Acute Otitis Media Caused by Antibiotic-Resistant *Streptococcus pneumoniae* in Southern Israel: Implication for Immunizing with Conjugate Vaccines

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The potential coverage of antibiotic-resistant pneumococci causing acute otitis media (AOM) by 7-, 9-, and 11-valent conjugate pneumococcal vaccines was studied in southern Israel. A total of 876 cases of pneumococcal AOM were studied in the context of various clinical conditions. Of the isolates, 68% were resistant to ≥1 drug, 61% were resistant to penicillin, and 13% were resistant to ≥3 antibiotic classes. Antibiotic resistance and coverage by the various candidates were age and population dependent and were higher among those with a complicated clinical course, as indicated by recent antibiotic use and recurrence of AOM. The results suggest that, if efficacious, the conjugate pneumococcal vaccines can substantially reduce the occurrence of pneumococcal AOM in general and complicated pneumococcal AOM in particular.

Acute otitis media (AOM) is the most common bacterial respiratory tract infection in early childhood worldwide and accounts for >30% of all pediatric health care visits in the United States [1]. In the United States, otitis media is diagnosed in >10 million children yearly, with an estimated annual cost of $5 billion [2]. It is estimated that 61%–93% of children have AOM before the age of 3 years and that up to 20% develop recurrent AOM or chronic otitis media with effusion [3–5].

*Streptococcus pneumoniae* causes 30%–50% of all cases of AOM worldwide [6]. When treated inappropriately, pneumococcal AOM is estimated to have a less favorable course than does AOM caused by other organisms [3, 7], with a lower frequency of spontaneous bacteriologic cure [8]. During the last 25 years and especially during the last decade, a rapidly growing emergence of antibiotic-resistant *S. pneumoniae* has impaired the ability to treat pneumococcal AOM appropriately with the currently available oral drugs [9–13].

Type-specific antipolysaccharide antibodies acquired either passively [14, 15] or through vaccination [16–20] protect against pneumococcal AOM, and the recent development of conjugate vaccines is promising [21, 22]. These new conjugate vaccines contain 7–11 serotypes, covering not only most strains of *S. pneumoniae* causing disease in children worldwide [23] but also most of the resistant strains [13, 24–27]. Results of the first studies of conjugate vaccines show their efficacy in the reduction of nasopharyngeal carriage of *S. pneumoniae* and antibiotic-resistant *S. pneumoniae* [28–32] and in the prevention of invasive infections [33]. Furthermore, preliminary results suggest that a 7-valent pneumococcal vaccine is efficacious in reducing clinic visits for AOM and insertion of ventilation tubes [34, 35].

In preparation for an efficacy trial, we have been conducting a prospective study to determine the prevalence of the various serotypes of AOM in southern Israel, the antibiotic resistance patterns in relation to the pneumococcal serotypes, and the potential coverage provided by the various vaccine candidates against *S. pneumoniae* and antibiotic-resistant *S. pneumoniae* isolates causing AOM in southern Israel.

Such an analysis will enable us not only to choose the appropriate vaccine candidate for an efficacy study but also to further plan the immunization schedule once conjugate vaccines are licensed.

Materials and Methods

**Background.** The southern region of Israel (the Negev) has a heterogeneous population, consisting of ~75% Jews, who live mainly in urban centers and a few rural communities, and ~25% Bedouin Moslem Arabs, who are in various stages of transition from seminomadism to settled modern life. The birth rate among Bedouins is significantly higher than that among Jews, and thus, despite the fact that they constitute only ~25% of the population, the number of births among them was similar to that among Jews in the Negev during recent years: 5648 versus 5471 in 1997 and 5649 versus 5471 in 1999 among Bedouins and Jews, respectively.

Most of the Negev’s Bedouins no longer maintain the traditional way of living in tents but, rather, live in permanent settlements consisting of concrete houses and huts. Recent access to modern
health services and rising standards of living have led to a great reduction in infant mortality, despite few visible changes in their lifestyle and health behavior. Although Bedouins and Jews live in separate communities, some contact does take place in such places as markets, buses, and hospitals. In a previous investigation, we showed that Jewish and Bedouin infants in the Negev region of Israel differ greatly with regard to their birth weights, feeding practices, growth patterns, and prevalence of malnutrition [36]. The latter, which is generally mild and characterized by stunting, is significantly more common among Bedouin infants than among Jewish infants. Differences in cultural socioeconomic status and in the nutritional status of the infants between ethnic groups result in different rates of hospitalization for diarrhea and respiratory illness [37, 38].

**Specimens.** All the pneumococcal isolates from middle ear fluid (MEF) obtained from children with AOM in the Negev area from 1 September 1997 through March 1999 were included. Specimens from spontaneously draining ears were obtained in 15% of the patients. Some of the patients were enrolled in various antibiotic studies, and the rest of the specimens were obtained by the physicians at the clinical service for clinical indications. Information regarding ethnic origin (Jewish or Bedouin), age, sex, previous number of AOM episodes, and previous antibiotic treatment in the last 3 months was obtained from the medical chart and completed by the parents when needed.

All specimens of MEF obtained from hospitalized patients and >90% of those obtained in the community are cultured in one laboratory, the Clinical Microbiology Laboratory of the Soroka University Medical Center (SUMC), which is the only medical center providing hospital services in the Negev. Fewer than 10% of the MEF samples obtained in the community are sent to another laboratory, but all pneumococcal MEF isolates from this laboratory were transferred during the study period to the Clinical Microbiology Laboratory, SUMC, for confirmation, typing, and antibiotic susceptibility testing. Thus, during the study period, all pneumococcal MEF isolates from the Negev region were collected and processed in one central laboratory.

Only 1 isolate was counted per episode (we chose the first isolate during the episode; if the same strain was isolated from both ears, we chose the isolate from the right ear). If >1 serotype was isolated from 1 child during the same episode, all isolates having different serotypes were counted. An episode was defined by a pathogen-free interval of 30 days between isolations if the 2 isolates were of the same serotype or by any interval if the 2 isolates were of different serotypes.

**Bacteriology.** Swabs were placed in MW173 Amies transport medium (Transwab; Medical Wire and Equipment, Potley, UK) and were processed within 4 h at the Clinical Microbiology Laboratory, SUMC. Swabs were plated immediately on trypticase agar media containing 5% sheep blood, and incubated aerobically at 35°C for 48 h. Presumptive identification of *S. pneumoniae* was based on the presence of α-hemolysis and inhibition by optochin and was confirmed by slide agglutination (Phadebact; Pharmacia Diagnostics, Uppsala, Sweden). Typing was done by quellung reaction [39] with use of reagents from Statens Seruminstitut (Copenhagen, Denmark). Susceptibility to trimethoprim-sulfamethoxazole, tetracycline, erythromycin, clindamycin, and chloramphenicol was determined by the disk diffusion method, interpreted according to the National Committee for Clinical Laboratory Standards. Isolates exhibiting inhibition zones of <19 mm with a 1-μg
Table 1. Resistance pattern of pneumococcal isolates from middle ear fluid by serotype (susceptibility pattern was known for 823 [96%] of the 858 strains that were serotyped).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Serotype</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>23F</td>
</tr>
<tr>
<td>No.</td>
<td>137</td>
</tr>
<tr>
<td>% of all isolates</td>
<td>16</td>
</tr>
<tr>
<td>No. tested</td>
<td>131</td>
</tr>
<tr>
<td>Resistance to penicillin</td>
<td></td>
</tr>
<tr>
<td>0.1 ≤ MIC ≤ 1.0</td>
<td>130 (99)</td>
</tr>
<tr>
<td>MIC &gt; 1.0</td>
<td>60 (46)</td>
</tr>
<tr>
<td>Resistance to ≥1 drug</td>
<td>131 (100)</td>
</tr>
<tr>
<td>Resistance to ≥2 drugs</td>
<td>119 (91)</td>
</tr>
<tr>
<td>Multidrug resistance</td>
<td>4 (3)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) unless indicated otherwise. MIC values are mg/mL.

Results

During the study period, a total of 876 S. pneumoniae isolates were obtained from MEF. The ethnicity of the patients was known for 874: 382 (44%) were Jews and 492 (56%) were Bedouins. Of the 876 MEF samples, 699 (80%) were obtained in the hospital (451 [65%] of these in the emergency room) and 176 (20%) were obtained in clinics in the community. For 1 sample, no information was available.

The age distribution of the 833 patients with a known age, by 6-month interval, was as follows: <6 months, 243 (29%); 6–11 months, 311 (37%); 12–17 months, 167 (20%); 18–23 months, 62 (8%); 24–35 months, 50 (6%); and ≥36 months, 0.

Of 858 isolates that were typed, antibiotic susceptibility results were available for 823 (96%). The 9 most common serotypes were 23F, 19F, 14, 19A, 9V, 6B, 6A, 1, and 3 (table 1). These 9 serotypes constituted 73% of all isolates. Other serotypes that were present at a frequency ≥1% but <2% were 18C, 5, 7F, and 5. Nine (1%) of 858 were untypeable. Most of the antibiotic-resistant strains were included among the most common serotypes. Resistance to penicillin was found mainly in (by descending order) serotypes 23F, 9V, 14, and 19A. Multidrug resistance (resistance to ≥3 drug classes) was found mainly in serotypes 6B, 19F, and 14.

For 796 patients, ethnic group, age, and antibiotic resistance patterns were known (table 2). Antibiotic resistance was common in both ethnic groups, although both penicillin resistance and multidrug resistance seemed slightly more common among Jews than among Bedouins.

Both penicillin resistance and resistance to ≥1 drug were age dependent: The peak prevalence of antibiotic resistance was found among patients aged 6–17 months, which was also the age at which most AOM cases were found (P = .01 for age effect for penicillin resistance and resistance to ≥1 drug in both Bedouins and Jews).

We examined the coverage of the MEF isolates by the various conjugate vaccine candidates according to age and ethnic group (table 3). According to the various conjugate pneumococcal vaccines currently studied in humans, we defined the vaccines for the purpose of analysis as follows: 7-valent vaccine, serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F; 9-valent vaccine, same as 7-valent vaccine but with the addition of serotypes 1 and 5; 11-valent vaccine, same as 9-valent vaccine but with the addition of serotypes 3 and 7F.

As expected, the coverage of the pneumococci isolates by the various conjugate pneumococcal vaccine candidates improved for all age groups when the number of serotypes in the vaccines increased from 7 to 11. The greatest difference between the vaccine candidates was seen in the youngest and oldest age groups (<6 months and ≥24 months). In all age groups, and for all 3 candidate vaccines, the vaccine coverage for the Jewish population was significantly superior to that for the Bedouin population (table 3).

The coverage of the antibiotic-resistant isolates and especially the multidrug-resistant isolates was higher with all 3 vaccines than was coverage of the antibiotic-susceptible isolates (table 4). Furthermore, for all isolates that were resistant to ≥1 drug, including penicillin-resistant and multidrug-resistant organisms, no significant difference could be observed in coverage rate when the 7-, 9-, or 11-valent vaccines were compared. The coverage of the antibiotic-resistant serotypes by all 3 vaccines was better for the Jewish population than for the Bedouins.

Two important prevalent serotypes that are not included in any of the vaccines are serotypes 6A and 19A, constituting 6% and 8%, respectively, of all isolates (table 1). Together they
constituted 5%–18% of all isolates in each age group. They were also important among the antibiotic-resistant isolates, constituting together 74 (15%) of 501 isolates that were penicillin resistant, 80 (14%) of 566 resistant to 1 drug, and 6 (6%) of 107 that were multiresistant.

Five serotypes (6B, 9V, 14, 19F, and 23F) included in all 3 vaccines were mostly associated with antibiotic resistance. They constituted 455 (53%) of all 858 isolates. However, they constituted 370 (74%) of 501 penicillin-resistant isolates, 388 (69%) of 566 isolates resistant to 1 drug, and 93 (87%) of 107 multidrug-resistant isolates (P < .001 for the representation of those 5 serotypes among all isolates vs. their representation among isolates belonging to each of the examined resistance patterns).

The coverage by the 5 serotypes (6B, 9V, 14, 19F, and 23F) was investigated in relation to previous antibiotic treatment and number of AOM episodes during the year before culture (figure 1). A striking correlation was found between history of antibiotic therapy before the culture sample was obtained and isolation of serotypes 6B, 9V, 14, 19F, and 23F. Similarly, children with no previous episodes during the year before culture had 44% coverage by these 5 serotypes, versus 60% of those with 1 episode during last year. In other words, there was a strong correlation between the presence of complicated AOM (as defined by AOM in children with frequent previous episodes or having received antibiotic recently) and presence of serotypes included in the candidate pneumococcal conjugate vaccines, which also covered most of the antibiotic-resistant strains.

Penicillin-susceptible isolates were found in 183 (56%) of 327 children not receiving antibiotics in the last 3 months, 19 (48%) of 40 children receiving antibiotics 1–2 months before tympanocentesis, 63 (33%) of 189 receiving antibiotics in the last 2–3 months but not at the time of tympanocentesis, and 50 (19%) of 261 receiving antibiotics at the time of tympanocentesis (P < .001). Similarly, isolates with MICs > 1.0 μg/mL were found in 18 (6%) of 327, 8 (20%) of 40, 29 (15%) of 189, and 65 (25%) of 261, respectively (P < .001). Isolates with MICs < 0.1 μg/mL and > 1.0 μg/mL were seen in 197 (48%) and 44 (11%), respectively, of 410 who did not have an episode of AOM in the last 12 months and in 121 (30%) and 75 (18%), respectively, of 407 with ≥ 1 AOM episode (P < .001).

Discussion

The present report is, to the best of our knowledge, the first prospective study examining the potential coverage of AOM by candidate conjugate pneumococcal vaccines in the context of various clinical conditions. Because the protection is expected to be provided through type-specific antipolysaccharide antibodies, understanding the relation of the pneumococcal serotypes to various clinical presentations of pneumococcal AOM

Table 2. Antibiotic resistance pattern among 796 pneumococcal isolates from middle ear fluid of patients with acute otitis media, by age and by ethnic group.

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Jews</th>
<th>Bedouins</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Penicillin resistant</td>
<td>Resistant to ≥ 1 drug</td>
<td>Multidrug resistant</td>
</tr>
<tr>
<td>&lt;6</td>
<td>80</td>
<td>41 (51)</td>
<td>45 (56)</td>
</tr>
<tr>
<td>6–11</td>
<td>131</td>
<td>92 (70)</td>
<td>98 (75)</td>
</tr>
<tr>
<td>12–17</td>
<td>86</td>
<td>63 (73)</td>
<td>69 (80)</td>
</tr>
<tr>
<td>18–23</td>
<td>34</td>
<td>23 (68)</td>
<td>23 (68)</td>
</tr>
<tr>
<td>≥24</td>
<td>22</td>
<td>13 (59)</td>
<td>16 (73)</td>
</tr>
</tbody>
</table>

Total 353 | 232 (66) | 251 (71) | 56 (16) | 443 | 251 (57) | 294 (66) | 45 (10) | 796 | 483 (61) | 545 (68) | 101 (13)

NOTE. Data are no. (%) unless indicated otherwise. 

a P = .011, Jews vs. Bedouins.

b P = .02, Jews vs. Bedouins.

c P = .001, Jews vs. Bedouins.

Table 3. Age-specific vaccine coverage of pneumococcal isolates from middle ear fluid of patients with AOM by 7-, 9-, and 11-valent candidate conjugate pneumococcal vaccines.

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>No.</th>
<th>7-valent</th>
<th>9-valent</th>
<th>11-valent</th>
<th>No.</th>
<th>7-valent</th>
<th>9-valent</th>
<th>11-valent</th>
<th>No.</th>
<th>7-valent</th>
<th>9-valent</th>
<th>11-valent</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6</td>
<td>82</td>
<td>36 (44)</td>
<td>41 (50)</td>
<td>50 (61)</td>
<td>157</td>
<td>58 (37)</td>
<td>70 (45)</td>
<td>85 (54)</td>
<td>239</td>
<td>94 (39)</td>
<td>111 (46)</td>
<td>135 (56)</td>
</tr>
<tr>
<td>6–11</td>
<td>135</td>
<td>94 (70)a</td>
<td>96 (71)</td>
<td>97 (72)</td>
<td>171</td>
<td>97 (57)a</td>
<td>103 (60)</td>
<td>109 (64)</td>
<td>306</td>
<td>191 (62)</td>
<td>199 (65)</td>
<td>206 (67)</td>
</tr>
<tr>
<td>12–17</td>
<td>87</td>
<td>66 (76)a</td>
<td>67 (77)a</td>
<td>70 (80)a</td>
<td>76</td>
<td>41 (54)a</td>
<td>44 (58)a</td>
<td>47 (62)a</td>
<td>163</td>
<td>107 (66)</td>
<td>111 (68)</td>
<td>117 (72)</td>
</tr>
<tr>
<td>18–23</td>
<td>32</td>
<td>26 (81)b</td>
<td>26 (81)b</td>
<td>27 (84)b</td>
<td>26</td>
<td>11 (42)b</td>
<td>14 (54)b</td>
<td>14 (54)b</td>
<td>58</td>
<td>37 (64)</td>
<td>40 (69)</td>
<td>41 (71)</td>
</tr>
<tr>
<td>≥24</td>
<td>24</td>
<td>17 (71)b</td>
<td>17 (71)</td>
<td>18 (75)</td>
<td>25</td>
<td>7 (28)</td>
<td>11 (44)</td>
<td>11 (44)</td>
<td>49</td>
<td>24 (49)</td>
<td>28 (57)</td>
<td>29 (59)</td>
</tr>
</tbody>
</table>

Total 360 | 239 (66) | 247 (69) | 262 (73) | 455 | 214 (47) | 242 (53) | 266 (58) | 815 | 453 (56) | 489 (60) | 528 (65) |
is essential to predicting the protective potential of the candidate conjugate pneumococcal vaccines against the entity.

We found that in southern Israel, many pneumococcal isolates were covered by all candidate conjugate vaccines. However, the coverage was increased from 55% for 5-valent vaccines to 60% and 65% for 9- and 11-valent vaccines, respectively. Studies of AOM in southern Israel showed that \textit{S. pneumoniae} was responsible for ~35% of all cases of AOM [9, 10, 41]. Thus, a vaccine efficacy of 50% can bring about a reduction in the occurrence of all AOM cases by 9%–12% at best, depending on the number of serotypes included in the vaccines. Similarly, a vaccine efficacy of 75% can bring about a reduction in AOM cases by 14%–17%.

The above calculation does not take into account two potential events of opposite effect: First, bacterial AOM is usually an opportunistic infection occurring in children compromised by underlying genetic and/or environmental conditions and is often a complication of a viral upper respiratory tract infection [42]. The chain of events includes introduction of nasopharyngeal bacteria to the middle ear cavity through the eustachian tube. Thus, one might expect that, at least in some cases, pathogens such as \textit{Haemophilus influenzae} or \textit{Moraxella catarrhalis} may replace \textit{S. pneumoniae} as the etiologic agents of AOM. Furthermore, because vaccination with conjugate vaccines is associated with a higher rate of nasopharyngeal colonization of \textit{S. pneumoniae} serotypes other than those included in the vaccine [30–32], an increase in AOM cases caused by the currently less frequent pneumococcal serotypes, and thus not included in the vaccine, could be observed in the future.

On the other hand, it is commonly believed that \textit{S. pneumoniae} causes more severe AOM than is caused by other pathogens [2, 7, 43]. This may be associated with increased inflammatory response, resulting in increased damage. Thus, the prevention of early pneumococcal AOM cases may reduce one predisposing factor for recurrent AOM. The higher representation of pneumococci of the vaccine serotypes than of other strains among children with recurrent AOM in our study suggests that the above-described scenario might often take place.

In the present study, the best potential coverage by the candidate conjugate vaccines was provided to children with complicated AOM, namely those not responding to antibiotics, those with recent antibiotic use, and those with repeated episodes of AOM. Such complicated cases are related to antibiotic resistance that occurs by selective pressure. The “pediatric” serotypes, such as 6A, 6B, 9V, 14, 19F, and 23F, are detected in higher frequency in the nasopharynx of infants and young children and are associated with nasopharyngeal persistence in this age group. Those strains are indeed the most common causing AOM in infants and young children, especially in settings that involve crowding, such as day care facilities [32, 44–48]. In such settings, because of increased frequency of infections, antibiotic use is extensive and thus enables acquisition and spread of antibiotic-resistant pneumococcal strains [44–48]. Indeed, in a recent French study, Cohen et al. [49] showed an increased representation of day care center attendees compared with children cared for by a babysitter or at home among cases of failure of antibiotic treatment in AOM associated with increased nasopharyngeal carriage of antibiotic-resistant pneumococci.

It was previously shown that the antibiotic resistance of \textit{S. pneumoniae} was associated with both bacteriologic failures [9, 10, 12, 41] and clinical failures [9, 11, 49]. Thus, the increasing failure of antibiotic treatment in AOM resulting from the presence of antibiotic-resistant pneumococci and the selection of resistant strains in the nasopharynx caused by antibiotic treatment [44–49] create a vicious cycle that enables the resistant clones to spread and causes a problem of increasing magnitude.

The logic described above makes it easy to understand why the internationally widespread antibiotic-resistant and multiresistant clones almost exclusively belong to the limited serotypes included in all candidate vaccines [24] and helps explain the almost complete coverage by all 3 candidate vaccines exemplified by the >90% coverage of all strains with penicillin MICs >1.0 \(\mu\text{g/mL}\) by all 3 vaccines in our study. By use of the same logic, it may be speculated that once the conjugate vaccines become widely used, this will not select for the successful spread of new resistant clones, because the strains not currently included in the vaccines are less likely to be carried extensively by infants and young children because of their different immunologic properties. Whether this speculation reflects the 

| Table 4. Vaccine coverage of pneumococcal isolates from middle ear fluid of patients with acute otitis media (821 isolates total) by 7-, 9-, and 11-valent candidate pneumococcal conjugate vaccines, according to antibiotic susceptibility patterns. |
|---------------------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Susceptibility pattern          | No.    | 7-valent | 9-valent | 11-valent | No.    | 7-valent | 9-valent | 11-valent | No.    | 7-valent | 9-valent | 11-valent |
| Susceptible to all drugs        | 104    | 34 (33)  | 40 (38)  | 55 (53)  | 151    | 28 (19)  | 36 (24)  | 60 (40)  | 255    | 62 (24)  | 76 (30)  | 115 (45)  |
| Resistance to penicillin        | 243    | 196 (81) | 197 (81) | 197 (81) | 258    | 174 (67) | 178 (69) | 179 (69) | 501    | 370 (74) | 375 (75) | 376 (75)  |
| 0.1 < MIC ≤ 1.0                 | 170    | 126 (74) | 127 (75) | 127 (75) | 212    | 134 (63) | 137 (65) | 138 (65) | 382    | 260 (68) | 264 (69) | 265 (69)  |
| MIC > 1.0                       | 73     | 70 (96)  | 70 (96)  | 70 (96)  | 46     | 40 (87)  | 41 (89)  | 41 (89)  | 119    | 110 (92) | 111 (93) | 111 (93) |
| Resistance to ≥1 drug           | 262    | 207 (79) | 210 (80) | 210 (80) | 304    | 184 (61) | 205 (67) | 206 (68) | 566    | 391 (69) | 415 (73) | 416 (73) |
| Multidrug resistance            | 62     | 56 (90)  | 56 (90)  | 56 (90)  | 45     | 37 (82)  | 37 (82)  | 38 (84)  | 107    | 93 (87)  | 93 (87)  | 94 (88)  |
| All isolates                    | 241    | 250      | 265      |          | 212    | 241      | 266      |          |

NOTE. Data are no. (%) unless indicated otherwise.

\( ^a P < .001, \) Jews vs. Bedouins.

\( ^b P = .001, \) Jews vs. Bedouins.
ality will be seen only after widespread introduction of the conjugate vaccines.

The pneumococcal conjugate vaccines are able to prevent colonization of *S. pneumoniae* of the serotypes included in the vaccines and, consequently, reduce carriage of antibiotic-resistant pneumococci [29, 31, 32]. It is hoped that this will create a herd immunity that will prevent pneumococcal AOM in general and AOM caused by antibiotic-resistant pneumococci in particular, not only in vaccinated persons but also in their contacts. This is mainly important for infants <6 months of age whose older siblings attend day care centers, for the following reasons. First, carriage of *S. pneumoniae* and antibiotic-resistant *S. pneumoniae* is increased in young infants with an older sibling compared with carriage among only children [50]. Early carriage is associated with early development of AOM [51, 52]. Second, acute respiratory tract infections predisposing to otitis are common in infants with older siblings attending day care centers. Also, AOM in the first 6 months of life particularly predisposes to the occurrence of recurrent episodes of middle ear infection. Finally, infants <6 months of age are not expected to be yet fully immunized even after the introduction of conjugate vaccines, because probably >1 dose will be needed to fully protect from AOM.

In southern Israel, two considerably different populations reside side by side: the Bedouins, who because of crowding, high birth rate, and low socioeconomic class resemble a developing world population, and the Jews, who resemble a middle–low class developed population. For all 3 candidate vaccines, the coverage was significantly superior for the Jewish than for the Bedouin segments of the population. This finding is consistent with the studies published about serotype distribution of strains causing invasive infections in the developed versus the developing world [22]. In these studies, the population in the developing world showed a wider variety of serotypes, and the coverage, especially for the 7-valent vaccine, was much reduced compared with that achievable in the developed world.

Two serotypes not included in the vaccine, namely, 6A and 19A, were significant in terms of both prevalence and antibiotic resistance rate. Although we may expect at least partial cross-protection against 6A by the 6B capsular antigen [32, 53–55], it is not clear whether such a cross-protection will occur between serotypes 19F and 19A. In fact, data available from experimental animals [55] suggest that no such cross-protection exists. If the new conjugate vaccines prove efficacious against AOM, the addition of at least 19A and, if needed, 6A to the vaccines should be considered to further extend the antipneumococcal coverage.

Two recent studies, one in northern California and one in Finland, suggest an efficacy of a 7-valent conjugate vaccine of 50%–60% against the serotypes included in the vaccine and 6%–9% against all cases of AOM [34, 35]. These studies could not examine the true effectiveness of the vaccine. The effectiveness of the vaccine will be influenced also by the immunization rate and its effect on colonization and spread, which may provide herd immunity and thus further reduce AOM caused by the vaccine types. Furthermore, the above studies were done in areas where antibiotic resistance among *S. pneumoniae* isolates is low. We believe that in areas where resistance is frequent, such as in southern Israel, the effectiveness of the vaccines may even be increased by reducing disease and carriage of the types mostly associated with resistance and recurrence. Additionally, it is important to remember that because AOM is extremely frequent, each 1% reduction in AOM cases represents substantial impact of the vaccine.

In conclusion, AOM caused by antibiotic-resistant *S. pneumoniae* is prevalent in southern Israel. Five serotypes found in all candidate pneumococcal conjugate vaccines are responsible for most of the cases caused by antibiotic-resistant *S. pneumoniae*. These serotypes were associated with previous antibiotic treatment and recurrent AOM. Although the candidate 11-valent conjugate vaccine has the best potential coverage for all *S. pneumoniae* cases, no significant difference in coverage of antibiotic-resistant *S. pneumoniae* cases was found among the 3 candidate conjugate vaccines. These results suggest that if efficacious, the conjugate pneumococcal vaccines can substantially reduce the occurrence of pneumococcal AOM in general and of complicated pneumococcal AOM in particular.

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