

Acute Otitis Media Caused by *Moraxella catarrhalis*: Epidemiologic and Clinical Characteristics

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(See the editorial commentary by Pichichero, on pages 1648–9.)

Background. This study describes the epidemiologic, microbiologic, and otologic features and selected signs and symptoms of acute otitis media (AOM) caused by *Moraxella catarrhalis* and compares them with AOM caused by other bacterial pathogens.

Methods. Patients aged <5 years with culture-positive AOM from whom a middle ear fluid specimen was obtained and cultured during 1999–2006 were enrolled in the study.

Results. Of a total of 12,799 AOM episodes, 8198 (64%) were culture positive, with isolation of 10,382 pathogens: *Haemophilus influenzae*, 4982 (48.0%); *Streptococcus pneumoniae*, 4450 (42.9%); *M. catarrhalis*, 501 (4.8%); and group A streptococci, 449 (4.3%). The distribution of single versus mixed *M. catarrhalis* infection was significantly different compared with the 3 other pathogens (165 cases [32.9%] as a single pathogen of all *M. catarrhalis* AOM episodes vs 3108 [62.4%] in AOM caused by *H. influenzae*, 2592 [58.2%] in AOM caused by *S. pneumoniae*, and 304 [67.7%] in AOM caused by group A streptococci; $P < .001$ for all comparisons). In multivariate analysis, *M. catarrhalis* AOM was more frequent in patients experiencing their first AOM episode versus recurrent AOM and mixed infections. *M. catarrhalis* AOM was associated with lower proportions of spontaneous perforation of tympanic membrane compared with all other pathogens. None of the AOM episodes caused by *M. catarrhalis* was associated with mastoiditis.

Conclusions. Compared with AOM caused by other pathogens, AOM caused by *M. catarrhalis* is characterized by a higher proportion of mixed infections, younger age at diagnosis, a lower proportion of spontaneous perforation of the tympanic membrane, and no mastoiditis.

The most common pathogens to cause acute otitis media (AOM) in children are *Streptococcus pneumoniae*, nontypeable *Haemophilus influenzae*, *Moraxella catarrhalis*, and group A streptococcus (GAS) [1]. Clinical and otologic aspects of AOM caused by *S. pneumoniae*, *H. influenzae*, or GAS have some characteristics that have been previously reported. *S. pneumoniae* more frequently causes severe AOM with high temperature, more severe otalgia, more frequent tympanic membrane redness and bulging, and higher middle ear fluid (MEF) and peripheral blood leukocyte and neutrophil

counts [2–7]. *H. influenzae* AOM is more frequently associated with conjunctivitis, bilateral AOM, previous antibiotic treatment, and recurrent disease [2, 8], and GAS AOM is more often severe in older children and is characterized by higher rates of spontaneous perforation and mastoiditis [9].

M. catarrhalis AOM is usually considered a relatively less virulent pathogen [10], but the clinical features of AOM caused by *M. catarrhalis* have not been described in detail. Animal models of *M. catarrhalis* AOM and human studies have suggested a weaker local immune response and fewer structural changes compared with AOM caused by *S. pneumoniae* or *H. influenzae* [11–13].

We sought to study the epidemiologic, microbiologic, and selected clinical and otologic features (temperature, vomiting, spontaneous perforation, and presence of mastoiditis at time of diagnosis) of AOM caused by *M. catarrhalis*. The main objective of the present study was to determine whether these clinical and otologic features of patients with *M. catarrhalis* AOM are indeed

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less severe than those of patients with AOM caused by *S. pneumoniae*, *H. influenzae*, or GAS.

PATIENTS AND METHODS

Study population and setting. The Negev region is a heterogeneously populated area, with >700,000 inhabitants (of whom >150,000 are children) belonging to 2 major ethnic groups, Jewish and Muslim Bedouin. The Jewish population lifestyle and standards of living can be compared with those of developed countries, whereas overcrowding, lower levels of education, lower income, and larger family size are more common among the Bedouins (a population still in transition from a seminomadic lifestyle to permanent settlement) than among the Jewish population. The Soroka University Medical Center (Beer Sheva, Israel) is the only hospital for the entire region, and its clinical microbiology laboratory provides services to both the hospital and 60% of the community. Thus, 95% of all MEF cultures from patients with AOM in the region are performed in this laboratory [14].

Patients and procedures. We enrolled patients aged <5 years with AOM from whom a specimen of MEF was obtained and cultured during January 1999 to December 2006. Culture specimens were obtained by either tympanocentesis or collection of pus that drained from the ear during the last 7 days before enrollment. The diagnosis of AOM was made by a pediatrician, a family physician, or an otolaryngologist. Demographic and clinical information was prospectively obtained from children with cultures positive for *S. pneumoniae*, *H. influenzae*, and/or *M. catarrhalis* from January 1999 through December 2006 and from children with positive cultures for GAS from November 2001 through December 2006. For each episode, we collected information on the patient's age, sex, and ethnicity; the patient's body temperature; the laterality of the AOM (ie, whether it was unilateral or bilateral); the method of acquisition of the culture specimen (ie, by tympanocentesis or from pus draining from the ear after spontaneous perforation of the middle ear cavity); and the patient's recent history of antibiotic treatment. In addition, data on the presence of vomiting and mastoiditis at diagnosis were recorded. Data were obtained from the medical records, the child's physician, or the child's parents, as appropriate. For an episode of infection to be classified as new, it had to occur ≥ 30 days after any previous episode caused by the same organism. If caused by a different organism (including β -lactamase-positive *H. influenzae* versus β -lactamase-negative *H. influenzae* or different serotypes of *S. pneumoniae*), an episode was classified as new even if it occurred <30 days after the previous episode. None of the patients has been immunized with a pneumococcal conjugate vaccine before enrollment.

Tympanocentesis and transport of specimens. Tympanocentesis was performed by an otolaryngologist as previously described [15].

Bacteriologic analysis. The swabs were plated on trypticase agar containing 5% sheep blood and 5.0 mg/mL of gentamicin and on chocolate agar. The plates were incubated aerobically at 35°C for 48 h. Presumptive identification of the 4 otopathogens has been previously described [15, 16]. Only *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and GAS were considered pathogens. An infection was defined as mixed if ≥ 2 pathogens were found in cultures of specimens obtained from the same ear or if different pathogens were found in cultures of specimens obtained from different ears during the same visit.

Statistical analysis. Data were recorded using Microsoft Office Access 2000 software (Microsoft). Statistical analysis was performed with SPSS statistical software, version 14.0 (SPSS). Univariate analysis was conducted by comparing variables between *M. catarrhalis* AOM and AOM caused by other pathogens. Variables included were age, sex, ethnicity, seasonality, previous AOM history, previous antibiotic treatment (during the 48 h preceding enrollment and also during 1 month preceding enrollment), previous tympanocentesis, fever, vomiting, concurrent pneumonia at diagnosis, laterality, and spontaneous perforation. The *P* value was calculated by the χ^2 test or Fisher exact test, as appropriate. Relative risk and 95% confidence intervals were used to compare the risk of isolation of *M. catarrhalis* among age groups. Odds ratios, as estimates of the relative risks from multivariate logistic regression models, were used to define independent risk factors associated with isolation of *M. catarrhalis* versus other pathogens as single-pathogen infections. Variables found to be significant on univariate analysis (ethnicity, age, previous antibiotic treatment, concurrent pneumonia at diagnosis, and spontaneous perforation) were further submitted to multivariable regression analysis. To determine whether the characteristics of single versus mixed *M. catarrhalis* AOM remained after adjustment for ethnicity, age, previous antibiotic therapy, concurrent pneumonia at diagnosis, and spontaneous perforation, the Mantel-Haenszel test was used. We calculated 95% exact binomial confidence intervals according to criteria established by Clopper and Pearson [17]. *P* $\leq .05$ was considered significant for all calculations.

RESULTS

A total of 12,799 episodes of AOM were recorded during the 7-year period from January 1999 through December 2006. Of these, culture specimens from 7395 episodes (57.8%) were obtained by tympanocentesis, and culture specimens from 1851 episodes (14.5%) were obtained by collection of pus that drained from the ear; information regarding the source of culture specimen (by tympanocentesis or from spontaneous perforation) was missing for 3553 episodes (27.8%). A total of 7407 episodes (57.9%) occurred in male subjects and 5392 episodes (42.1%) occurred in female subjects (Table 1). Of the 12,793 episodes (99%) for which ethnicity was recorded, 5436

Table 1. Epidemiologic and Demographic Data for 8193 Subjects with Culture-Positive Acute Otitis Media

Characteristic	<i>Moraxella catarrhalis</i>		<i>Haemophilus influenzae</i>		<i>Streptococcus pneumoniae</i>		GAS		<i>H. influenzae</i> and <i>S. pneumoniae</i>		<i>M. catarrhalis</i> and <i>S. pneumoniae</i>		<i>M. catarrhalis</i> , <i>S. pneumoniae</i> , and <i>M. catarrhalis</i>		<i>S. pneumoniae</i> and <i>M. catarrhalis</i>		<i>H. influenzae</i> and <i>M. catarrhalis</i>		<i>M. catarrhalis</i> , <i>S. pneumoniae</i> , and <i>M. catarrhalis</i>				
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	
No. of episodes	165		3108		2592		304		1553		96		113		122		140						
No. of Jewish children/Bedouin children	92/73 ^a		1401/1705 ^a		1210/1381 ^a		193/110		534/1019		38/58		52/61		35/87		64/76						
No. of males/females	94/71		1794/1314		1521/1071		164/140		871/682		49/47		68/45		70/52		88/52						
Age, months																							
<12	125 (75.8) ^b		1911 (61.5) ^b		1650 (63.7) ^b		110 (36.2) ^b		883 (56.9)		51 (53.1)		86 (76.1)		79 (64.8)		43 (30.7)						
13–23	35 (21.2)		972 (31.3)		733 (28.3)		96 (31.6)		523 (33.7)		30 (31.3)		22 (19.5)		32 (26.2)		63 (45)						
24–35	5 (3.0)		185 (6.0)		152 (5.9)		54 (17.8)		118 (7.6)		11 (11.5)		3 (2.7)		8 (6.6)		22 (15.7)						
36–59	0 (0)		40 (1.3)		57 (2.2)		44 (14.5)		29 (1.9)		4 (4.2)		2 (1.8)		3 (2.5)		12 (8.6)						
Previous AOM episodes																							
0	75 (50.3) ^c		956 (33.9) ^c		991 (41.3) ^c		69 (46.0)		455 (32.2)		28 (31.5)		51 (52.0)		45 (39.8)		41 (32.5)						
1–3	36 (24.2)		869 (30.8)		701 (29.2)		36 (24.0)		433 (30.7)		27 (30.3)		22 (22.4)		30 (26.5)		38 (30.2)						
>3	38 (25.5)		995 (35.2)		705 (29.4)		45 (30.0)		523 (37)		34 (38.2)		25 (25.5)		38 (33.6)		47 (37.3)						
No. (%) of patients with previous tympanocentesis episodes																							
0	111 (75.0)		2006 (74.4)		1775 (76.9)		118 (79.7)		990 (73.1)		66 (78.6)		74 (81.3)		97 (87.4)		100 (78.7)						
1–3	28 (18.9)		560 (20.8)		427 (18.6)		20 (13.5)		273 (20.1)		15 (17.9)		15 (16.5)		9 (8.1)		18 (14.2)						
>3	9 (6.1)		132 (4.9)		98 (4.3)		10 (6.8)		92 (6.8)		3 (3.6)		2 (2.2)		5 (4.5)		9 (7.1)						
Previous receipt of antibiotic treatment																							
No treatment at diagnosis	71 (47.7) ^d		948 (33.9) ^d		976 (41.3)		93 (65.0) ^d		541 (38.8)		28 (31.5)		41 (42.3)		48 (43.2)		56 (46.3)						
Treatment during past month ^e	78 (52.3)		1851 (66.1)		1385 (58.7)		50 (35.0)		855 (61.2)		61 (68.5)		56 (57.7)		63 (56.8)		65 (53.7)						

NOTE. Data are no. (%) of children, unless otherwise indicated. Data were not available for some patients. Data not shown on 3 patients with *M. catarrhalis* and group A streptococcus and 2 patients with *M. catarrhalis*, *S. pneumoniae*, and group A streptococcus (GAS).

^a $P < .02$ between *M. catarrhalis* versus *H. influenzae* and *M. catarrhalis* versus *S. pneumoniae*.

^b $P < .001$ between *M. catarrhalis* versus *H. influenzae*, *M. catarrhalis* versus *S. pneumoniae*, and *M. catarrhalis* versus GAS.

^c $P < .03$ between *M. catarrhalis* versus *H. influenzae* and *M. catarrhalis* versus *S. pneumoniae*.

^d $P < .03$ between *M. catarrhalis* versus *H. influenzae* and *M. catarrhalis* versus GAS.

^e Excluding last 48 h; data not available for some patients.

(42.5%) occurred in Jewish children and 7357 (57.5%) occurred in Bedouin children, an ethnic distribution resembling that of the healthy population aged ≤ 3 years in southern Israel.

Of the 12,793 episodes, a total of 10,382 pathogens were isolated: *H. influenzae*, 4982 (48.0%); *S. pneumoniae*, 4450 (42.9%); *M. catarrhalis*, 501 (4.8%); and GAS, 449 (4.3%). All *M. catarrhalis* isolates were β -lactamase producers. Culture-negative AOM was recorded in 4601 episodes (36.0%).

Of the 8198 culture-positive episodes, in 2029 (24.8%) >1 pathogen was involved. Of these, 1553 were mixed infection with *S. pneumoniae* and *H. influenzae*, 336 were mixed infection with *M. catarrhalis* and the other 3 pathogens causing AOM, and 140 were mixed infection with other combinations (without *M. catarrhalis*). *M. catarrhalis* was isolated in 501 (3.9%) of 12,799 episodes, of which 165 (32.9%) of 501 were single-pathogen episodes and 336 (67.1%) were mixed infection episodes. Episodes with combinations of pathogens isolated together with *M. catarrhalis* included *M. catarrhalis* and *S. pneumoniae* ($n = 113$); *M. catarrhalis* and *H. influenzae* ($n = 96$); *M. catarrhalis* and GAS ($n = 3$); *M. catarrhalis*, *S. pneumoniae*, and *H. influenzae* ($n = 122$); *M. catarrhalis*, *S. pneumoniae*, and GAS ($n = 1$); and *M. catarrhalis*, *H. influenzae*, and GAS ($n = 1$). The distribution of single versus mixed infection for *M. catarrhalis* was significantly different compared with *H. influenzae* and *S. pneumoniae* (165 cases [32.9%] as a single pathogen of all AOM caused by *M. catarrhalis* vs 3108 [62.4%] in AOM caused by *H. influenzae*, 2592 [58.2%] in AOM caused by *S. pneumoniae*, and 304 [67.7%] in AOM caused by GAS; $P < .001$ for all comparisons) (Figure 1). These

findings remained significant after adjusting for each of the following variables: age, ethnicity, current antibiotic therapy, first AOM episode, and diagnosis of spontaneous perforation at enrollment ($P < .001$ for all comparisons).

The mean age (\pm standard deviation) of all enrolled patients was 12.6 ± 9.7 months (11.9 ± 8.9 months for culture-positive and 13.7 ± 10.9 months for culture-negative patients). The mean ages (\pm standard deviation) for patients with AOM caused by *M. catarrhalis*, *H. influenzae*, *S. pneumoniae*, and GAS as single pathogens were 9.0 ± 6.7 , 11.5 ± 7.9 , 11.2 ± 8.7 , and 19.3 ± 14.4 months, respectively. A higher proportion of single-pathogen *M. catarrhalis* episodes was recorded in children aged <12 months than in all other single-pathogen episodes ($P \leq .001$) (Table 1). Previous AOM episodes were reported in significantly lower proportions of single-pathogen *M. catarrhalis* episodes compared with single-pathogen *H. influenzae* or *S. pneumoniae* episodes (74 [45%] of 165, 1864 [60%] of 3108, and 1406 [54%] of 2592, respectively; $P \leq .01$). Single-pathogen *M. catarrhalis* episodes were associated with higher proportions of patients previously treated with antibiotics versus single-pathogen GAS episodes ($P = .03$), lower proportions versus single-pathogen *H. influenzae* episodes ($P < .001$), and similar proportions versus single-pathogen *S. pneumoniae* episodes ($P = .10$) (Table 1). No significant differences were found in the seasonality of *M. catarrhalis* AOM as a single pathogen compared with the other 3 pathogens: 111 (67.3%) of 165 during winter season (October-March) versus 2107 (67.8%) of 3108 cases of *H. influenzae*, 1633 (63.0%) of 2592 cases of *S. pneumoniae*, and 190 (62.5%) of 304 cases of GAS.

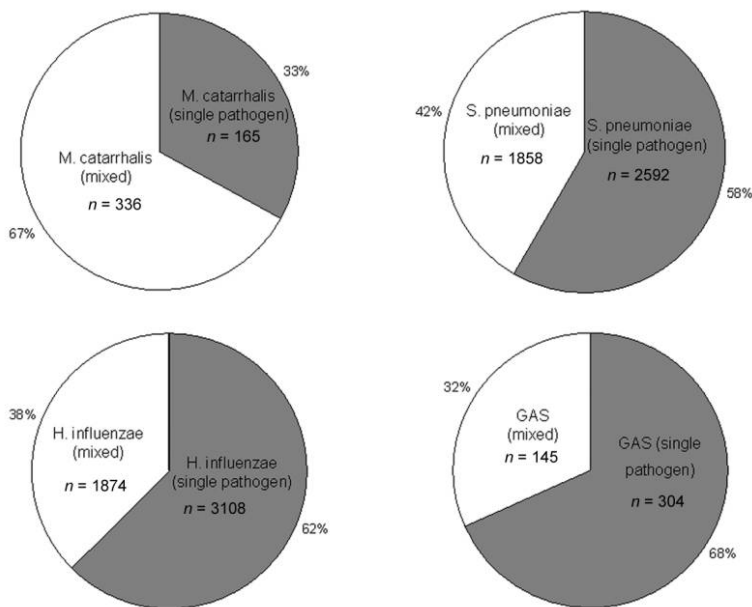


Figure 1. Distribution of single versus mixed infections in acute otitis media episodes caused by *Moraxella catarrhalis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and group A streptococcus (GAS). $P < .001$ between *M. catarrhalis* and the 3 other pathogens.

Thirty-one (6%) of the 501 patients with *M. catarrhalis* AOM were enrolled in 9 double-tympanocentesis studies performed during 1999–2004 evaluating the efficacy of 7 antibiotic drugs. Bacteriologic eradication of the pathogen on days 4–6 of treatment was achieved in 29 patients (94%).

We compared selected clinical data in single and mixed *M. catarrhalis* episodes to those reported in episodes caused by other pathogens (Table 2). No differences in the proportion of episodes with temperatures $\geq 38^{\circ}\text{C}$ or vomiting were found except for GAS as a single pathogen, for which significantly fewer patients had temperatures $\geq 38^{\circ}\text{C}$ or vomiting ($P < .001$). Bilateral AOM caused by *M. catarrhalis* was diagnosed in a significantly higher proportion of episodes compared with GAS ($P < .01$) but in a comparable proportion of episodes with AOM caused by *H. influenzae* or *S. pneumoniae* or their combination. Spontaneous perforation occurred in significantly lower proportions of episodes with *M. catarrhalis* as a single pathogen compared with each of the other 3 pathogens ($P < .001$ for all comparisons).

Univariate analysis revealed that Jewish ethnicity, age of < 1 year, first AOM episode, and decreased rates of spontaneous perforation were associated with *M. catarrhalis* AOM. Multivariate analysis revealed that Jewish ethnicity and decreased rates of spontaneous perforation in *M. catarrhalis* AOM remained significant variables compared with *H. influenzae* or *S. pneumoniae*.

Of a total of 23 cases of acute mastoiditis (28 pathogens recovered) recorded during the study period, there were no cases of acute mastoiditis with isolation of *M. catarrhalis*, compared with 12 of 2592, 6 of 304, and 1 of 3108 associated with *S. pneumoniae* (as a single pathogen; $P = .40$), GAS ($P = .07$), and *H. influenzae* ($P = .80$). The 4 additional cases were caused by *S. pneumoniae* and *H. influenzae* ($n = 3$) and *S. pneumoniae* and *H. influenzae* and GAS ($n = 1$).

DISCUSSION

In this comprehensive study of 8198 episodes of culture-positive AOM episodes in children across a 7-year study period, we were able to identify some characteristics of AOM caused by *M. catarrhalis*. *M. catarrhalis* AOM was associated with significantly higher proportions of mixed infections and first episodes of AOM and significantly lower rates of spontaneous perforation of the tympanic membrane and no mastoiditis at the time of diagnosis compared with the other 3 AOM pathogens.

Previous studies performed in a rat model of AOM showed that *M. catarrhalis* caused the mildest histopathologic changes when compared with *S. pneumoniae* or *H. influenzae*. These changes included less eustachian tube goblet cell formation and shorter duration of increased density of goblet cells [12], new bone formation, mucosal polyps, or fibrous adhesions [11].

Furthermore, in a study of 61 children with AOM caused by *H. influenzae* or *M. catarrhalis*, the local immune response associated with *M. catarrhalis* AOM was milder with less immunoglobulin (Ig) G, IgM, and IgA production within MEF when compared with *H. influenzae*, with less severe purulent response and lower bacterial counts in the MEF [13]. Therefore, it is expected that AOM caused by *M. catarrhalis* should have milder clinical features compared with *S. pneumoniae* or *H. influenzae* AOM. Indeed, we found that AOM caused by *M. catarrhalis* was associated with significantly lower rates of spontaneous perforation of the tympanic membrane at the time of diagnosis of AOM and did not cause mastoiditis in our patients. Mastoiditis caused by *M. catarrhalis* as a single pathogen is extremely rare and has been reported only once in the English literature [18]. Furthermore, in a study of 17 children aged < 13 years with *M. catarrhalis* bacteremia, Ahmed et al [19] showed that only 3 of 17 had a temperature $> 38.5^{\circ}\text{C}$ and only 7 of 17 had a leukocyte count of $> 15,000$ cells/ μL . Coinfection was documented in 6 of 17 patients.

In some reports, an increased proportion of *M. catarrhalis* isolation from the MEF in AOM has been shown. Kilpi et al [20] have reported an increase from 10% to 23% within 15 years, and a similar pattern has also been reported in the United States [1]. In Costa Rica, the prevalence of *M. catarrhalis* isolated from the MEF of children with AOM aged 3–144 months increased from 2.5% of all pathogens during 1992–1997 to 7% during 1999–2004 and was most commonly found in children aged < 24 months during the dry season [21]. However, in the present study, *M. catarrhalis* has been consistently found as a single pathogen in only $\sim 1\%$ of MEF isolates. The reasons for the higher relative importance of *M. catarrhalis* as a pathogen in AOM in certain geographical areas and the different rates of *M. catarrhalis* AOM in other areas are unknown. However, similar to our findings, a younger age at diagnosis and higher representation of *M. catarrhalis* in the first episode of AOM have also been reported in Finland [20].

In the present study, *M. catarrhalis* was associated with mixed infections with ≥ 1 of the other 3 AOM pathogens in significantly higher proportions than *S. pneumoniae*, *H. influenzae*, or GAS. In fact, developing populations (such as American Natives or Australian Aborigines and also the Bedouin population described in our studies) are thought to be more otitis prone and more often have recurrent AOM, chronic suppurative otitis media, or spontaneous perforations of the tympanic membrane [22–24]. This could be related to biofilm production (leading to prolonged colonization and resistance to antibiotics) or other anatomical or genetic mechanisms that might be more common in otitis-prone children [25].

The involvement of *M. catarrhalis* in mixed infections, its much lower rates of spontaneous perforation, the lack of local complications as mastoiditis, the milder local inflammation

Table 2. Clinical Data for 8193 Children with Culture-Positive Acute Otitis Media (AOM)

Characteristic	No. (%) of children									
	<i>Moraxella catarrhalis</i> (n = 165)	<i>Haemophilus influenzae</i> (n = 3108)	<i>Streptococcus pneumoniae</i> (n = 2592)	GAS (n = 304)	<i>H. influenzae</i> and <i>S. pneumoniae</i> (n = 1553)	<i>H. influenzae</i> (n = 96)	<i>M. catarrhalis</i> and <i>S. pneumoniae</i> (n = 113)	<i>S. pneumoniae</i> (n = 122)	<i>M. catarrhalis</i> , <i>S. pneumoniae</i> , and <i>H. influenzae</i> (n = 140)	Other mixed without <i>M. catarrhalis</i> (n = 140)
Temperature >38.1°C	120 (72.7)	2116 (68.1)	1762 (68.0)	81 (26.6)	1009 (65.0)	69 (71.9)	76 (67.3)	73 (59.8)	58 (41.4)	
Vomiting	49 (29.7)	826 (26.6)	637 (24.6)	18 (5.9)	418 (26.9)	38 (39.6)	34 (30.1)	39 (32.0)	11 (7.9)	
Bilateral AOM	82 (49.7)	1576 (50.7)	1232 (47.5)	39 (12.8)	827 (53.2)	48 (50.0)	62 (54.9)	66 (54.1)	37 (26.4)	
Spontaneous perforation	11 (6.7) ^a	462 (14.9) ^a	458 (17.7) ^a	129 (42.4) ^a	344 (22.2)	21 (21.9)	12 (10.6)	29 (23.8)	37 (26.4)	
Acute mastoiditis	0	1	12	6	3	0	0	0	1	

^a P ≤ .003.

process and immune response, and the relatively rare and benign course of *M. catarrhalis* bacteremia suggests that *M. catarrhalis* is a less virulent pathogen by itself. This evidence is to be taken into consideration in the present and future era of immunization with the pneumococcal—and, we hope, anti-*H. influenzae*—vaccines.

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