

ORIGINAL ARTICLES

A Cross-National Study of Acute Otitis Media: Risk Factors, Severity, and Treatment at Initial Visit. Report from the International Primary Care Network (IPCN) and the Ambulatory Sentinel Practice Network (ASPN)

Jack Froom, MD, Larry Culpepper, MD, MPH, Larry A. Green, MD, Ruut A. de Melker, MD, Paul Grob, MD, Timothy Heeren, PhD, and Frank van Balen, MD

Background: Treatment of acute otitis media (AOM) differs worldwide. The Dutch avoid antimicrobials unless fever and pain persist; the British use them for 5 to 7 days, and Americans use them for 10 days. If effects of therapies are to be compared, it is necessary to evaluate rates of risk factors, severity of attacks, and their influence on treatment decisions. We wanted to compare the prevalence of risk factors for AOM and evaluate their association with severity of attacks and of severity with antimicrobial treatment.

Methods: We undertook a prospective cohort study of 2,165 patients with AOM enrolled by primary care physicians; 895 were enrolled from North America, 571 were enrolled from the United Kingdom, and 699 were enrolled from The Netherlands. The literature was searched using the key words “acute otitis media,” “severity,” and “international comparisons.”

Results: The prevalence of several AOM risk factors differs significantly among patients from the three country networks; these factors include race, parent smoking habits, previous episodes, previous episodes without a physician visit, tonsillectomy or adenoidectomy, frequency of upper respiratory tract infections, day care, and recumbent bottle-feeding. Dutch children have the most severe attacks as defined by fever, ear discharge, decreased hearing during the previous week, and moderate or severe ear pain. In country-adjusted univariate analyses, increasing age, exposure to tobacco smoke, day care, previous attacks of AOM, previous attacks without physician care, past prophylactic antimicrobials, ear tubes, adenoidectomy, and tonsillectomy all contribute to severity. Only country network, age, history of AOM, previous episode without physician care, and history of adenoidectomy and tympanostomy tubes are independently related to increased severity, while current breast-feeding is protective.

Severity of attacks influences treatment decisions. Dutch children are least likely to receive antimicrobials, and even for severe attacks the British and Dutch physicians usually use amoxicillin or trimethoprim-sulfa; North American children with severe attacks are more likely to receive a broad-spectrum second-line antimicrobial.

Conclusion: Dutch children have the highest ratings in all severity measures, possibly reflecting parental decisions about care seeking for earaches. When comparing groups of patients with AOM, it is necessary to adjust for baseline characteristics. Severity of episode affects physician treatment decisions. Adoption of Dutch guidelines restricting use of antimicrobials for AOM in the United States could result in annual savings of about \$185 million. (J Am Board Fam Pract 2001;14:406–17.)

Submitted, revised, 19 April 2001.

From the Department of Family Medicine (JF), State University of New York at Stony Brook; the Department of Family Medicine (LG) and the Department of Biostatistics and Epidemiology (TH), Boston University, Boston; the Department of Family Medicine (LAG), University of Colorado, Denver; the Department of Family Medicine (RAM, FB), University of Utrecht, The Netherlands; and the De-

partment of General Practice (PG), University of Surrey, England. Address reprint requests to Larry Culpepper, MD, MPH, Department of Family Medicine, Boston University School of Medicine, One Boston Medical Center Place, Boston, MA 02118-2393.

This work was supported by the Agency for Health Care Policy and Research, Grant No. RO1 HS07035-03. Tympanometers were purchased at a discounted rate from Welch Allyn.

Bacterial resistance to antimicrobial medications increases morbidity, mortality, and costs.¹⁻⁸ The most frequent use of antimicrobials in United States outpatients is for acute otitis media (AOM).⁹ Worldwide, the three most common bacterial causes of AOM are becoming increasingly resistant to antimicrobials,¹⁰⁻¹⁵ and benefit from antimicrobial treatment has not been firmly established.¹⁶ It is therefore essential to reevaluate management of this disease.

Health care systems, health-seeking behavior, and medical management differ worldwide. Both the British and Dutch health care systems provide almost universal medical coverage, with physician visits and medications provided at little or no cost to the patient; in addition, patients and their families are enrolled with a family physician, providing continuity of care and easy follow-up, if necessary. Access and costs in these countries are not deterrents to receipt of initial or follow-up care for symptoms of AOM. In contrast, children in the United States might not receive desired medical care for financial reasons. A national Dutch guideline recommends that children be treated for symptoms, but not receive antimicrobials unless fever or pain persists.¹⁷ British children usually receive antimicrobials for 5 to 7 days; those in North America for 10 days.¹⁸ If different therapies are to be compared, it is necessary to evaluate differences in rates of risk factors, severity of attacks, and the influence of severity on treatment decisions in the patient populations.

Risk factors for occurrence of AOM episodes have been described and include sex,¹⁹ race,²⁰ day care attendance,²¹⁻²⁸ bottle-feeding,^{29,30} family history of otitis media,^{31,32} exposure to tobacco smoke,^{33,34} upper respiratory tract infections during the past week and year,^{35,36} and others.^{37,38} Associations of these risk factors to severity and of severity to therapeutic decisions, however, have not been reported. From a study of patients with AOM who consulted participating physicians in primary care practice-based research networks in The Netherlands, the United Kingdom, and North America, we report the interactions of risk factors, severity of attacks, and initial antimicrobial use.

Methods

Primary care physician members of practice-based research networks in the United States and Canada

(Ambulatory Sentinel Practice Network), the United Kingdom, and The Netherlands were asked to enroll consecutive patients 6 to 180 months old who consulted for a new episode of AOM. Physicians were instructed not to alter treatment because of study participation. Human subjects approval was obtained centrally and within each participating country.

Physician Inclusion Criteria

Physician members of each network were asked to participate if they reported that their routine practice for prescribing antimicrobials at the initial visit for AOM was the same as their country's standard. Routine practice for uncomplicated cases in North America is 10 days of antimicrobial treatment, in the United Kingdom, 5 to 7 days. For the Dutch, none is given at the initial visit. If symptoms persist, Dutch children age 2 years and older are reevaluated after 3 days, those younger than 2 years are reevaluated after 24 hours.^{17,18}

Physicians completed training and demonstrated competence in conducting a standardized ear examination, tympanometry, and entering and reporting data electronically. Photographs of abnormal tympanic membranes were used for otoscopy training, and dual-headed teaching otoscopes were used for pneumatic otoscopy instruction. Except for physicians in England, training and demonstrated competence in pneumatic otoscopy were required (British otoscope heads generally are not designed for pneumatic otoscopy). Analyses of pneumatic otoscopy data added little to those of tympanometry, and because no data were obtained from the United Kingdom, they are not reported. A total of 131 family physicians-general practitioners and pediatricians participated, 48 (7 pediatricians) in the United States and Canada, 33 in the United Kingdom, and 50 in The Netherlands.

Patient Inclusion Criteria

Patients were enrolled if they received initial care for a new episode of AOM and had the following ear-related symptoms for 4 days or less (most attacks of AOM are preceded by symptoms of an upper respiratory tract infection; duration of these symptoms was also recorded): either pus draining from the middle ear, a bulging tympanic membrane, or redness of the tympanic membrane accompanied by ear pain (for children unable to report ear pain, parent assessment of pain was used).

Patients who had taken antimicrobials within 2 weeks before the visit, those referred to another physician at the time of the initial visit, and those with cholesteatoma, mastoiditis, suspicion of sepsis, genetic abnormality of the ear, or current symptoms from a chronic disease, such as diabetes, asthma or epilepsy, were excluded.

Data

Parent Questionnaire

At the index visit parents completed a self-administered questionnaire eliciting the following information: patient characteristics (date of birth, sex, race or ethnicity, breast-feeding history, supine bottle-feeding, school attendance, hours of day care attended each week, number of children in the day care group, household smokers and number of cigarettes consumed per day, otitis media in siblings), visit characteristics (date, location, time of day), illness characteristics (days of ear-related symptoms including ear pain, ear discharge, decreased hearing; onset of symptoms from an upper respiratory tract infection during the preceding 7 days; other symptoms since illness onset, including fever, diarrhea, vomiting, and assessment of severity of pain and of the current attack), and history (age at first attack; number of attacks presumed to be AOM during the previous 18 months that were seen by a physician and the number not treated by a physician; history of decreased hearing, otitis media with effusion, receipt of prophylactic antimicrobials, tympanocentesis, tympanostomy tubes, tonsillectomy and adenoidectomy). Questions were answered by checking one or more of a list of choices and reviewed by the physician after completion. For patients in The Netherlands and the United Kingdom, the answers were translated into Dutch and British English and back translated into American English to assure comparability.

Physician Report

Physicians examined each ear and described the appearance of the tympanic membrane, performed tympanometry, and except for those in the United Kingdom, performed pneumatic otoscopy. To assure comparability between countries, physicians were provided with forehead skin thermometers.³⁹ Physicians reported patient age, race or ethnicity, number of previous episodes of AOM cared for by a physician, duration of AOM symptoms, temperature, examination findings for each ear (not visu-

alized, redness, bulging, retraction, discharge and type, perforation, tympanostomy tube presence), hearing status, pneumatic otoscopy results, tympanometry results (Peak Ya [peak acoustic admittance], TPP [tympanic peak pressure], VEA [volume of ear canal]), tympanogram interpretation using the modified Jerger classification,⁴⁰ and their clinical assessment of severity. Physicians reported the type and duration of antimicrobial prescribed.

Participating practices were provided with a Welch Allyn MicroTymp II tympanometer and printer; physicians mailed copies of their tympanograms to the country coordinator for blinded independent interpretation using the modified Jerger classification. Physician tympanogram interpretation was validated against that of highly skilled interpreters. The same method was used in all three networks, with a kappa value of 0.65 for tympanograms obtained at initial visit.

Data Management

Practices mailed the parent questionnaire to country coordinators for entry into an electronic database. Physician data were entered into hand-held Newton computers and transmitted to the country coordinator office for import to the database. All data were transmitted electronically to the international data center at Brown University.

Data Analysis

There is no criterion standard for severity. We chose to define severity of an attack using four factors evident to parents and discernible by primary care clinicians: patient or parent report of pain (none or mild vs moderate or severe), draining ear or decreased hearing during the week preceding the initial visit, and fever at the physician examination. If two or more of these factors were reported, the child was considered to have increased severity. This model was chosen for its parsimony and simplicity from 10 models evaluated using these and additional risk factors and alternative scoring methods. Likelihood ratio chi-square analyses were used to compare group differences, with *P* values of < .05 considered to be statistically significant.

Logistic regression models determined the network-adjusted relation of individual risk factors and increased severity, adjusting for the relative sample size of each network. Logistic regression models calculated the independent contribution of risk factors, including models (not shown) that assessed all

Table 1. Geographic, Age, and Sex Distribution of Study Population (N = 2,165).

Age	North America n = 895	United Kingdom n = 571	The Netherlands n = 699
6–24 months, No.	314	160	177
Male, %	54.5	51.9	53.8
Female, %	45.5	48.1	46.2
25–180 months, No.	581	411	522
Male, %	50.9	53.5	52.8
Female, %	49.1	46.5	47.2

potential interactions of individual risk factors and either age or network. The only significant interaction term, adenoidectomy by country, is included in the final model reported. A Hosmer-Lemeshow chi-square value of $P = .986$ shows the goodness-of-fit of this final model.

Results

A total of 2,165 patients with AOM were enrolled in the study, 895 from the North America, 571 from the United Kingdom, and 699 from The Netherlands. The age and sex distribution of these patients is given in Table 1.

Risk Factors for Occurrence of AOM

A comparison of prevalence of risk factors reported by parents of enrolled children among the three networks is displayed in Table 2. Age less than 2 years has been described as a major risk factor for attacks of AOM^{18,31,41}; data are therefore displayed separately for each of the age groups.

There are significant differences in prevalence of risk factors for attacks of AOM between patients enrolled in the three networks. Previous attacks of AOM were least frequent in Dutch children, and those with previous attacks were most likely to have had an earache that parents considered an episode of AOM for which they did not consult a physician. Dutch children aged 25 to 180 months were least likely to have had attacks of AOM during the first year of life and most likely to have had tonsillectomy or adenoidectomy or both, while British infants and children were least likely to receive prophylactic antimicrobials.

Dutch parents smoked the most, and their children aged 25 to 180 months had the highest number of upper respiratory tract infections during the previous year. In all three networks, children were

highly likely to have had upper respiratory tract infection symptoms in the week preceding the AOM attack. American children aged 6 to 24 months were most likely to be in day care, but the opposite was true for children aged 25 to 48 months. For all ages, size of the day care group was smallest in North America.

A history of breast-feeding in the three networks was similar at about 70%; Americans tended to breast-feed the longest (up to age 12 months; North America 25%, the United Kingdom 17%, The Netherlands 3.9%, $P < .001$), and fewer stopped before 4 months. North American children aged 6 to 24 months were most likely both to be breast-feeding currently and to be put to bed with a bottle (milk intake in a recumbent position).

In summary, several risk factors for AOM attacks differ significantly among the enrolled children in North America, the United Kingdom, and The Netherlands.

Physical Findings

There were significant differences between children from the three networks in physical findings reported by physicians (Table 3). The most notable of these were the highest rates of fever, tympanic membrane perforations, abnormal tympanograms, and ear discharge in Dutch children. The prevalence of retracted membranes (19% in those aged 24 months or younger, 24% in those aged 24 to 180 months), which might have been contralateral to a bulging membrane, and tympanostomy tubes in place (2.8% in those older than 24 months) did not differ significantly among countries. Physicians in all three networks were equally certain of their diagnosis of AOM, (94% to 96% certain or very certain in both age groups).

Severity of Attacks of AOM

Severity of attacks of AOM is defined by fever at the initial examination, parent reports of ear discharge, decreased hearing during the previous week, and either moderate or severe ear pain. Patients with two or more of these findings were compared with those having one or none. By these criteria, both by individual factors (except for decreased hearing, which was slightly more prevalent in British children) and those combined, Dutch children had the highest frequency of severe attacks (Table 4).

Table 2. Prevalence of Risk Factors for Acute Otitis Media (AOM) in Children Aged 6 to 24 and 25 to 180 Months.

Factor	North America	United Kingdom	The Netherlands	P Value
White				
6–24 mo	87.9	98.1	93.2	.000
25–180 mo	90.4	93.9	93.1	.087
Parent smokes				
6–24 mo	17.2	16.9	35.4	.000
25–180 mo	25.9	27.8	42.4	.000
Sibling history of ≥ 3 AOM episodes				
6–24 mo	37.5	33.1	31.3	.355
25–180 mo	48.5	36.7	31.6	.000
History of tonsillectomy				
12–24 mo	1.3	0.0	1.1	.378
25–180 mo	4.1	4.6	12.1	.000
History of adenoidectomy				
6–24 mo	0.6	0.6	1.7	.502
25–180 mo	4.0	5.1	20.4	.000
History of tympanostomy tubes				
6–24 mo	0.3	0.6	1.2	.552
25–180 mo	11.7	8.6	13.9	.043
History of prophylactic antimicrobial				
6–24 mo	11.0	2.6	12.3	.001
25–180 mo	20.1	5.1	14.7	.000
Any history of AOM				
6–24 mo	54.5	61.9	39.5	.000
25–180 mo	88.3	80.0	70.3	.000
1st attack age <1 yr				
2–24 mo	20.2	15.7	33.3	.129
25–180 mo	60.5	36.6	33.0	.000
Previous attack without physician visit among those with previous episode(s)				
6–24 mo	4.8	7.4	18.6	.005
25–180 mo	6.7	9.3	20.9	.000
More than 3 URIs in past year				
6–24 mo	26.3	40.8	45.9	.000
25–180 mo	34.3	35.7	37.0	.097
URI in past week				
6–24 mo	78.1	83.0	84.1	.218
25–180 mo	81.9	74.5	80.8	.016
Day care attendance				
6–24 mo	46.2	31.2	23.3	.000
25–48 mo	60.6	70.8	80.5	.000
Group size ≥ 6 of those in day care				
6–24 mo	42.4	71.4	75.7	.000
25–48 mo	66.3	91.8	99.2	.000
Diarrhea or vomiting this episode				
6–24 mo	35.3	32.7	39.1	.485
25–48 mo	17.7	13.2	19.8	.027
Currently breast-feeding				
6–24 mo	15.2	7.8	5.7	.002
25–48 mo	1.9	0.5	0.6	.049
Recumbent bottle-feeding				
6–24 mo	32.0	25.3	11.4	.000
25–180 mo				

URI—upper respiratory tract infection.

Table 3. Prevalence of Physical Findings at Initial Visit for Acute Otitis Media by Age.

Variable	North America	United Kingdom	The Netherlands	P Value
Fever $\geq 101^{\circ}\text{F}$				
6–24 mo	9.1	20.9	35.4	.000
25–180 mo	10.8	15.4	15.7	.390
Tympanic membrane red				
6–24 mo	99.4	98.8	94.3	.002
25–180 mo	98.6	98.5	95.2	.001
Tympanic membrane bulging				
6–24 mo	48.8	36.8	47.2	.042
25–180 mo	53.7	48.1	49.1	.158
Tympanic membrane perforated				
6–24 mo	1.0	0.6	9.7	.000
25–180 mo	1.4	2.0	6.6	.000
Clear discharge				
6–24 mo	2.9	3.8	10.7	.001
25–180 mo	3.8	4.6	8.0	.007
Pustular discharge				
6–24 mo	1.6	2.5	9.6	.000
25–180 mo	2.9	2.9	5.9	.021
Tympanometry abnormal				
6–24 mo	78.8	77.9	90.0	.036
25–180 mo	70.4	75.5	87.1	.000

Risk Factors and Severity

Table 5 presents a country-adjusted univariate analysis of the relation between risk factors and severity of attacks. As compared with those from North America, British and Dutch children had an increased risk for severe attacks, with the risk highest in the latter. Increasing age, previous attacks of AOM, previous presumed attacks without physician care, and exposure to tobacco smoke, all contribute to the severity of symptoms. Children with at least one bulging tympanic membrane or ear tube, or who had ear tubes present in both ears, had increased severity, whereas those with at least one red tympanic membrane (compared with those with the study inclusion criteria of drainage pus without redness) had less severe attacks. Attacks in children who received prophylactic antimicrobials, ear tubes, adenoidectomy, or tonsillectomy were more severe than those without a history of those events. Current but not past breast-feeding was protective. Children younger than 4 years old in day care had less severe attacks than those who were older.

A multivariate analysis (Table 6) reveals that only country network, age, current breast-feeding, history of AOM, a previous episode without phy-

sician care, and a history of adenoidectomy are independently related to severity. Compared with children in The Netherlands, both British and North American children had less severe attacks at initial examination for AOM. Children younger than 2 years had less severe attacks than older children. History of AOM, history of a presumed attack not cared for by a physician, and history of tympanostomy tubes all increased risks for severity, whereas current breast-feeding was protective. Although British and North American children with a history of adenoidectomy were more likely to have severe attacks, Dutch children who had had this surgery were at reduced risk. Adenoidectomy had occurred in 65% of Dutch children with a history of tympanostomy tubes; comparable British and North American figures are 47% and 26%.

Severity of Attacks of AOM and Antimicrobial Treatment

In our sample, overall, 97% of North American children were treated with an antimicrobial for 10 days, and only 0.3% did not receive an antimicrobial. Ninety-nine percent of British children received an antimicrobial for 5 to 7 days; 17% of Dutch children received an antimicrobial, 16% for

Table 4. Prevalence of Indicators of Severity (Febrile at Examination, Parent Report of Moderate or Severe Pain, Decreased Hearing, or Ear Drainage) of Acute Otitis Media at Initial Visit for Children Aged 6 to 24 and 25 to 180 Months.

Symptomatic Severity Indicators	North America	United Kingdom	The Netherlands	P Value
<i>Age 6–24 mo</i>				
Pain*				
None	10.2	5.6	4.2	
Mild	32.0	22.5	17.5	
Moderate	46.8	51.4	45.5	
Severe	10.9	20.4	32.9	.000
Decreased hearing in past week	1.2	14.6	12.8	.000
Drainage from ear	10.5	10.0	17.1	.085
Febrile	9.1	20.9	35.4	.000
<i>Age 25–180 mo</i>				
Pain*				
None	7.0	2.8	5.4	
Mild	24.9	16.7	14.3	
Moderate	44.7	48.5	44.7	
Severe	23.3	32.1	35.6	.000
Decreased hearing in past week	29.4	37.2	42.1	.001
Drainage from ear	8.9	9.4	12.8	.095
Febrile	10.8	15.4	15.7	.039
<i>Two or more symptomatic severity indicators</i>				
6–24 mo	10.5	21.3	31.1	.000
25–180 mo	24.4	34.3	39.1	.000

*Moderate or severe pain considered an indicator of severity.

5 to 7 days. Of those receiving an antimicrobial, 79% of North American, 80% of British, and 84% of Dutch children received a first-line agent.

Table 7 presents antimicrobial prescription patterns for the three networks. Both North American and British physicians adhered to the duration of antimicrobial routine for their countries (10 days and 5 to 7 days, respectively). Dutch physicians were more likely to prescribe an antimicrobial to children younger than 2 years old and to children with increased severity. Even for children younger than 2 years old with severe attacks, however, Dutch physicians followed their national treatment guideline of observation and withholding antimicrobials in more than one half of the cases. For older children with increased severity, Dutch physicians prescribed antimicrobials for only 20%.

For all groups, except those aged 25 to 180 months with increased severity, there was no difference among networks in whether physicians

chose first-line antimicrobials (amoxicillin or trimethoprim-sulfa, which are relatively inexpensive) or a second-line antimicrobial, such as cephalosporins or amoxicillin clavulanate, which are generally expensive. For those aged 25 to 180 months with increased severity, North American physicians were more likely than British and Dutch physicians to chose a second-line antimicrobial for their initial prescription. In all age and severity groups, when British and Dutch physicians chose a second-line antimicrobial, it was most commonly either an amoxicillin-clavulanate or an erythromycin preparation, whereas in North America, cephalosporin antimicrobials were most commonly chosen (data not shown).

Discussion

We found significant differences in known risk factors for attacks of AOM among patients in the

Table 5. Country Adjusted Risk Factors for Presence of 2 or More Severity Indicators (Febrile at Examination, Parent Report of Moderate or Severe Pain, Decreased Hearing, or Ear Drainage).

Risk Factor	Number	Percent with ≥2 Symptoms	Odds Ratio	95% Confidence Interval
<i>Age and environmental factors</i>				
Country				
North America	895	19.6		
United Kingdom	571	30.6	1.8	1.4–2.3
Netherlands	699	37.1	2.4	1.9–3.0
Age				
6–24 months	651	18.7		
25–180 months	1,514	32.2	1.9	1.6–2.4
Breast-feeding				
No	2,041	29.1		
Current	85	10.6	0.35	0.17–0.71
Day care attendance among those <4 years old				
No	538	25.3		
Yes	548	19.9	0.72	0.54–0.97
Smoking in household				
No	1,507	26.6		
Yes	624	32.1	1.2	0.98–1.5
<i>History</i>				
Previous episodes of AOM				
None	616	22.1		
Yes	1,549	30.5	1.8	1.4–2.2
Previous episodes				
All with physician visit	1,929	26.8		
At least one without physician visit	166	46.4	2.1	1.5–2.9
History of prophylactic antimicrobials				
No	184	27.4		
Yes	270	35.6	1.6	1.2–2.2
History of ear tubes				
No	1,940	26.8		
Yes	179	47.5	2.4	1.8–3.4
History of adenoidectomy				
No	1,976	27.1	1.8	1.3–2.5
Yes	154	45.5		
History of tonsillectomy				
No	2,020	27.7		
Yes	110	41.8	1.6	1.1–2.4
<i>Physical examination</i>				
At least one red tympanic membrane				
No	53	52.8		
Yes	2,107	27.4	0.41	0.23–0.71
At least one bulging tympanic membrane				
No	1,067	25.6		
Yes	1,029	30.8	1.3	1.1–1.6
One or more tympanostomy tubes present				
No	2,120	27.7		
Yes	45	46.7	2.1	1.1–3.8
Bilateral ear tubes present				
No	2,149	27.8		
Yes	16	68.8	5.7	2.0–16.9

Table 6. Variables Independently Associated with Severity (at Least Two of the Following: Febrile at Examination, Parent Report of Moderate or Severe Pain, Decreased Hearing, Ear Drainage) at Initial Visit for Acute Otitis Media Among Children Aged 6 to 180 Months in North America, United Kingdom, and The Netherlands (N = 2,062).

Variable	Odds Ratio	95% Confidence Interval	
		Lower	Upper
North America*	0.41	0.32	0.53
United Kingdom*	0.71	0.54	0.92
Aged 6–24 months†	0.66	0.51	0.84
Breast-feeding now	0.46	0.22	0.95
History of acute otitis media	1.39	1.08	1.79
Previous episode without physician visit	1.71	1.21	2.42
History of tympanostomy tubes	1.73	1.20	2.49
History of adenoidectomy in:			
North America	2.23	0.88	5.65
England	3.75	1.27	11.0
Netherlands	0.72	0.49	1.06

*Compared with The Netherlands.

†Compared with those aged 25 to 180 months.

three networks. North American children were most likely to have had previous episodes of AOM, a family history of recurrent otitis, and a history of current breast-feeding and of recumbent bottle-feeding. British children were most likely to have had a history of AOM but were least likely to have received prophylactic antimicrobials. In contrast, Dutch children were most likely to be enrolled in day care with larger group sizes, to have parents who smoke, and have had more episodes of upper respiratory tract infection in the past year. International as well as national studies of AOM, therefore, requires careful assessment of baseline characteristics of populations enrolled.

Although several investigators of therapeutic trials compared rates of selected symptoms and physical findings in their enrolled populations,^{41–44} few have defined severity or investigated contributing factors. Kaleida et al⁴⁵ used two variables to dichotomize severity—ear pain and fever. His otalgia rating scale included “estimated parental anxiety and reliability” and assigned 1, 3, or 12 points for each hour of ear pain rated as mild, moderate, or severe and for an oral fever of 39°C or 39.5°C if measured per rectum. Using these criteria, 23% of cases were classified as severe, similar to the 28.6%

we rated as severe using the four parent-assessed factors described above. We were unable to locate any studies that assessed associations between risk factors and severity.

In our study, several factors associated with severity are similar to those for the occurrence of attacks of AOM. It is not surprising that children who have had previous attacks, received prophylactic antimicrobials, ear tubes, or adenoidectomy or tonsillectomy had subsequent attacks that were more severe than those with no history of these events. Current breast-feeding is protective. Children in day care had less severe attacks at initial assessment, possibly because they were brought to physicians earlier than those in home care.²⁷

Our data reconfirm that behavior of patients and physicians depend upon the setting. By all measures, Dutch children who obtain medical care for AOM as a group had more severe attacks than did those in North America and the United Kingdom. Dutch children had significantly higher ratings in all severity measures, including fever, parent-assessed severity of pain, decreased hearing, and ear discharge (Table 4). Differences in severity among network populations also might be explained by differences in prevalence of risk factors for AOM. The high prevalence of smoking among Dutch parents and exposure to larger day care groups might have been more potent causes of severity than the risk factors that predominated in children from the other two networks. Another possible explanation for the difference in severity in the three networks is that AOM was caused by different organisms. There is no evidence, however, that such was the case.⁴⁶ To the contrary, organisms associated with AOM in The Netherlands were the same as those reported in other networks⁴⁷ and were less likely to be resistant to antimicrobials than those in the rest of Europe.⁴⁸

Most likely, therefore, the increased severity of Dutch children was due to care-seeking decisions of Dutch parents. In our study, Dutch children were most likely either to be experiencing their first lifetime episode of otitis or to have indications of difficult previous episodes. For those with recurrent AOM, Dutch children were most likely to have had a history of tonsillectomy or adenoidectomy and a history of previous episodes for which a physician was not consulted. Less than one third of Dutch children younger than 2 years and only 12%

Table 7. Association of Severity Indicators (Febrile at Examination, Parent Report of Moderate or Severe Pain, Decreased Hearing, or Ear Drainage) with Duration and Type of Antimicrobial Treatment (%).

Antimicrobial Type	North America	United Kingdom	The Netherlands	P Value
Aged 6–24 months with 0–1 symptom				
None	0.4	0.0	70.5	
5–7 days	1.4	99.2	27.0	
10 days	96.4	0.0	0.8	
Other	1.8	0.8	1.6	.000
First-line antimicrobial*	83.2	83.3	83.3	
Other antimicrobial	16.8	16.7	16.7	.99
Aged 6–24 months with ≥ 2 symptoms				
None	0.0	0.0	54.5	
5–7 days	0.0	100	45.5	
10 days	97.0	0.0	0.0	
Other	3.0	0.0	0.0	.000
First line*	75.8	82.4	88.0	
Other antimicrobial	24.2	17.6	12.0	.48
Aged 25–180 months with 0–1 symptom				
None	0.5	1.1	93.4	
5–7 days	1.4	98.1	6.0	
10 days	97.7	0.0	.6	
Other	0.5	0.7	0.0	.000
First-line antimicrobial*	81.0	77.9	71.4	
Other antimicrobial	19.0	22.1	28.6	.41
Aged 25–180 months with ≥ 2 symptoms				
None	0.0	0.0	80.4	
5–7 days	3.5	100	17.2	
10 days	95.1	0.0	2.5	
Other	1.4	0.0	0.0	.000
First-line antimicrobial*	64.8	81.6	90.0	
Other antimicrobial	35.2	18.4	10.0	.000

*First-line antimicrobials include ampicillin, amoxicillin and sulfa-trimethoprim preparations.

of those aged 2 years or older received antimicrobials for an attack of AOM. The low probability of receiving antimicrobials, symptom resolution in more than 60% of episodes within 48 hours,⁴⁵ and easy access to care should the child's symptoms not subside could have caused Dutch parents to reserve medical care only for attacks perceived as severe.

Dutch and North American physicians altered their antimicrobial treatment practices in response to indicators of severity at the initial visit for an episode of AOM. For Dutch physicians, increased severity resulted in an increased likelihood of prescribing an antimicrobial, although the antimicrobial was highly likely to be a first-line agent. In North America, increased severity was likely to result in physicians' initial prescription of a second-

line (often cephalosporin) antimicrobial. British physicians did not alter their antimicrobial choice in response to severity. In all networks severity did not alter duration of treatment.

The consequences of the Dutch approach to AOM care and care-seeking behavior were reduction in the development of antimicrobial resistance⁴⁸ and costs. If the Dutch approach yields similar outcomes, large cost savings accrue. The difference in history of nonattendance for attacks of AOM between patients in The Netherlands and North America is 8.1%. At an average cost of \$115 for an episode of AOM,⁴⁹ a similar reduction of the 20,009,000 office visits for AOM in 1997⁵⁰ in the United States would result in an annual saving of about \$185 million.

Participating Physicians

Ambulatory Sentinel Practice Network: Arlis Adolf, Jules Amer, John Anderson, Robert Baker, Gordon Blakeman, Brian Caplan, Paul Collins, Bill Davis, Richard Douglass, Patricia Fibiger, Stephen Fischer, Ed Friedler, Ronald Gagne, Thomas Gilbert, Susan Girardeau, John Glennon, Gary Gray, Cindy Hansen, Terry Hankey, Michael Hartzell, Joseph Hildner, Robert Howse, Jr., Robert James, Roger Kimber, Gary Knaus, Paula Leonard-Schwartz, Mary Maguire, Kim Manning, Kathleen McGarr, Doreen McMahon, Jasmine Moghissi, Michael Mulligan, William Nietert, Spiro Papadopoulos, Donya Powers, Thomas Overholt, Steve Perry, Paul Schmitt, John Scott, Susan Shapiro, Brian Stray, Kimball Spence, Jon Sternburg, Linda Stewart, Lynne Studebaker, James Wickerath, Elizabeth Wise, Lloyd Wollstadt.

Surrey GP Network: Nick Barrie, G. Bennett, S. Brown, Jace Clarke, Mark Cornbloom, I. Davies, Niall Ferguson, N. Fisher, Richard France, Paul Grob, Mark Hanan, Robert Harvey, John Healey, David William Holwell, R. N. Jeffery, Murdo Macleod, Mather, Philip Moore, Julia Oxenbury, Margaret Palmer, C. A. Pearson, C. Pidgeon, M. Pujara, David Skipp, A. Smith, K. Tarrant, Chris Tibbott, Brett J. Whitby-Smith, Hamish Whitaker, Mary Anne Whitehead, P. R. Wilks, Sidney Worthington, J. Young.

University of Utrecht Network: Atyvan Aarnhem, G. Ploosvan Amstel, D. B. van Baarda, Marja Baeten, P. J. van Beek, H. C. V. Berkum, R. Bohm, J. C. M. van Campen, J. W. Cirkel, H. J. R. Dorman, J. H. Duistermaat, H. van Es, N. Goudswaard, N. de Grunt, Ax. M. E. J. Hoeberichts, M. E. van der Hoek, J. M. P. M. Janssen, E. G. A. de Jong, L. Klaphake, A. W. K. Kramer, J. Kuiper, N. Kwakernaak, Hans Kootte, Jaap R. van der Laan, O. J. M. Lackamp, C. G. Lameris, Marjan Lamers, H. C. de Lathouder, P. J. Luyendijk, G. A. M. Maathuis, R. H. L. Morshuis, W. P. G. Mulder, P. L. W. Pijman, F. G. Pinggen, Pricleer, Liesbeth Redeke, M. J. G. van Roosmalen, C. J. Rovers, S. H. A. Schmeets, J. F. Scholte, B. P. Schreuder, T. Steenkamer, Jette Timmer-Martijn, F. Trip, de Vries, Christine Weenink, H. C. P. M. van Weert, P. Willems, Boes Willemsse, P. van de Woestijne.

References

1. Cohen ML. Epidemiology of drug resistance: implications for a post-antimicrobial era. *Science* 1992; 257:1050-5.
2. Gold HS, Moellering RC Jr. Antimicrobial-drug resistance. *N Engl J Med* 1996;335:1445-53.
3. Koshland DE Jr. The microbial wars. *Science* 1992; 257:1021.
4. Neu HC. The crisis in antibiotic resistance. *Science* 1992;257:1064-73.
5. Berkowitz FE. Antibiotic resistance in bacteria. *South Med J* 1995;88:797-804.
6. Lederberg J, Shope RE, Oaks SC Jr. Emerging infections: microbial threats to health in the United States. Washington, DC: National Academy Press, 1992.
7. LeDuc JW. World Health Organization strategy for emerging infectious diseases. *JAMA* 1996;275:318-20.
8. Addressing emerging infectious disease threats. At-

lanta: Centers for Disease Control and Prevention, 1994.

9. McCaig LF, Hughes JM. Trends in antimicrobial drug prescribing among office-based physicians in the United States. *JAMA* 1995;273:214-9.
10. Barnett ED, Klein JO. The problem of resistant bacteria for the management of acute otitis media. *Pediatr Clin North Am* 1995;42:509-17.
11. Kaplan SL. The emergence of resistant pneumococcus as a pathogen in childhood upper respiratory infections. *Semin Respir Infect* 1995;10:31-6.
12. Johnson AP, Speller DC, George RC, Warner M, Domingue G, Efstratiou A. Prevalence of antibiotic resistance and serotypes in pneumococci in England and Wales: results of observational surveys in 1990 and 1995. *BMJ* 1996;312:1454-6.
13. Faden H, Doern G, Wolf J, Blocker M. Antimicrobial susceptibility of nasopharyngeal isolates of potential pathogens recovered from infants before antibiotic therapy: implications for the management of otitis media. *Pediatr Infect Dis J* 1994;13:609-12.
14. Henderson FW, Gilligan PH, Wait K, Goff DA. Nasopharyngeal carriage of antibiotic-resistant pneumococci by children in group day care. *J Infect Dis* 1988;157:256-63.
15. Appelbaum PC. Worldwide development of antibiotic resistance in pneumococci. *Eur J Clin Microbiol* 1987;6:367-77.
16. Culpepper L, Fromm J. Routine antimicrobial treatment of acute otitis media: is it necessary? *JAMA* 1997;278:1643-5.
17. Appelman CLM, Bossen PC, Dunk JHM, van de Lisdonk EH, de Melker RA, van Weert HCPM. Guideline Dutch College of Family Doctors acute otitis media. Utrecht: Dutch College of Family Doctors, 1990.
18. Fromm J, Culpepper L, Grob P, et al. Diagnosis and antibiotic treatment of acute otitis media: report from International Primary Care Network. *BMJ* 1990;300:582-6.
19. Infante-Rivard C, Fernandez A. Otitis media in children: frequency, risk factors, and research avenues. *Epidemiol Rev* 1993;15:444-65.
20. Marchant CD, Shurin PA, Turczyk VA, Wasikowski DE, Tutihasi MA, Kinney SE. Course and outcome of otitis media in early infancy: a prospective study. *J Pediatr* 1984;104:826-31.
21. Wald ER, Dashefsky B, Byers C, Guerra N, Taylor F. Frequency and severity of infections in day care. *J Pediatr* 1988;112:540-6.
22. Strangert K. Respiratory illness in preschool children with different forms of day care. *Pediatrics* 1976;57:191-6.
23. Fleming DW, Cochi SL, Hightower AW, Broome CV. Childhood upper respiratory tract infections: to what degree is incidence affected by day-care attendance. *Pediatrics* 1987;79:55-60.
24. Louhiala PJ, Jaakkola N, Ruotsalainen R, Jaakkola JJ.

- Form of day care and respiratory infection among Finnish children. *Am J Public Health* 1995;85:1109–12.
25. Dawson DA, Cain VS. Child care arrangements: health of our nation's children, United States, 1988. Hyattsville, Md: Department of Health and Human Services. Public Health Service. National Centers for Disease Control and Prevention, National Center for Health Statistics, 1990.
 26. Hardy AM, Fowler MG. Child care arrangements and repeated ear infections in young children. *Am J Public Health* 1993;83:1321–5.
 27. Froom J, Culpepper L. Otitis media in day-care children: a report from the International Primary Care Network. *J Fam Pract* 1991;32:289–94.
 28. Bell DM, Gleiber DW, Mercer AA, et al. Illness associated with child day care: a study of incidence and cost. *Am J Public Health* 1989;79:479–84.
 29. Aniansson G, Alm B, Andersson B, et al. A prospective cohort study on breast-feeding and otitis media in Swedish infants. *Pediatr Infect Dis J* 1994;13:183–8.
 30. Sassen ML, Brand R, Grote JJ. Breast-feeding and acute otitis media. *Am J Otolaryngol* 1994;15:351–7.
 31. Teele DW, Klein JO, Rosner B. Epidemiology of otitis media during the first seven years of life in children in greater Boston: a prospective cohort study. *J Infect Dis* 1989;160:83–94.
 32. Casselbrant ML, Mandel EM, Fall PA, et al. The heritability of otitis media: a twin and triplet study. *JAMA* 1999;282:2125–30.
 33. Stenstrom R, Bernard PA, Ben-Simhon H. Exposure to environmental tobacco smoke as a risk factor for recurrent acute otitis media in children under the age of five years. *Int J Pediatr Otorhinolaryngol* 1993;27:127–36.
 34. Blakley BW, Blakley JE. Smoking and middle ear disease: are they related? A review article. *Otolaryngol Head Neck Surg* 1995;112:441–6.
 35. Daly KA. Epidemiology of otitis media. *Otolaryngol Clin North Am* 1991;24:775–86.
 36. Arola M, Ziegler T, Ruuskanen O. Respiratory virus infection as a cause of prolonged symptoms in acute otitis media. *J Pediatr* 1990;116:697–701.
 37. Niemela M, Uhari M, Mottonen M. A pacifier increases the risk of recurrent acute otitis media in children in day care centers. *Pediatrics* 1995;96(5 Pt 1):884–8.
 38. Alho OP, Laara E, Oja H. Public health impact of various risk factors for acute otitis media in northern Finland. *Am J Epidemiol* 1996;143:1149–56.
 39. Shann F, Mackenzie A. Comparison of rectal, axillary, and forehead temperatures. *Arch Pediatr Adolesc Med* 1996;150:74–8.
 40. van Balen FA, de Melker RA. Validation of a portable tympanometer for use in primary care. *Int J Pediatr Otorhinolaryngol* 1994;29:219–25.
 41. Burke P, Bain J, Robinson D, Dunleavy J. Acute red ear in children: controlled trial of non-antibiotic treatment in general practice. *BMJ* 1991;303:558–62.
 42. Froom J, Culpepper L, Bridges-Webb C, et al. Effect of patient characteristics and disease manifestations on the outcome of acute otitis media at two months. *Arch Fam Med* 1993;2:841–6.
 43. van Buchem FL, Dunk JH, van't Hof MA. Therapy of acute otitis media: myringotomy, antibiotics, or neither: a double-blind study in children. *Lancet* 1981;2:883–7.
 44. Appelman CL, Claessen JQ, Touw-Otten FW, Hordijk GJ, de Melker RA. Co-amoxiclav in recurrent acute otitis media: placebo controlled study. *BMJ* 1991;303:1450–2.
 45. Kaleida PH, Casselbrant ML, Rockette HE, et al. Amoxicillin or myringotomy or both for acute otitis media: results of a randomized clinical trial. *Pediatrics* 1991;87:466–74.
 46. Bluestone CD, Stephenson JS, Martin LM. Ten-year review of otitis media pathogens. *Pediatr Infect Dis J* 1992;11(8 Suppl):S7–S11.
 47. van Dishoeck HA, Derkes AC, Voorhorst R. Bacteriology and treatment of acute otitis media in children. *Acta Otolaryngol* 1959;50:250–61.
 48. Machka K, Braveny I, Dabernat H, et al. Distribution and resistance patterns of *Haemophilus influenzae*: a European Cooperative Study. *Eur J Clin Microbiol Infect Dis* 1988;7:14–24.
 49. Kaplan B, Wandstrat TL, Cunningham JR. Overall cost in the treatment of otitis media. *Pediatr Infect Dis J* 1997;16:S9–S11.
 50. Woodwell DA. National ambulatory medical care survey: 1997 summary. *Adv Data* 1999 May 20:1–28.