)</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>≥10</td>
<td>14 (100)</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>≥8</td>
<td>14 (100)</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>1/19–2/38</td>
<td>14 (100)</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>≥32</td>
<td>14 (100)</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>≥2</td>
<td>1 (7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 (71)</td>
</tr>
</tbody>
</table>

**NOTE.** Oxacillin disk zone size was <20 mm for resistant isolates.
child from whom a culture was obtained carried the resistant strain on hospital admission (figure 1).

Fourteen carriers (78%) received at least one course of antimicrobial therapy in the month preceding hospitalization, compared with 15 noncarriers (38%; OR = 5.6, 95% CI = 1.4–25.1, P < .01) (table 2). In addition, carriers were more likely than noncarriers to have received two or more courses (sometimes concurrently) of antimicrobial drugs during hospitalization prior to culture (11 [58%] and 12 [30%], respectively; P < .05). There was no difference in the frequency of antimicrobial drug use at the time of culture: 17 carriers (89%) and 32 noncarriers (82%).

When use of specific antimicrobial drugs was evaluated, carriers were more likely than noncarriers to have received erythromycin during current hospitalization prior to culture (10 [53%] and 9 [23%], respectively; P = .02) (table 3). Associations seen for penicillin, ampicillin, cotrimoxazole, and cephalosporins were not statistically significant. Carriers were also more likely than noncarriers to have taken erythromycin (5 [28%] and 3 [8%], respectively; P < .04) or cephalosporins (4 [22%] and 0, respectively; P < .01) in the month prior to hospitalization. Associations seen for penicillin, ampicillin, and cotrimoxazole were not statistically significant (table 3). When analysis was restricted to children who had not been hospitalized in the month preceding current hospitalization, taking erythromycin or a cephalosporin prior to current hospitalization was not significantly associated with carriage of the resistant strain (erythromycin use: OR = 2.9, P = .31; cephalosporin use: OR = undefined, P = .11).

Upper and lower respiratory tract infections were the most frequent admitting diagnoses for both carriers (all 19) and noncarriers (33 [85%]). Among these, 17 (22%) had pneumonia, 30 (52%) bronchitis, 2 (7%) pharyngitis or rhinitis, 2 (5%) tracheitis or laryngitis, and 1 (2%) bronchiolitis. There were no significant differences in day care attendance, number of siblings, outpatient clinic, village of residence,

Table 2. Antimicrobial drug use among carriers and noncarriers of drug-resistant pneumococci at Hospital A in Topolcany, Slovakia.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Carriers (n = 19)</th>
<th>Noncarriers (n = 40)</th>
<th>Odds ratio (95% CI)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 antibiotic course in month before hospitalization</td>
<td>14 (78)</td>
<td>15 (38)</td>
<td>5.6 (1.4–25.1)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>≥ 2 antibiotic courses during hospitalization before culture</td>
<td>11 (58)</td>
<td>12 (30)</td>
<td>3.2 (0.9–11.7)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Antibiotic course at time of culture</td>
<td>17 (89)</td>
<td>32 (82)</td>
<td>1.9 (0.3–14.7)</td>
<td>.47</td>
</tr>
</tbody>
</table>

NOTE. Denominators for risk variables sometimes differed because information for these variables was incomplete for a few respondents.

* Statistical comparisons were made with Mantel-Haenzel χ² tests [27] and Cornfield’s approximation of 95% confidence intervals (CIs) [28], using statistical software [29].
Table 3. Specific antimicrobial drug use among carriers and noncarriers of drug-resistant pneumococci at Hospital A in Topolcany, Slovakia.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Carriers (n = 19)</th>
<th>Noncarriers (n = 40)</th>
<th>Odds ratio (95% CI)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic during hospitalization before culture</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>1 (5)</td>
<td>2 (5)</td>
<td>1.1 (0.0–16.5)</td>
<td>.97</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>7 (37)</td>
<td>8 (20)</td>
<td>2.3 (0.6–9.3)</td>
<td>.17</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>6 (32)</td>
<td>17 (43)</td>
<td>0.6 (0.2–2.3)</td>
<td>.43</td>
</tr>
<tr>
<td>Any β-lactam</td>
<td>14 (74)</td>
<td>25 (63)</td>
<td>1.7 (0.4–6.7)</td>
<td>.40</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>10 (53)</td>
<td>9 (23)</td>
<td>3.8 (1.0–14.6)</td>
<td>.02</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>5 (26)</td>
<td>9 (23)</td>
<td>1.2 (0.3–4.9)</td>
<td>.79</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>4 (22)</td>
<td>0 (0)</td>
<td>Undefined</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Any β-lactam</td>
<td>11 (61)</td>
<td>11 (28)</td>
<td>3.5 (1.0–13.0)</td>
<td>.03</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>5 (28)</td>
<td>3 (8)</td>
<td>4.7 (0.8–30.0)</td>
<td>&lt;.04</td>
</tr>
<tr>
<td>TMP-SMZ</td>
<td>3 (16)</td>
<td>3 (8)</td>
<td>2.3 (0.3–16.7)</td>
<td>.33</td>
</tr>
</tbody>
</table>

NOTE. Denominators for risk variables sometimes differed because information for these variables was incomplete for a few respondents.

* Statistical comparisons were made with Mantel-Haenzel χ² tests [27] and Cornfield’s approximation of 95% confidence intervals (CIs) [28], using statistical software [29].

or underlying medical conditions between carriers and noncarriers.

Discussion

Following the first report of highly penicillin-resistant pneumococcal infections in South Africa in 1977 [2], highly penicillin-resistant and multidrug-resistant strains of S. pneumoniae have emerged in many parts of the world. The increasing prevalence of such strains has greatly complicated therapy of pneumococcal infections, which until recently were routinely treated with penicillin. Antimicrobial drug regimens used to treat meningitis do not consistently achieve the sustained high levels of bactericidal antimicrobial drug in cerebrospinal fluid that are required to successfully treat infections due to penicillin-resistant pneumococci [18]. Furthermore, middle ear fluid levels of drug achieved with most oral antimicrobial agents may not be sufficient to treat acute otitis media due to such strains [30, 31]. Effective strategies to limit the spread of highly drug-resistant pneumococci are urgently needed.

Nosocomial transmission of drug-resistant pneumococcal strains has been suspected [4, 8, 32–34]; in the present prospective study, we document the nosocomial acquisition of drug-resistant pneumococci and correlate the spread of such strains with the length of hospital stay. Prior hospitalization and length of current hospital stay were strongly associated with carriage of the resistant strain. Furthermore, one-quarter of the subjects who were noncarriers at hospital A at the beginning of the study acquired the resistant strain during hospitalization. However, since a single nasopharyngeal culture lacks the sensitivity to rule out colonization with a drug-resistant strain, we cannot exclude the possibility that some patients classified as noncarriers were truly carriers at the time of the initial culture. Nevertheless, the fact that demonstrable carriage of the resistant strain was associated with increasing days of hospital exposure clearly demonstrates that nosocomial acquisition of the resistant strain did occur at hospital A during the study period.

Detection of the resistant strain in specimens from children and staff on a pediatric ward but not from children at day care centers and outpatient clinics in the surrounding community provides further evidence of a nosocomial niche for this drug-resistant pneumococcal strain in Topolcany.

Most persons exposed to and infected with S. pneumoniae do not develop serious illness. Nonetheless, transmission of a multiply drug-resistant pneumococcal strain in Topolcany among hospitalized children is of substantial importance because of the demonstrated potential of this strain to cause invasive disease [22], the presence in hospitals of many persons with altered susceptibility to infection, and the potential risk of spread into the surrounding community.

Hospitals are a potential reservoir for resistant S. pneumoniae because of the frequent use of antimicrobial drugs and physical conditions facilitating transmission of respiratory pathogens. Exposure to previously hospitalized patients occurs frequently in hospitals, and drug-resistant organisms acquired by 1 patient during a prior hospitalization can potentially be transmitted to other patients. Exposure to previously hospitalized children carrying the drug-resistant strain may be particularly important in Topolcany, where persistent carriage of this strain has been documented for up to 8 months (unpublished data). Crowding, a frequent situation in hospital environments, facilitates transmission of pneumococci and other respiratory pathogens [32, 35].

Day care centers have been implicated as the site of transmission of drug-resistant pneumococcal strains in several recent studies [10, 20, 32, 36, 37]. In contrast to these reports, our investigation found no evidence that such centers played a role in transmission of the drug-resistant strain in Topolcany. Young children in Topolcany infrequently attend day care centers, and the drug-resistant strain was not detected during surveys at six different centers. Pneumococcal transmission has also been described in other institutional settings, including nursing homes, shelters for homeless persons, military camps, and a correctional facility [38–42]. With the exception of nursing homes, none of these institutions were present in Topolcany. Furthermore, a previous investigation in Topolcany found no evidence of spread within the adult population [22]. Thus, hospital A was the only site of transmission of the drug-resistant strain identified in this community.

Frequent antimicrobial use and use of prophylactic doses of antibiotics have been implicated in other studies as risk factors
for spread of drug-resistant pneumococci [2, 4, 10, 12, 19, 22, 32]. In Topolcany, we identified frequent antimicrobial drug use during hospitalization (particularly erythromycin) and antimicrobial drug use in the month prior to hospital admission as risk factors for carriage of the drug-resistant pneumococcal strain. None of the children in our study had received prophylactic doses of antimicrobial drugs. Antibiotics are known to suppress normal nasopharyngeal bacterial flora [43], permitting selective nasopharyngeal colonization with drug-resistant pneumococci in settings in which such strains have been introduced. In our study, erythromycin use during hospitalization was associated with carriage of the drug-resistant strain, but penicillin, ampicillin, cephalosporin, and cotrimoxazole use were not. Although erythromycin and cephalosporin use in the month prior to hospitalization were also associated with carriage of the drug-resistant strain, this finding may reflect either more frequent prior hospitalization among carriers or a true association with use of these drugs prior to hospitalization (or both).

Our investigation identified several practices that may have increased the risk of nosocomial transmission of the resistant strain in Topolcany. First, hospitalization was one of the only group exposures for young children in this rural district, in which >90% of children remain at home at least until 2 years of age. Thus, hospitalization was likely a major source of first exposure to new pneumococcal strains.

Second, children in our study attending outpatient clinics and day care centers had been hospitalized much more frequently and for longer mean stays than children of similar age in a recent survey in the United States: 21% (27/130) of Topolcany children <6 years old attending outpatient clinics or day care centers had been hospitalized within the previous 12 months, with a mean hospital stay of 10 days, compared with an estimated 8% of children <5 years old in the United States, with an estimated mean stay of 4.9 days [44]. In Topolcany, after a resistant strain had been introduced, frequent and prolonged hospitalization likely contributed to transmission. Of note, 4 children identified as carriers of the drug-resistant strain during a prior hospitalization were readmitted to hospital A shortly before our investigation; these children may have contributed to transmission of the resistant strain during the study period.

Third, pneumococci are transmitted by respiratory droplets, and illnesses involving cough and rhinorrhea have been associated with pneumococcal spread [32, 34, 35, 45, 46]. As nearly all admissions to hospital A during the study period were for respiratory diseases, this likely enhanced the spread of this strain among hospitalized children.

Fourth, crowding, implicated in spread of pneumococcal infection in a variety of settings [32, 35, 40, 42], may also have facilitated transmission of the resistant strain in Topolcany. Up to 5 children occupied a single room, and children’s cribs were frequently only centimeters apart.

Last, frequent use of broad-spectrum antimicrobial drugs during hospitalization likely contributed to spread of the resistant strain at hospital A (83% of children hospitalized during the survey received at least one macrolide drug or β-lactam drug other than penicillin).

While not all oxacillin-resistant pneumococci identified in Topolcany during the study period remained viable after shipment to CDC, we feel confident that the nonviable isolates were of the same strain because of the uniformity of results for those isolates that remained viable as well as the excellent past concordance between results of screening for oxacillin resistance in Topolcany and antimicrobial susceptibility testing at CDC [22]. In a study of 116 consecutive pneumococcal isolates screened to be oxacillin-resistant in Topolcany, 115 (99%) were confirmed to be penicillin-resistant by antimicrobial susceptibility testing at CDC, and nearly all (96%) penicillin-resistant isolates were of a single serotype (14) [22]. Results of agglutination tests (using latex beads coated with type 14 pneumococcal polysaccharide) done in Topolcany during the current investigation provide further evidence that penicillin-resistant pneumococci isolated during the study were serotype 14.

Controlling the spread of drug-resistant pneumococcal strains is of substantial importance, particularly in institutional settings such as hospitals, nursing homes, and day care centers. Given the current global nature of this problem, development and use of a pneumococcal conjugate vaccine that is immunogenic in young children would clearly be the most effective prevention strategy. In all settings, other important strategies should include encouraging the judicious use of all antimicrobial drugs, implementing a system of routine screening of all sterile-site pneumococcal isolates, and compilation of those data into timely reports on local prevalence and patterns of drug-resistant S. pneumoniae. On the basis of the epidemiologic findings in this study, other approaches that might be considered in Topolcany and similar epidemic settings in hospitals include promoting hospital policies that minimize transmission of respiratory pathogens, such as placing no more than 2 children in one hospital room and cohorting children with respiratory diseases, limiting nonessential hospitalizations, and minimizing the length of hospital stay.

Acknowledgments

We thank Nan E. Pigott and John A. Elliott for technical assistance in serotyping, Bertha Hill for technical assistance in antimicrobial susceptibility testing, and Fred Tenover for oversight and advice on interpretation of drug susceptibility testing.

References


378 Reichler et al. JID 1996; 173 (February)


