Association of Clinical Signs and Symptoms with Pneumococcal Acute Otitis Media by Serotype—Implications for Vaccine Effect

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Background. Clinical symptoms and signs in acute otitis media (AOM) may differ depending on the various pneumococcal serotypes causing the disease. Alteration in clinical presentation of AOM could be expected after wide-scale pneumococcal vaccinations if there were considerable differences between vaccine serotypes and non-vaccine serotypes.

Methods. In this study, data from 831 children in the control arm of the Finnish Otitis Media Vaccine Trial were used. The children were followed up prospectively in 8 study clinics from 2 to 24 months of age. If AOM was diagnosed, myringotomy was done, and middle ear fluid was aspirated for bacterial culture. Clinical symptoms and signs of AOM were routinely recorded on structured case report forms.

Results. Consistent with previous studies, 60% of pneumococcal episodes were caused by vaccine serotypes. There were no major differences between the clinical presentations of AOM due to different serotypes or serotype categories. However, earache was more often associated with AOM caused by vaccine and cross-reactive serotypes, compared with AOM caused by non–vaccine-related serotypes (42% vs. 29%; odds ratio, 1.66; 95% confidence interval, 1.02–2.70).

Conclusions. Introduction of the currently available pneumococcal conjugate vaccine is unlikely to result in a remarkable alteration in the clinical presentation of pneumococcal AOM in infants.

The first pneumococcal conjugate vaccine has been approved by authorities in the United States and the European Union for prevention of invasive disease due to pneumococcal serotypes present in the vaccine. The Advisory Committee on Immunization Practices [1] and the American Academy of Pediatrics [2] have recommended routine immunization of all infants with the vaccine, which has resulted in large-scale vaccinations in the United States. This conjugate vaccine has also proven efficacious against acute otitis media (AOM) caused by the 7 serotypes included in the vaccine [3]. However, the overall impact of the conjugate vaccine on AOM has been quite small [3, 4], and evidence for serotype replacement by serotypes other than those in the vaccine has been reported in patients with AOM [3], as well as in subjects with asymptomatic carriage [5]. Consequently, large-scale use of the pneumococcal conjugate vaccine may change the epidemiology and serotype distribution of pneumococcal AOM; the vaccine and cross-reactive serotypes may become less common and the nonvaccine serotypes more common.

Some serotypes are more prevalent than others in AOM [6]. The 7 serotypes included in the vaccine cover a majority of cases of pneumococcal AOM in Western countries [7]. These common serotypes may have specific virulence factors that would affect the propensity to cause AOM and also affect the clinical severity of AOM. However, in general, the serotypes found most often in asymptomatic carriers [8] are the same as those found in AOM [9].

In our previous study [10], pneumococci were found to be associated with fever, earache, and generally more-severe clinical signs and symptoms of AOM, compared with other bacterial species obtained by culture of mid-
dle ear fluid (MEF). Thus, by reducing the proportion of pneumococcal AOM, the conjugate vaccine has the potential to shift the clinical picture of AOM toward less-severe forms. Similarly, when a lower proportion of pneumococcal AOM is caused by vaccine-related serotypes, the clinical characteristics of pneumococcal AOM may change.

In the Finnish Otitis Media Vaccine Trial, the bacterial etiology of AOM was assessed by culture and by serotyping of all pneumococcal isolates. Clinical findings were thoroughly documented. Our objective herein is to assess the severity of symptoms and signs due to different pneumococcal serotypes and serogroups in AOM, with our main interest being in the differences between vaccine and potentially cross-reactive serotypes, compared with nonvaccine serotypes.

PATIENTS, MATERIALS, AND METHODS

Subjects and follow-up. This study comprised the 831 children in the control arm of the Finnish Otitis Media Vaccine Trial who were vaccinated with hepatitis B vaccine [3, 11]. The study children were prospectively followed up in special study clinics from 2 to 24 months of age, as described elsewhere (along with details of the data collection methods) [10].

Bacteriologic methods. MEF samples were cultured immediately on agar plates that were incubated overnight and transported daily to the laboratory [9, 10]. Streptococcus pneumoniae was serotyped by counterimmunoelectrophoresis and latex agglutination with antisera obtained from Statens Serum Institut. Serotyping was confirmed by the Quellung reaction when needed.

Data analysis and statistics. On the basis of our previous analysis of the symptoms and signs associated with pneumococcal etiology [10], special attention was paid to fever, earache, and signs of severe AOM (i.e., spontaneous perforation or bulging tympanic membrane detected in either ear). For description of the data, the pneumococcal serotypes were divided into 3 categories: those included in the 7-valent conjugate vaccine (that is, vaccine-specific serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F); cross-reactive serotypes 6A, 9N, 18B, 19A, and 23A; and non–vaccine-related serotypes (i.e., serotypes other than vaccine-specific and cross-reactive serotypes).

Our main interest was to explore whether large-scale vaccination would potentially result in an altered clinical picture of AOM because of the anticipated change in the serotype distribution. Therefore, for statistical analysis, the dependent variable was coded as binary: vaccine-specific serotypes and cross-reactive serotypes combined against non–vaccine-related serotypes. Marginal logistic regression was used to assess whether the relative frequencies of these 2 categories were clinically different. The results of the univariate analyses are presented both in percentages and as ORs with the corresponding 95% CIs.

Recurrent diagnoses of AOM for the same child required special attention in the analysis. First, isolation of the same serotype on separate occasions that were only a few days apart was most likely an instance of repeated measurement of the same AOM episode. Therefore, the following definition of an AOM episode was used: a new episode was considered to have started if ≥30 days had elapsed since a previous isolation of the same serotype or if a different serotype was detected (at any interval). Thus, in the case of multiple isolations of the same serotype as a causative agent within any 30-day interval, only the first AOM event (defined as an office visit with an AOM diagnosis) was included in the analysis of episodes. If >1 serotype was detected in a sample or samples (e.g., separate samples taken in bilateral infections) obtained on the same day, the findings were considered to represent only 1 episode. In the data analysis, a combination category was used for such episodes if the identified serotypes belonged to different categories (i.e., vaccine-specific serotypes, cross-reactive serotypes, and non–vaccine-related serotypes).

Second, when the analysis was restricted to episodes, preliminary investigation of the data indicated that, if a child had a recurrent episode, the new episode was more likely to be of the same category as the previous episode. This dependence was accounted for in the model by assuming a temporal (first-order Markov) association between repeated episodes [12]. However, similar results were obtained when this dependence was not accounted for in the model (data not shown). Descriptive data are presented for the most common individual serotypes.

RESULTS

Study Visits and Samples
Of the 831 children enrolled at 2 months of age, 799 (96%) were followed up until 24 months of age. Altogether, 587 children (71%) were given a diagnosis of AOM during follow-up, with a total of 1966 AOM events documented. At least 1 MEF sample was available from 1819 events; pneumococci were diagnosed 535 times altogether, and pneumococci were isolated from 709 MEF samples (1–2 samples per event). When identical serotype findings from subsequent events within the same 30-day period were excluded, a total of 479 serotype-specific pneumococcal AOM episodes were documented.

Pneumococcal Serotype Findings
The serotype distribution of pneumococcal AOM episodes is presented in table 1. There were 10 episodes with a double-serotype finding; in 6 episodes, 2 serotypes were detected in the same MEF sample, whereas in 4 episodes, different serotypes

Clinical Findings by Pneumococcal Serotype in AOM • CID 2005:40 (1 January) • 53
Table 1. Distribution of pneumococcal serotypes in acute otitis media episodes in 831 children \( \leq 2 \) years old.

<table>
<thead>
<tr>
<th>Serotype</th>
<th>No. (%) of children (n = 479)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23Fa</td>
<td>104 (21.7)</td>
</tr>
<tr>
<td>19Fa</td>
<td>67 (14.0)</td>
</tr>
<tr>
<td>6B*</td>
<td>62 (12.9)</td>
</tr>
<tr>
<td>6A</td>
<td>48 (10.0)</td>
</tr>
<tr>
<td>14a</td>
<td>31 (6.5)</td>
</tr>
<tr>
<td>19A</td>
<td>28 (5.8)</td>
</tr>
<tr>
<td>11</td>
<td>25 (5.2)</td>
</tr>
<tr>
<td>15</td>
<td>25 (5.2)</td>
</tr>
<tr>
<td>18Ca</td>
<td>18 (3.8)</td>
</tr>
<tr>
<td>3</td>
<td>15 (3.1)</td>
</tr>
<tr>
<td>9Va</td>
<td>11 (2.3)</td>
</tr>
<tr>
<td>35</td>
<td>10 (2.1)</td>
</tr>
<tr>
<td>9N</td>
<td>9 (1.9)</td>
</tr>
<tr>
<td>22</td>
<td>7 (1.5)</td>
</tr>
<tr>
<td>10</td>
<td>6 (1.3)</td>
</tr>
<tr>
<td>4a</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>23A</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>7</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>18B</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Other non–vaccine-related serotypes</td>
<td>9 (1.9)</td>
</tr>
<tr>
<td>Noncapsulated</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Total</td>
<td>489 (102.1)</td>
</tr>
</tbody>
</table>

NOTE. Only serotypes included in the heptavalent pneumococcal conjugate vaccine were typed to the subtype level; for the rest, only group level is shown. There were 10 double-serotype findings (serotypes 3 and 11, 6A and 15, 6A and 19F, 6A and 23F twice, 6B and 14, 6B and 18C, 14 and 19A, 19F and 23F twice).

a Serotype included in the heptavalent pneumococcal conjugate vaccine.

were detected in samples obtained from opposite ears. The serotypes identified in the 479 pneumococcal AOM episodes were distributed between the serotype categories as follows: 289 (60%) vaccine-specific serotypes, 85 (18%) cross-reactive serotypes, 100 (21%) non–vaccine-related serotypes, and 5 (1%) combinations of the categories (4 vaccine-specific and cross-reactive, 1 cross-reactive and non–vaccine-related).

Association of Clinical Findings with the Pneumococcal Serotype

In 433 (90%) of the 479 pneumococcal episodes, the tympanic membrane was, according to previous examinations, intact before the diagnosis of AOM; in 29 (7%) of these episodes, a spontaneous perforation of the tympanic membrane was detected at the time of the diagnosis. In 46 episodes (10%), there was a previous perforation in at least 1 tympanic membrane, mainly because of the presence of tympanostomy tubes. There were no differences in the distribution of serotype categories in relation to whether there was a tympanic membrane perforation (data not shown).

For the following analysis of clinical findings by serotype detected during the episode, all 46 episodes in patients with previous perforations were excluded, because these children were usually taken to the study clinic because of discharge from the ear(s), irrespective of other symptoms. Of the remaining 433 episodes, 4 with serotype category combinations were also excluded.

Symptoms and general signs by serotype categories. Symptoms of AOM are presented in table 2. The only difference found between the serotype categories was the frequency of earache, which was more common in the vaccine-specific serotype and cross-reactive serotype categories than in the non–vaccine-related serotype category (42% vs. 29%; OR, 1.66; 95% CI, 1.02–2.70).

General clinical findings and AOM characteristics are presented in table 3. There were no distinct differences between pneumococcal AOM episodes caused by different serotype categories. AOM episodes due to vaccine-specific serotypes and cross-reactive serotypes tended to be more commonly unilateral, but the difference was not statistically significant (OR, 1.57; 95% CI, 0.97–2.56). The severe episodes were equally common among those in the vaccine-specific and cross-reactive serotype category (49%) and those in the non–vaccine-related serotype category (54%; OR, 0.84; 95% CI, 0.54–1.31).

In multivariate analysis, the ORs remained unchanged; earache was the only covariate remaining significant in the model (data not shown). Additionally, adjusting for age did not affect the OR estimate.

Otological findings by serotype categories. Pneumococci were isolated from 638 MEF samples obtained at the beginning of the 479 pneumococcal AOM episodes described above. Because tympanic membrane status is commonly obscured by the draining ear, the 79 samples obtained from the discharging ears (those with either spontaneous or preexisting perforations) were excluded from the analysis. Also, 2 cases in which pneumococcal serotypes belonging to different categories were isolated from the same sample were excluded. As shown in table 4, no clear differences between serotype categories were found among the remaining 557 tympanic membrane findings and their respective MEF characteristics.

Symptoms and signs by individual serotypes. The symptoms and signs of the most common serotypes found in AOM are shown in table 5. The clinical characteristics of AOM episodes caused by these 5 serotypes were quite similar.

DISCUSSION

The distribution of pneumococcal serotypes causing episodes of AOM was similar to those distributions described in previous reports [7, 9]: 60% of pneumococcal isolates belonged to the serotypes included in the current 7-valent vaccine, and an additional 20% belonged to the serotypes that are immunologi-
Table 2. Symptoms of 429 pneumococcal acute otitis media (AOM) episodes in subjects aged 2–24 months
during the 2 days preceding the diagnosis of AOM, by pneumococcal serotype categories of middle ear fluid
samples obtained at diagnosis.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Vaccine-specific serotypes (n = 261)</th>
<th>Cross-reactive serotypes (n = 76)</th>
<th>Non–vaccine-related serotypes (n = 92)</th>
<th>All pneumococci (n = 429)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature ≥38°C</td>
<td>57</td>
<td>62</td>
<td>61</td>
<td>59</td>
</tr>
<tr>
<td>Cough</td>
<td>70</td>
<td>74</td>
<td>77</td>
<td>72</td>
</tr>
<tr>
<td>Runny nose</td>
<td>95</td>
<td>96</td>
<td>96</td>
<td>95</td>
</tr>
<tr>
<td>Eye symptoms</td>
<td>16</td>
<td>20</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Earacheb</td>
<td>43</td>
<td>39</td>
<td>29</td>
<td>39</td>
</tr>
<tr>
<td>Ear pulling</td>
<td>51</td>
<td>55</td>
<td>39</td>
<td>49</td>
</tr>
<tr>
<td>Excessive crying</td>
<td>76</td>
<td>78</td>
<td>74</td>
<td>76</td>
</tr>
<tr>
<td>Any symptoms present for &gt;2 weeks</td>
<td>23</td>
<td>17</td>
<td>23</td>
<td>22</td>
</tr>
</tbody>
</table>

NOTE. Data are percent of patients with the specified symptom.

¹ 4 episodes in subjects with double-serotype findings from different categories and 46 episodes in subjects with a known previous perforation in the tympanic membrane were excluded.

*b* Statistically significant difference by marginal logistic regression between vaccine-specific and cross-reactive serotype categories and the non–vaccine related serotype category (42% vs. 29%; OR, 1.66; 95% CI, 1.02–2.70).

cally cross-reactive with the vaccine serotypes. The isolations of vaccine and cross-reactive serotypes were not associated with a more severe clinical picture of AOM, compared with non–vaccine-related serotypes. The only minor difference was the higher proportion of children with earache who experienced episodes of AOM due to vaccine-specific and cross-reactive serotypes.

The children in this study were followed up to 2 years of age. Accordingly, our results are not directly applicable to children >2 years old. For infants, the symptoms are interpreted by their parents or caregivers; subjective parental interpretation and reporting of infants’ symptoms may increase variation in the responses and decrease the reliability of the measurement. Also, the report of earache was based on parents’ interpretation of the child’s behavior, because most of the children were not able to express their feelings verbally. However, the presence of earache symptoms was equally common in all age groups, and adjustment for age did not affect the OR estimates for earache. Clinical physical findings recorded by the physicians are likely to be more objective than are parental observations. Prestudy education, standard operating procedures, and standard case report forms were used to increase reliability. Another feature producing variability in the measurements is the time frame of the assessment. The infants were not routinely checked at identical time points but were brought to the study clinics at their parents’ discretion, although general advice on when to seek care was given at enrollment.

Table 3. General clinical and bacteriologic findings of 429 pneumococcal acute otitis media (AOM) episodes at diagnosis in subjects aged 2–24 months, by pneumococcal serotype categories of middle ear fluid samples obtained at diagnosis.

<table>
<thead>
<tr>
<th>Clinical or bacteriologic finding</th>
<th>Vaccine-specific serotypes (n = 261)</th>
<th>Cross-reactive serotypes (n = 76)</th>
<th>Non–vaccine-related serotypes (n = 92)</th>
<th>All pneumococci (n = 429)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, median days</td>
<td>385</td>
<td>389</td>
<td>416</td>
<td>392</td>
</tr>
<tr>
<td>Mean rectal temperature, °C</td>
<td>37.9</td>
<td>38.0</td>
<td>38.1</td>
<td>37.9</td>
</tr>
<tr>
<td>Temperature ≥38°C</td>
<td>38</td>
<td>34</td>
<td>41</td>
<td>38</td>
</tr>
<tr>
<td>Eye discharge or redness</td>
<td>8</td>
<td>14</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Unilateral AOM</td>
<td>43</td>
<td>37</td>
<td>30</td>
<td>39</td>
</tr>
<tr>
<td>Severe AOM (bulging tympanic membrane or spontaneous perforation)</td>
<td>49</td>
<td>49</td>
<td>54</td>
<td>50</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> copathogen</td>
<td>6</td>
<td>5</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em> copathogen</td>
<td>16</td>
<td>17</td>
<td>18</td>
<td>16</td>
</tr>
</tbody>
</table>

NOTE. Data are percent of patients with the specified characteristic, unless otherwise indicated.

¹ 4 episodes in subjects with double-serotype findings from different categories and 46 episodes from subjects with a known previous perforation in the tympanic membrane were excluded.
Table 4. Tympanic membrane findings and characteristics of middle ear fluid (MEF) samples for subjects with acute otitis media (AOM) aged 2–24 months, by pneumococcal serotype category.

<table>
<thead>
<tr>
<th>Clinical characteristic or finding</th>
<th>Vaccine-specific serotypes (n = 332)</th>
<th>Cross-reactive serotypes (n = 102)</th>
<th>Non–vaccine-related serotypes (n = 123)</th>
<th>All pneumococci (n = 557)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tympanic membrane color</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yellow</td>
<td>27</td>
<td>14</td>
<td>27</td>
<td>24</td>
</tr>
<tr>
<td>Opaque or cloudy</td>
<td>68</td>
<td>82</td>
<td>71</td>
<td>71</td>
</tr>
<tr>
<td>Color on &gt;50% of tympanic membranes</td>
<td>80</td>
<td>70</td>
<td>84</td>
<td>79</td>
</tr>
<tr>
<td>Tympanic membrane position</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulging</td>
<td>41</td>
<td>37</td>
<td>48</td>
<td>42</td>
</tr>
<tr>
<td>Retracted</td>
<td>12</td>
<td>15</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Tympanic membrane immobile</td>
<td>45</td>
<td>46</td>
<td>42</td>
<td>44</td>
</tr>
<tr>
<td>Tympanometry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type B curve</td>
<td>76</td>
<td>85</td>
<td>75</td>
<td>77</td>
</tr>
<tr>
<td>Negative pressure (less than −100 daPa)</td>
<td>6</td>
<td>4</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>MEF quality purulent*</td>
<td>72</td>
<td>71</td>
<td>76</td>
<td>73</td>
</tr>
<tr>
<td>MEF quantity low*</td>
<td>11</td>
<td>15</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>

NOTE. MEF samples were obtained by myringotomy through intact tympanic membranes (discharging ears excluded) at the beginning of a pneumococcal AOM episode. Data are percent of patients with the specified characteristic or finding.

* Assessed by the study physician after myringotomy with aspiration.

There are no previous studies comparing the clinical picture of AOM caused by different pneumococcal serotypes. Our previous report of the same study [10], comparing different bacterial species, showed pneumococci to be more commonly associated with fever, earache, and severe tympanic membrane findings. However, within pneumococcal serotype categories and individual serotypes, the differences were minor.

High vaccination coverage with the pneumococcal conjugate vaccine most likely causes serotype replacement of vaccine-specific serotypes and cross-reactive serotypes by non–vaccine-related serotypes in pneumococcal AOM [3, 11]. This phenomenon decreases the overall effect of the vaccination on mucosal infections. However, resistant pneumococcal isolates more commonly belong to vaccine-specific and cross-reactive serotypes [7], and vaccination has the potential to slow down the spread of these resistant isolates. Although vaccine-specific and cross-reactive serotypes are most commonly found in cases of pneumococcal AOM, they are not necessarily more virulent otitis pathogens than are non–vaccine-related serotypes, but their commonness may merely reflect the higher prevalence of carriage of these serotypes in children [8].

This study implies that the changes in serotype distribution within pneumococcal AOM will probably not result in any major change in the clinical picture of AOM during the vaccination era. The small, yet significant, effect on the presence of earache cannot be discerned in clinical practice, because pneumococci cause only a proportion of all AOM cases. Nevertheless, because pneumococcal AOM is associated with a more severe course of illness [10], wide use of the 7-valent pneumococcal conjugate vaccine has the potential to alleviate the clinical manifestations of AOM.

Table 5. Symptoms and clinical findings of acute otitis media (AOM), by the most common pneumococcal serotypes recovered from samples of middle ear fluid obtained at the time of diagnosis.

<table>
<thead>
<tr>
<th>Symptom or finding</th>
<th>Serotype 6A (n = 36)</th>
<th>Serotype 6B (n = 56)</th>
<th>Serotype 14 (n = 26)</th>
<th>Serotype 19F (n = 57)</th>
<th>Serotype 23F (n = 88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever*</td>
<td>56</td>
<td>66</td>
<td>62</td>
<td>58</td>
<td>46</td>
</tr>
<tr>
<td>Earache</td>
<td>33</td>
<td>36</td>
<td>38</td>
<td>44</td>
<td>43</td>
</tr>
<tr>
<td>Any symptoms present for &gt;2 weeks</td>
<td>17</td>
<td>31</td>
<td>13</td>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td>Severe AOM (bulging tympanic membrane or spontaneous perforation)</td>
<td>56</td>
<td>48</td>
<td>62</td>
<td>54</td>
<td>42</td>
</tr>
<tr>
<td>Spontaneous perforation</td>
<td>8</td>
<td>11</td>
<td>15</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Unilateral AOM</td>
<td>36</td>
<td>45</td>
<td>54</td>
<td>58</td>
<td>34</td>
</tr>
</tbody>
</table>

NOTE. Data are percent of patients with the specified symptom or finding.

* Temperature, ≥38°C.
Acknowledgments

We are grateful to all families for participation in this study. We also appreciate the study personnel for the detailed recording of a huge amount of data. We warmly thank the laboratory personnel for meticulous work in bacterial isolation.

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Potential conflicts of interest. A.A.I.P. has had travel paid for by Wyeth-Lederle and GlaxoSmithKline as an invited speaker at symposia and has received an honorarium from Wyeth-Lederle. J.T.J. has had travel paid for by Wyeth-Lederle when attending a scientific symposium and as an expert at a US Food and Drug Administration Vaccines and Related Biological Products Advisory Committee meeting. T.M.K. has provided consultancies on advisory boards for Aventis Pasteur, Wyeth-Lederle, and GlaxoSmithKline; has had travel paid for by Aventis Pasteur, GlaxoSmithKline, and Wyeth-Lederle as an invited speaker at symposia; and has received honoraria from Aventis Pasteur and Wyeth-Lederle. All other authors: no conflicts.

References