MAJOR ARTICLE

Nasopharyngeal Carriage of *Streptococcus pneumoniae* by Adults and Children in Community and Family Settings

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The rate of *Streptococcus pneumoniae* carriage among adults was compared with that among children (age, ≤6 years) in the same population. Nasopharyngeal culture results for 1300 adults and 404 children were analyzed. *S. pneumoniae* was carried by only 4% of the adults, compared with 53% of children in the same community. Young age, day care center attendance, having young siblings, and no antibiotic use during the month before screening were associated with the high carriage rate among children, whereas the only risk factor associated with carriage among adults was the presence of a respiratory infection on the screening day. *S. pneumoniae* serotype distribution and antibiotic resistance patterns differed between adults and children. Isolates of the same serotype—even of the same clone—differed in their antibiotic susceptibility patterns between children and adults. In a subanalysis of 151 pairs of children and their parents and of 32 pairs of siblings, intrafamilial transmission of *S. pneumoniae* could not be demonstrated.

Streptococcus pneumoniae is responsible for most cases of community-acquired pneumonia, meningitis, and sinusitis. Although the rate of mortality due to invasive pneumococcal infection has deceased considerably since the advent of antibiotic therapy, it is still as high as 20%–55% in some populations [1, 2]. The transmission rate of *S. pneumoniae* is directly influenced by the carriage rate in a given population. Thirty percent to 70% of young children carry *S. pneumoniae* in their nasopharynx, and up to 40% of the carriers are colonized with penicillin-nonsusceptible *S. pneumoniae* (PNSP) [3–5].

In contrast to the vast information available on *S. pneumoniae* carriage among children, only scarce data exist on carriage among adults. It is known that the rate of *S. pneumoniae* carriage is low in adults, compared with children: prevalence rates, risk factors for carriage, and factors promoting spread of the organism are limited among adults [6–8].

Several studies have examined household transmission of *S. pneumoniae.* Most have suggested that children are the source of transmission to adults in the family [9–13]. However, there is still a controversy regarding the significance of intrafamilial transmission as a mode of spread [14]. The objective of this study was to further understand the dynamics of transmission of *S. pneumoniae* in the community and in family settings before routine vaccination of children was initiated in Israel.

METHODS

Study population. Fifty primary care clinics that belonged to Maccabi Healthcare Services (MHS; one of

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the major health management organizations in Israel) and that were located in 4 large cities in central Israel participated in the study. The study population comprised children (age, ≤6 years) and adults (age, ≥18 years) who arrived at any of the clinics attending the study for any reason and who agreed to participate and to sign an informed consent statement; for children, parental consent was obtained. Each individual was included only once in the study. Guidelines for human experimentation were followed in the conduct of clinical research.

A subpopulation of family members included both (1) parents who accompanied their children to the pediatrician and who agreed to be screened, and (2) pairs of siblings. Pairs of siblings were either both ill, or one was a healthy child accompanying an ill sibling.

Study design. The study took place during a 6-week period in winter 2001. Nasopharyngeal samples were obtained for culture, and patients or parents responded to an interviewer-administered questionnaire. Data collected included the reason for the specific visit, demographic characteristics, the number of children aged ≤6 years in the household, whether the children attended a day care center (DCC), smoking habits of members of the family, and prior antibiotic treatment. Medical history, immunization history, data on previous infections (respiratory tract infections as well as others), and the diagnosis on the screening day were obtained from the patients' electronic medical file. Records of antibiotics received by each of the participating individuals during the year preceding the study (an antibiotic course was defined as ≥5 days of therapy) were retrieved from the MHS central computer.

Laboratory procedures. Nasopharyngeal samples were obtained for culture with rayon-tipped wire swabs and were placed in Amies transport medium (Copan). Specimens were transferred to the laboratory within 6 h. Swabs were streaked onto tryptic soy agar plates supplemented with 5% sheep blood and gentamicin, 5 μg/mL, and were incubated aerobically at 35°C in 5% CO_2-enriched air. Suspected colonies (α hemolytic colonies with optochin inhibition) were isolated, and susceptibility to oxacillin, erythromycin, tetracycline, trimethoprim-sulfamethoxazole, and ofloxacin was tested using the disk diffusion test in accordance with NCCLS recommendations [15].

All isolates suspected of being PNSP (i.e., those with an oxacillin disk diffusion of <19 mm) were further tested by Etest (AB Biodisk) for susceptibility to penicillin G and ceftriaxone on Mueller-Hinton agar. PNSP isolates had an MIC of penicillin of ≥0.1 μg/mL. All isolates were frozen at −70°C and later serotyped using antisera (Statens Serum Institute of Copenhagen). PFGE was performed for 61 isolates of serotypes 6A, 6B, and 14. Chromosomal DNA fragments, which were generated by *sma*I and *apa*I digestion, were analyzed on agarose gels using the CHEF-DRIII apparatus (Bio-Rad), as described elsewhere [16]. Interpretation of strains' relatedness on the basis of PFGE pattern was performed in accordance with the current consensus [17].

Statistical analysis. The following factors were examined as possible risk factors in the adult population: age, socioeconomic status (size of house and number of habitants per room), smoking habits (active and passive smoking [i.e., inhalation of second-hand smoke]), number of young children at home, number of young children attending a DCC, previous infections, antibiotic use during the month before screening (as registered by MHC pharmacies), and diagnosis on the day of screening. The following factors were assessed in the children: age, socioeconomic status, passive smoking, attendance at a DCC, number of hours at the DCC, number of children in the DCC, number of siblings, previous infections, antibiotic use during the month before screening, and diagnosis on the screening day.

These factors were analyzed by univariate and multivariate analyses. Separate analyses were performed for adults and children. Differences between children and adults were assessed by the Z test. SPSS software, version 10.0 (SPSS), was used. $P < .05$ was considered to be statistically significant.

RESULTS

A total of 1748 persons were screened, of whom 1319 were adults and 429 were children. Thirty-five percent of the adults were male, and the median age of adults was 43 years (range, 18–91 years; 90th percentile, 70 years). Fifty percent of the children were male, and the median age was 2 years (range, 3 weeks to 6 years). Because of data loss, full analysis was performed for 1300 adults and 404 children. A subgroup analysis of family members included 151 pairs of children and their parents and 32 pairs of siblings. These persons were analyzed separately. The rate of refusal of participation in the study was <5%.

S. pneumoniae *carriage.* *S. pneumoniae* was isolated from 265 (16%) of 1704 evaluable individuals (49 [3.7%] of 1300 adults and 216 [53%] of 404 children; $P < .001$) (figure 1). The only significant risk factor for *S. pneumoniae* carriage among adults (by both univariate and multivariate analysis) was diagnosis of a respiratory infection on screening day (OR, 1.93; 95% CI, 0.99–3.77; $P = .05$). The risk factors for *S. pneumoniae* carriage among children were age, attendance at a DCC, having young siblings, and prior antibiotic use.

The rate of carriage among children was highly associated with young age ($P < .001$); it was 41.9% among children aged <1 year, 68.6% among those aged 2–3 years, and 46.4% among those aged 4–6 years. In the adult population, age was not significantly related to the carriage rate (figure 1).

Fifty-eight percent of the examined children attended a DCC. DCC attendance was highly associated with *S. pneumoniae* carriage (OR, 4.7; 95% CI, 2.5–8.6; $P < .001$). Longer duration of stay at the DCC (i.e., a full day of ≥8 h) was associated with

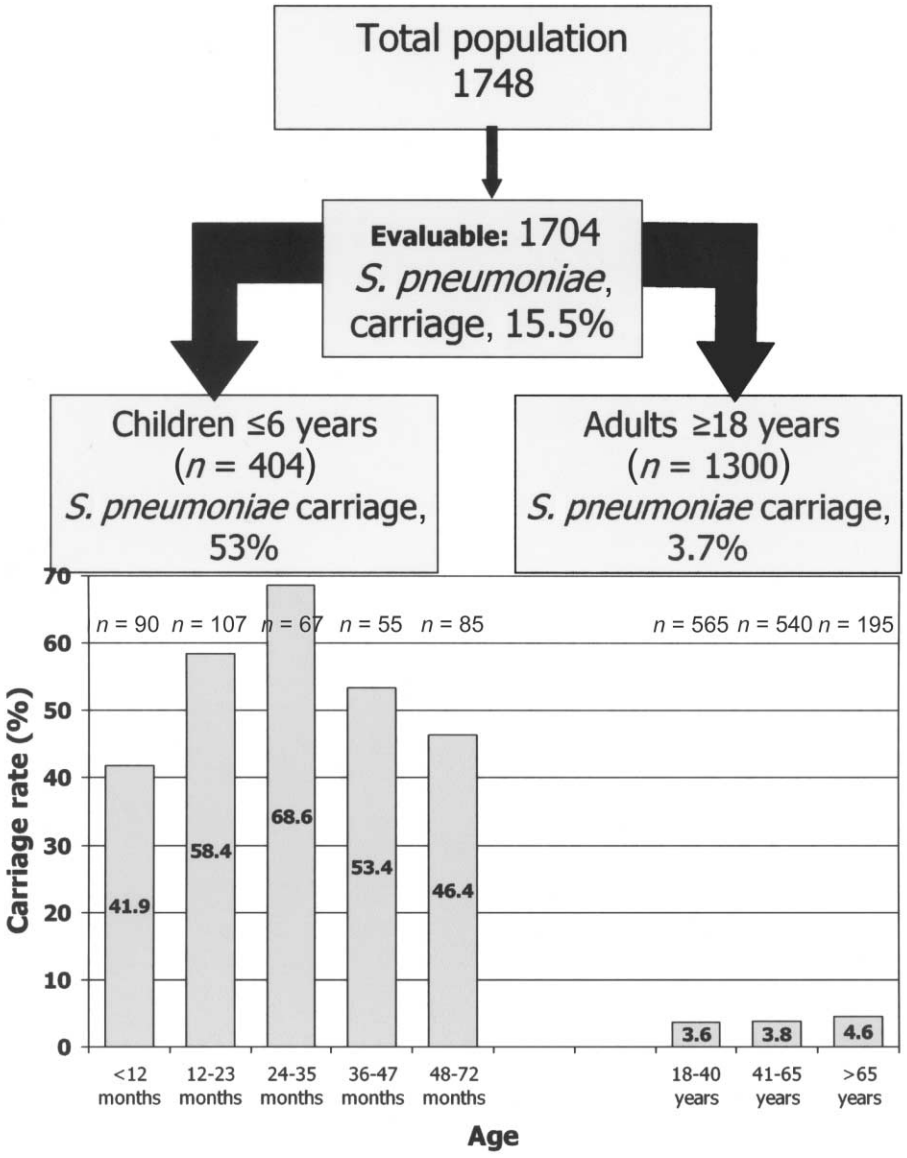

Figure 1. Population and carriage rates in a study of nasopharyngeal carriage of *Streptococcus pneumoniae*

higher carriage rates (OR, 2.04; $P = .03$) than was attendance for one-half of a day or less (i.e., <5 h).

One hundred ninety-eight children (49%) had siblings aged <6 years. Having a young sibling was associated with a higher rate of *S. pneumoniae* carriage (OR, 2.3; 95% CI, 0.95–5.6; $P = .06$). Among the adults, 31% had offspring who were aged <6 years. Of these children, 70% attended a DCC. Adults who were parents to ⩾2 young children were shown to have a trend toward a higher rate of *S. pneumoniae* carriage (OR, 1.89; 95% CI, 0.8–4.0; $P = .11$).

Of the 404 screened children, 173 (43%) received a diagnosis of upper respiratory tract infection (URTI) on the screening day. These children had only a slightly higher carriage rate than did the "healthy" children (i.e., those who arrived at the clinic for any other reason; 56.9% vs. 48.2%; OR, 1.4; 95% CI, 0.96–2.2; $P = .08$). Of the adult population screened, 192 (15%) had a URTI diagnosed on the screening day. The carriage rate among adults who had a URTI was 6.3%, compared with 3.4% among "healthy" adults (OR, 1.9; 95% CI, 0.97–3.72; $P = .065$).

Antibiotic consumption during the month before screening was reported by 16% of adults. However, only 68% of these agents were received at MHS pharmacies. Antibiotic use was not associated with higher or lower rates of *S. pneumoniae* carriage in adults (3.3% vs. 3.9%; $P = .82$).

One-fourth (25.5%) of the children were treated with an antibiotic during the month before screening, according to their

parents' report. Only 75% of these regimens were purchased from the MHS pharmacies. The antibiotic disposition rate during the 3 months before screening was 40.4%; thus, the true rate of use may have been >50%. Antibiotic treatment during the month before screening significantly lowered the *S. pneumoniae* carriage rate, from 56.8% for those who did not receive antibiotics to 40.8% for those who received an antibiotic course (OR, 0.52; 95% CI, 0.33–0.82; $P = .01$).

Antibiotic resistance among* S. pneumoniae *isolates. A total of 92 (34.8%) of 264 isolates were PNSP. Seventy-nine (36.7%) of 216 isolates recovered from children were PNSP, and 13 (26.5%) of 49 isolates recovered from adults were PNSP. Full resistance to penicillin (MIC, >1.0 μg/mL) was not detected in isolates recovered from either population.

The prevalence of resistance to erythromycin, penicillin, tetracycline, and trimethoprim-sulfamethoxazole was lower among adults than among children (figure 2). Resistance to fluoroquinolones was not observed in persons from either age group. A significant difference in resistance rates between children and adults was observed for erythromycin and for multidrug resistance (i.e., resistance to ⩾3 antibiotic classes; for erythromycin, 23.3% vs. 6.1% [$P = .02$]; for multidrug resistance, 19.1% vs. 4.1% [$P = .03$]).

Because of the small number of PNSP carriers among adults, it was impossible to determine risk factors. Risk factors for PNSP carriage in children have been described in detail elsewhere [18]. The only significant independent risk factor was antibiotic use during the 3 months before screening (OR, 2.24; 95% CI, 1.64–3.05; $P < .001$). Trends toward higher PNSP carriage rates were observed for age of <24 months (OR, 1.77; 95% CI, 0.8–3.7; $P = .1$) and DCC attendance (OR, 1.54; 95% CI, 0.8–3.0; $P = .2$) but did not reach significance.

Pneumococcal serotypes. The distribution of serogroups and serotypes of *S. pneumoniae* is shown in table 1. Of the 265 isolates, 229 (92%) belonged to 33 serotypes, 20 were nontypeable, and 8 were lost before serotyping was performed. The most frequently isolated serotypes among adults were 6A, 14, 6B, 33F, 11A, 3, and 10, which accounted for 47.4% of all isolates recovered from adults and for 24.1% of all isolates recovered from children ($P = .02$). Nontypeable *S. pneumoniae* accounted for 23.7% of all isolates recovered from adults and for 5.2% of all isolates recovered from children ($P < .001$). In children, serotypes 6B, 19F, 23F, 6A, 14, 35B, and 23A were the most common, accounting for 53.1% of all isolates. These serotypes accounted for only 26.3% of all isolates recovered from adults ($P = .01$).

Serotypes included in the currently available pneumococcal 7-valent conjugate vaccine (types 4, 6B, 9V, 14, 18C, 19F, and 23F) were identified in 42.2% of isolates recovered from children; if the cross-reactive serotypes are included, the rate increases to 59.24%. These serotypes represented only 21% of isolates recovered from adults (if the cross-reactive types were included, the rate is 36.8%) (for vaccine types, $P = .01$ for children vs. adults; for cross-reactive serotypes, $P = .007$ for children vs. adults). Of the isolates recovered from adults, 52.6% belonged to the serotypes included in the 23-valent pneumococcal polysaccharide vaccine.

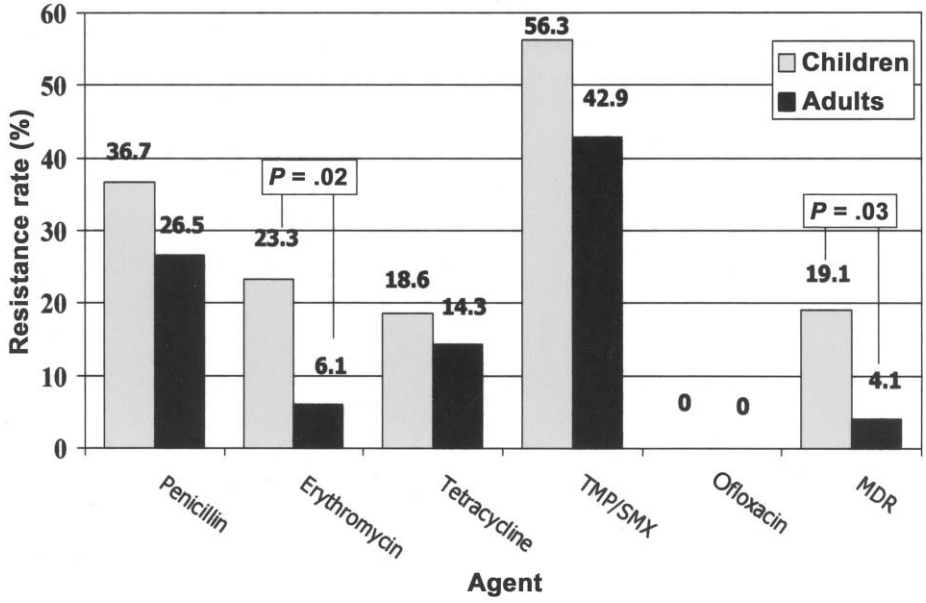

Figure 2. Resistance pattern among *Streptococcus pneumoniae* carriers (215 children and 49 adults). MDR, multidrug resistance; TMP/SMX, trimethoprim-sulfamethoxazole.

Table 1. Distribution of *Streptococcus pneumoniae* serotypes among children and adults.

Serotype	No. (%) of isolates	
	Children (n = 211)	Adults (n = 38)
6B	23 (10.9)	2 (5.26)
23F	21 (9.95)	0 (0)
19F	21 (9.95)	0 (0)
6A	17 (8.06)	5 (13.16)
14	11 (5.21)	3 (7.89)
35B	11 (5.21)	0 (0)
23A	8 (3.79)	0 (0)
33F	0 (0)	2 (5.26)
11A	0 (0)	2 (5.26)
10	0 (0)	2 (5.26)
3	0 (0)	2 (5.26)
Nontypeable	11 (5.21)	9 (23.68)
Other	88 (41.71)	11 (28.95)

Comparison of common serotypes carried by adults and children. Carriage of serotypes 6A, 6B, and 14 was common among both adults and children. Resistance rates of the same serotype were higher in children. Serotype 6A, which was isolated in 17 children and 5 adults, was frequently resistant in children (59% of isolates were PNSP, and 24% were multidrug resistant), whereas isolates recovered from adults were susceptible to all antibiotics. The 3 serotypes common to both adults and children (6A, 6B, and 14) were further analyzed by PFGE. All isolates of serotype 14 were found to be of the international Spain^{9V}-3 clone (figure 3) [19]. Among serotype 6A isolates, the major clone (denoted as "clone A") was common among both adults and children (figure 4). Although all strains of this clone recovered from adults were penicillin susceptible, all but 1 of the strains recovered from children were PNSP. Most isolates recovered from children were also resistant to erythromycin, whereas all isolates recovered from adults were susceptible to erythromycin (figure 5).

S. pneumoniae *carriage in family members.* Of the 151 pairs of children and accompanying parents, 76 (50.3%) had a nonconcordant *S. pneumoniae* carriage state. In 74 pairs, the child was a *S. pneumoniae* carrier and the parent was not a concurrent carrier, and, in 2 pairs, the parent was the carrier and the child was not. In 72 of the 75 remaining pairs, both members were noncarriers; in the remaining 3 pairs in which both members were carriers of *S. pneumoniae,* only 1 pair was found to have been carrying an identical strain, according to serotype, antibiotic susceptibility, and PFGE pattern.

Among the 32 pairs of siblings examined, 24 had concordant *S. pneumoniae* carriage. In 14 of these pairs, both siblings were *S. pneumoniae* carriers. However, only 4 (12.5%) of the pairs carried identical strains.

DISCUSSION

The main findings of our study are that *S. pneumoniae* carriage rate differs significantly between children and adults. *S. pneumoniae* was carried by only 3.7% of the adults, whereas 53% of children of the same population were concurrently carriers. The isolates carried by adults differed from those carried by children with regard to serotype distribution and antibiotic resistance pat-

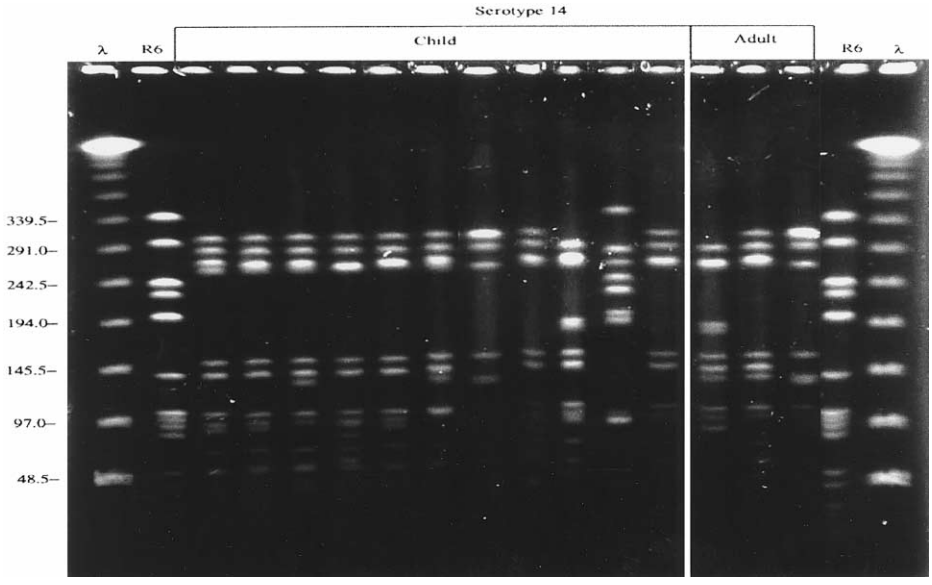

Figure 3. PFGE findings for *Streptococcus pneumoniae* serotype 14

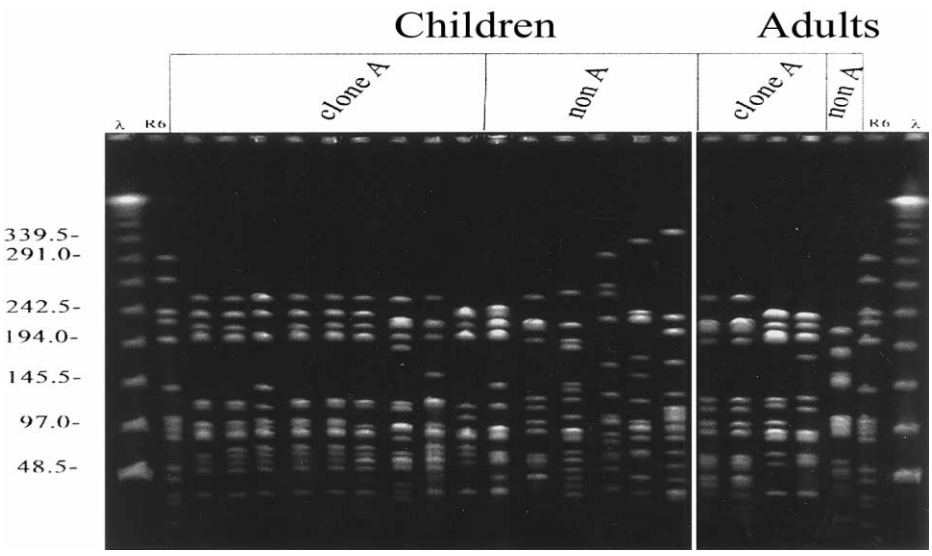

Figure 4. PFGE findings for *Streptococcus pneumoniae* serotype 6A

tern. Isolates of the same serotype, and even isolates of the same clone, recovered from children differed in antibiotic susceptibility pattern from those recovered from adults.

Although the carriage rate among children was found to be within the high range of previously reported *S. pneumoniae* rates, the extremely low carriage rate concurrently found in adults is surprising. Only scarce information exists on adult *S. pneumoniae* carriage, and this was reported in distinct populations [6, 7]. Different carriage rates in children have been reported in different geographical areas [3, 20–25]. Some studies included school-aged children [22], whereas others included younger children [3, 5, 23–25], and the rate of DCC attendance was different in the various studies [20, 23, 25]. Several studies included only healthy children [22], whereas others included children with concomitant respiratory infections [23]. To increase our understanding of the reasons for the extreme difference in carriage rates among adults and children from the same population (3.7% vs. 54%), we analyzed the possible risk factors for the 2 populations separately. The extreme difference could not be solely explained by the different rates of concomitant respiratory illness, nor by the different rates of antibiotic use, the amount of contact with young children (i.e., attending a DCC or having young siblings or offspring), or sex distribution. Therefore, an additional factor is apparently responsible for the low rate of carriage by adults. Optional explanations could be the presence of antibodies to *S. pneumoniae* in adults (boosted by the presence of *S. pneumoniae* in their children) or a decreased number of receptors in the nasopharyngeal epithelium [26–29].

The currently available 7-valent pneumococcal conjugate vaccine covers only 42.2% of the strains carried by children and 21% of strains carried by adults in our study. Similar serotype distribution among isolates recovered from children, as observed in this study, have been previously reported from Israel and from several developing countries [30, 31]. Thus, although the use of this particular vaccine is expected to reduce the rate of pneumococcal illness in children, it may not profoundly reduce the rate of carriage [32].

We assessed *S. pneumoniae* carriage by culture of nasopharyngeal samples, which is considered to be the best sampling method for children [33, 34]. Whether this is the best sampling method for adults was previously questioned [35]. Recent data from our group show that up to 50% of cultures positive for *S. pneumoniae* could derive from a positive throat culture in the presence of negative nasopharyngeal cultures. However, even when using both methods simultaneously for adults, the carriage rate would probably not surpass 10%.

In contrast to previous studies [7, 36], our study did not demonstrate a significantly higher rate of *S. pneumoniae* carriage among elderly individuals, compared with young adults. A sampling error can be excluded, because 10% of the adults sampled were aged >70 years. The discrepancy in results might be explained by the fact that the elderly patients in this study were all living independently at home and were mobile, whereas other such studies have been performed in nursing homes [36].

DCC attendance was shown to be a risk factor for *S. pneumoniae* carriage [3, 14]. Our study also identified DCC attendance as the most significant risk factor for *S. pneumoniae* carriage for children. One-third of the adults sampled were parents of young children. Among these children, 70% attended DCCs. However, an association between being a parent to young children and carrying *S. pneumoniae* was demonstrable only if there was intense exposure, such as exposure to $\geqslant 2$ young children.

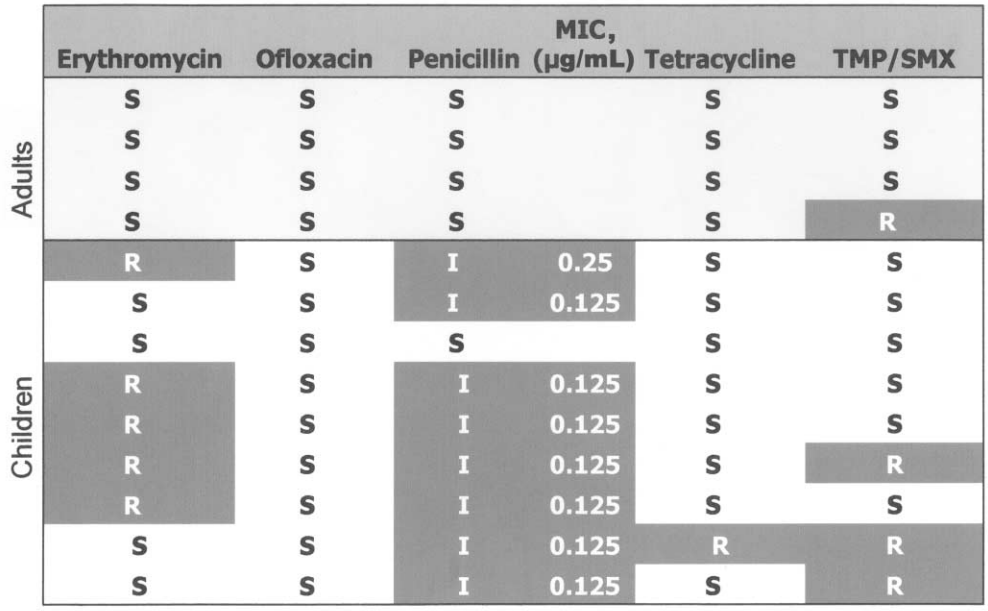

Figure 5. Resistance patterns of the major clone of *Streptococcus pneumoniae* serotype 6A. I, intermediate resistance; R, resistance; S, susceptibility; TMP/SMX, trimethoprim-sulfamethoxazole.

S. pneumoniae isolates recovered from adults tended to have lower antibiotic resistance rates than did those recovered from children. This trend was statistically significant for erythromycin-resistant and multidrug-resistant *S. pneumoniae*. Several explanations are plausible. First, *S. pneumoniae* isolates recovered from adults differed in their serotype distribution from isolates recovered from children. Second, serotypes common to both adults and children (6A, 6B, and 14) differed in their antibiotic resistance patterns; this was observed even in the same clone of the same serotype (6A). The higher antibiotic pressure to which children are exposed has traditionally been used to explain this finding.

Several studies have reported intrafamilial spread of *S. pneumoniae* [9–14, 27]. Recently, Shimada et al. [13] evaluated household transmission of *S. pneumoniae* among siblings with acute otitis media and demonstrated that most siblings had identical nasopharyngeal strains. Hoshino et al. [12] evaluated pairs of *S. pneumoniae* isolates recovered from children and their parents and reported that most were identical. A recent study from Finland [11] that assessed household transmission of *S. pneumoniae* found that the presence of a family member carrying *S. pneumoniae* was a significant risk factor for colonization in infants aged >6 months. On the other hand, Borer et al. [14] showed that strains carried by children residing in a closed community in Israel (a kibbutz) were isolated neither from the children's parents nor from other adults in this community, despite there being a high relatedness of isolates among children, especially among those attending DCCs. Our study showed similar results: only 3 of 151 paired children and parents were both *S. pneumoniae* carriers, and only 1 pair of these carried an identical strain. However, because adults are known to carry *S. pneumoniae* for shorter time periods, and because only a single swab specimen was obtained from each individual, the correlation between carriage rates in children and adults and the concordance of serotypes/clones between children and their parents may have been partially underestimated. Whitney et al. [37] recently found that, after the use of pneumococcal conjugate vaccine in children, a reduction in the rate of pneumococcal infection occurred not only in children, but also in adults. This proves that child-to-parent transmission does play a key role in the adults' pneumococcal morbidity.

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