Incidence and clinical presentation of acute otitis media in children aged <6 years in European medical practices


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SUMMARY

We conducted an epidemiological, observational cohort study to determine the incidence and complications of acute otitis media (AOM) in children aged <6 years. Data on physician-diagnosed AOM were collected from retrospective review of medical charts for the year preceding enrolment and then prospectively in the year following enrolment. The study included 5776 children in Germany, Italy, Spain, Sweden, and the UK. AOM incidence was 256/1000 person-years [95% confidence interval (CI) 243–270] in the prospective study period. Incidence was lowest in Italy (195, 95% CI 171–222) and highest in Spain (328, 95% CI 296–363). Complications were documented in <1% of episodes. Spontaneous tympanic membrane perforation was documented in 7% of episodes. Both retrospective and prospective study results were similar and show the high incidence during childhood in these five European countries. Differences by country may reflect true differences and differences in social structure and diagnostic procedures.

Key words: Acute otitis media, children, Europe.

INTRODUCTION

Acute otitis media (AOM) is the commonest paediatric bacterial infection, affecting up to 75% of children at some time before age 5 years [1]. Streptococcus pneumoniae and Haemophilus influenzae, in particular the non-typeable strains (NTHi), are responsible for up to 80% of bacterial AOM [2–4]. AOM is among the primary reasons for antibiotic prescriptions in paediatric outpatients [5–8]; however, many countries recommend a ‘wait and watch’ approach as it has been found that symptomatic treatment without antibiotics...
is estimated incidence after AOM of 1·8/10000 episodes after antibiotics and 3·2/10000 episodes without antibiotics) [14].

Existing data on AOM incidence vary considerably due to different case definitions, study designs, age groups, time periods of study, geographical locations, and other factors [15–19]. Previous studies have used either retrospective data from medical chart reviews [15, 19], parental reports [18], or prospective follow-up of subjects [20, 21]. These approaches can be criticized for different reasons: retrospective reviews might underestimate the true incidence since suspected milder cases might be missed, parental reports are subjective and non-specific to AOM that lacks clinical confirmation, and prospective follow-up is sensitive to selection of subjects and diagnostic criteria used, which may result in data which are difficult to compare and generalize across studies. To our knowledge, no study has addressed all these different approaches, leaving the potential bias of incidence figures by study design uncertain, while in this cohort study of AOM the same study design was applied to each country. Data were obtained with a standardized methodology from retrospective review of medical charts and prospective follow-up based on physician and parental reports to assess all potential AOM including suspected, probable, and confirmed episodes. The objective of the study was to estimate the incidence, clinical presentation and severity of childhood AOM in clinical practice in five European countries with different healthcare systems.

METHODS

This was a large, multi-country, multi-centre, epidemiological, observational cohort study which utilized retrospective review of medical charts in addition to prospective follow-up data collection through both physician and parental reports to collect information on incidence, complications and symptoms of AOM. Data on clinical management, health economics, and quality of life, which were also collected during the study, are presented elsewhere [22, 23]. The study took place in Germany, Italy, Spain, Sweden, and the UK. The target enrolment was 1250 subjects per country, with no signs or symptoms of AOM or other upper respiratory tract infections at the time of enrolment, for whom medical records covering the previous year (or since birth, if aged <1 year) were available at the investigational site and who were expected to be available for 12 months of follow-up. All sites made attempts to balance enrolment between the 0–2 and 3–5 years age groups in order to achieve about the same number of children in each group.

Children were enrolled from July 2008 to January 2009 at 26 paediatric practices in Germany, 21 family paediatric practices in Italy, 12 paediatric practices in Spain, and at ten general practices in the UK. In all countries except Sweden, the majority of children were enrolled during a visit to the investigators’ practices; however, investigators could also recruit patients through mailings or phone calls. In Sweden, children were recruited through about 7000 mailings based on the computerized population registers. Primary care for children is mostly provided by paediatricians in Germany, Italy, and Spain. In the UK and Sweden sick children are usually taken to general practitioners. Depending on the nature of the health condition and its severity, these primary-care physicians may then refer their patients to specialists for secondary or tertiary care. Informed consent was obtained prior to performance of any study-specific procedures. A total of 5882 children were enrolled at 73 medical practices, resulting in a cohort of 5776 children for the retrospective period of the study, following exclusion of 106 children who did not meet the inclusion criteria. The 106 exclusions were due to five children outside the study age group, 27 without medical records available, two for whom consent was not provided, one not available for 12 months of follow-up, 28 who had AOM at enrolment, and 47 who had signs of an upper respiratory infection. Four children had two reasons for exclusion. After exclusion of 12 more children due to lack of follow-up contact information, a total of 5764 children were followed-up prospectively.

Information on basic demographics, medical history, and pneumococcal vaccination history was collected. Data on Hib vaccination, which was introduced in Europe in the early 1990s, was not collected; however, available vaccination rates suggest that Hib immunization coverage in 1-year-olds was >93% in all five countries in 2011 [24]. Data on the frequency of suspected, probable and confirmed AOM, severity and complications of any AOM episodes, and AOM
symptoms were collected through retrospective review of medical charts and prospective follow-up using physician and parental reports. For the retrospective period of the study, the chart was examined for AOM-related visits in the year prior to enrolment (encompassed time period from 2007 to 2008) for children aged ≥1 year old at enrolment. For children aged <1 year at enrolment, all available medical history in the medical chart for was reviewed by the investigator. For the prospective period of the study, enrolled children were followed-up prospectively for 1 year (encompassed time period from 2008 to 2010) to collect data on all AOM episodes.

Data for the prospective study period were collected at visits for AOM at the investigator’s practice or through any available case report giving details of the AOM symptoms, AOM-related medical procedures/therapy and concomitant medication if the visit was to another medical practice or emergency department. Parents were contacted every 2 months and asked about any respiratory/AOM-related symptoms lasting more than 48 h (even if no medical care was sought) and about visits to the emergency department or other healthcare providers.

Every month local investigators in participating practices logged the total number of AOM-related visits and total number of visits for any children within the 0–2 and 3–5 years age groups. In Sweden these data were obtained through the computerized registers. Data on AOM-related and total number of visits were used to compare incidence rates in the study population to the overall incidence in the total population at participating centres.

Definitions

A suspected episode was defined as any AOM-related symptom reported only by the parents including ear pain or discharge or tugging plus one of the following: fever, runny nose, sore throat, cold-like symptoms, conjunctivitis, decreased appetite, vomiting, diarrhoea, trouble sleeping, irritability or apathy. A probable episode was defined as an AOM episode diagnosed by a physician and documented in the medical chart, regardless of any documentation of symptoms. A confirmed episode was defined as a probable case in addition to a visual appearance of the tympanic membrane, i.e. redness, bulging, loss of light reflex, the presence of acute middle-ear effusion (as shown by otoscopy or tympanometry), and the presence of at least two of the following symptoms: ear pain, ear discharge, hearing loss, lethargy, irritability, anorexia, vomiting, diarrhoea, or fever (≥38·0 °C, rectal temperature ≥38·5 °C). Alternatively, during the prospective study, a confirmed episode could be a probable episode supported by a positive bacterial culture of the middle ear fluid (after spontaneous perforation or tympanocentesis), if this procedure was routinely undertaken by the treating physician.

A new episode of AOM was defined as an AOM episode after a 30-day symptom-free interval since the resolution of the previous AOM episode. Complicated AOM was defined as medically documented AOM associated with mastoiditis, labyrinthitis, Bell’s palsy, petroitis, meningitis, epidural abscesses, sepsis, cerebral vein thrombosis or any other medically documented complication with a timely and causal relationship to AOM.

Statistical analysis

The formula used to calculate the AOM episode incidence rate (number of episodes/1000 subject-years) was the following:

\[
\text{Incidence AOM episodes} = \frac{\sum_{i=1}^{n} \epsilon_i}{\sum_{i=1}^{n} \delta_i} \times 1000 \times 365,
\]

where \( n \) is the total number subjects in the cohort under study or in a subgroup of this cohort (e.g. age group strictly <3 years), \( \epsilon_i \) is the number of AOM episodes for subject \( i \), and \( \delta_i \) is the number of days of the surveillance period for subject \( i \). For the prospective study, the surveillance period of one subject was defined as the duration from the enrolment until the last follow-up contact for this subject or until the subject was aged 6 years: end date – start date +1. For calculation of incidence by age group, \( \epsilon_i \) and \( \delta_i \) were computed over the period starting from enrolment or entry date in the given age group (e.g. third birthday for the 3–5 years age group) until the last follow-up or leaving date from the given age group (e.g. third birthday for the 0–2 years age group, and sixth birthday for the 3–5 years age group). The exact Poisson confidence limit method was used to calculate confidence intervals [25]. The categories of confirmed, probable, and suspected AOM episodes were considered as mutually exclusive in the analysis. All statistical analyses were performed using SAS, version 9.1 or later (SAS Institute Inc., USA), and Microsoft Excel (2002 SP3 or later), for graphical purposes.
The study protocol was reviewed and approved by both local and national ethics committees.

RESULTS

The mean age of the 5764 children at enrolment was 31·5 months (S.D.=20·8), and 48·7% (n = 2806) were female (Table 1). At the beginning of the prospective study, 58·2% (n = 3357) of children reported having received at least one dose of the 7-valent pneumococcal conjugate vaccine (PCV7; Prevnar™/Prevenar™, Pfizer Inc., USA), ranging from 23·3% in Sweden to 49·1% in Italy, 67·2% in Germany, 74·5% in the UK, and 84·0% in Spain. PCV7 vaccination status was unknown for 355 children, mainly based in Sweden and Italy.

Retrospective study period

Frequency and incidence of AOM

Based on the retrospective period of the study, 18% (1038/5764) of children experienced 1376 AOM episodes in the previous year. The proportion of medically diagnosed episodes that were confirmed episodes was lowest in Italy (12·1%, 24/198) and the UK (12·3%, 19/154), and highest in Sweden (23·3%, 74/309) (Table 2a). Of children who experienced at least one AOM episode, 22·8% (237/1038) had more than one episode, 6·7% (70/1038) had more than two episodes, and 2% (21/1038) had more than three episodes (Fig. 1). The percentage of children who experienced only one episode varied by country from 69·4% (188/271) in Spain to 86·1% (142/165) in Italy. The overall incidence rate of AOM based on the retrospective study was 268/1000 person-years [95% confidence interval (CI) 254–283], and was lowest in Italy (176, 95% CI 153–203) and highest in Spain (387, 95% CI 350–427) (Fig. 2).
Five of the seven complications were in the 0–2 years age group and two were in the 3–5 years age group. Spontaneous perforation of the tympanic membrane was recorded for 4.3% (59/1376) of episodes, ranging from <2% in Germany, Italy, and the UK to 3.7% in Spain and 12.1% in Sweden.
Spontaneous perforation was reported for a similar proportion of episodes in children in both age ranges.

**Prospective study period**

*Frequency and incidence of AOM*

A total of 1419 AOM episodes, as diagnosed by physician, were experienced by 1113 children during the prospective study. Overall, 34.9% (495/1419) of these medically diagnosed episodes of AOM were classified as confirmed, ranging from 18.3% (33/180) in the UK to 44% (142/323) in Germany, and 65.1% (924/1419) as probable, ranging from 56% (181/323) in Germany to 81.7% (147/180) in the UK (Table 2b). Of children who experienced at least one AOM episode, 20.3% (226/1113) had more than one, 5.5% (61/1113) had more than two, and 1% (11/1113) had more than three (Fig. 1). The percentage of children who experienced only one episode varied by country, from 72.8% (198/272) in Spain to 85.3% (168/197) in Italy.

The overall incidence rate of AOM episodes as diagnosed by a physician during the prospective study was 256/1000 person-years (95% CI 243–270). The incidence rate was lowest in Italy (195, 95% CI 171–222) and highest in Spain (328, 95% CI 296–363) (Fig. 2). The incidence rate was higher in the 0–2 years age group (299, 95% CI 279–320) than in the 3–5 years age group (212, 95% CI 195–230) (Table 3). In Italy incidence rates were very similar between the age groups. The incidence rate of confirmed AOM was 90 (95% CI 82–98), and the incidence rate of probable AOM was 167 (95% CI 156–178).

The number of children under surveillance for prospective visits was relatively stable from November 2008 to August 2009 (ranging from 5026 to 4381, respectively). Over this time period the monthly number of AOM visits was higher during the winter period, with the highest number of AOM visits in December 2008, when there were 240 AOM visits among the 5182 children under surveillance (4.6%), and the lowest number of visits during August of 2009, when there...
were 25 AOM visits among the 4381 children under surveillance (0.6%).

**Signs, symptoms and complications of AOM during the prospective study**

Overall, 98.9% (1403/1418) of episodes were associated with at least one sign or symptom in the prospective study (data missing for one child). The most frequently experienced symptoms were ear pain, reported for 68.3% (968) of episodes, followed by redness of the tympanic membrane, reported for 67.3% (955) of episodes. The proportion of children with ear pain was higher in those aged 3–5 years than in those aged 0–2 years (84.3% vs. 57.2%). Ear discharge was reported in 16.9% (n=240) of episodes, ranging from 12.1% in Italy and 12.7% in Germany to 17.3% in the UK, 17.4% in Spain and 24.5% in Sweden. Four complications were reported for the 1419 episodes. There were no reports of sepsis, mastoiditis, labyrinthitis, Bell’s palsy, petrositis, meningitis, epidural abscess or cerebral vein thrombosis.

Three of the complications occurred in children in the 0–2 years group. Spontaneous perforation of the tympanic membrane was reported for 7.1% (101/1419) of episodes, ranging from 2.1% of episodes in Italy and 2.2% in the UK, to 4.8% in Spain, 6.8% in Germany and 17.2% in Sweden.

**Parent-reported episodes**

Over the prospective study period, 600 suspected new episodes of AOM were reported by parents (Table 2b). The overall incidence of suspected episodes was 110/1000 person-years (95% CI 102–120), and varied widely from 42 (95% CI 31–55) in Spain and 50 (95% CI 38–64) in Italy, to 135 (95% CI 115–158) in Sweden, 161 (95% CI 139–185) in Germany, and 190 (95% CI 160–223) in the UK.

**DISCUSSION**

The results of this multi-centre cohort study confirm the relatively high burden of AOM during childhood in five European countries. The incidence of AOM varied between countries, with the lowest incidence based on both the retrospective and prospective study periods occurring in Italy, and the highest in Spain. Overall, the incidence of AOM was slightly higher in younger children (aged 0–2 years), than in older children (aged 3–5 years). The incidence in our study based on the prospective period of 256/1000 person-years (95% CI 243–270) is noticeably lower than the AOM incidence reported in the USA and Finland [21, 26], but is within the same range of recent estimates of AOM incidence in children in Europe, which ranged from 154 (95% CI 152–158) to 400 (95% CI 397–403) [27, 28]. There were very few complications in children with AOM. Spontaneous perforations of the tympanic membrane were common.

The majority of physician-diagnosed AOM in this study met the criteria for probable rather than confirmed AOM. This indicates that most of the burden of medically attended AOM might be captured by records of AOM diagnosis in medical charts. Because parents may have used pain-relieving medications to treat fever before the AOM visit, the recorded level of fever was probably underestimated, which may have resulted in an underestimate of the overall occurrence of confirmed episodes. Symptoms were associated with most AOM episodes. Ear pain was the most frequently reported symptom and redness of the tympanic membrane was the sign most often
seen. The frequency of symptoms also varied between the retrospective and prospective study periods and was higher during the prospective study (98.9% vs. 87.6%), indicating that prospective data collection may be necessary to fully capture the signs and symptoms associated with AOM episodes. Variations in symptoms recorded in medical charts by country suggest documentation differences by country and indicate that some medical files may be incomplete.

The large size and prospective design of this study along with the well-defined criteria for confirmed and probable AOM allow for a clearer understanding of the burden of AOM in these five European countries and of the best way to collect information on AOM in order to avoid potential underestimation and bias. The use of a standardized protocol in each of the five countries also facilitates comparisons between countries, which is often difficult to do with published studies due to variations in study design, age groups, and data collection methods. The approach of using varied sources of data, from historical medical charts to prospective follow-up based on both physician and parental reports, allowed us to collect data on all cases and episodes of possible AOM (suspected, probable, confirmed), with a holistic view to capture the entire burden of disease, considering under-reporting of undiagnosed episodes. A more specific approach, as is often taken in studies of AOM, which focuses only on clinically confirmed AOM, is likely to miss mild cases and episodes for which medical care is not sought. The approach of multiple data sources provides a broader public health perspective. The incidence of AOM based on the retrospective study was very similar to the incidence based on the prospective study (268 vs. 256), suggesting that in this setting, using data based on cases documented in medical charts may not lead to any major problems of underestimation vs. prospective follow-up data based on physician reports. The incidence of suspected cases of AOM based on parental reports suggests that there may be an additional 110 AOM episodes per 1000 person-years which are missed when focusing only on medical attendance data. These potentially missed events may represent less severe cases for which medical care is not sought, and are an important consideration when attempting to estimate the total incidence of AOM.

The difference in AOM incidence in this study compared to the incidence previously reported in the USA and Finland may be explained by the fact that studies from those countries were partially conducted in a clinical trial setting where patients represent a selected group of the population followed more stringently than in our study. The differences in AOM incidence between the countries in our study may represent a combination of true differences and differences in healthcare systems, social structure, and diagnostic procedures between physicians. The range of parent-reported incidence, which was lowest in Spain and highest in the UK, may be useful in assessing the overall burden of AOM and understanding true differences in incidence, as it may reflect a combination of the variable tendencies of parents to adhere to ‘wait and watch’ recommendations and to consult a physician during a child’s illness [29]. For example, the incidence of confirmed AOM in the UK was lower than in other countries, while the incidence of parent-reported AOM was higher, which may suggest parents are adhering to ‘wait and watch’ recommendations. In Spain, which had the highest incidence of physician-diagnosed AOM and lowest incidence of parent-reported AOM, parents may have more access to their paediatrician due to the structure of the healthcare system and, therefore, may be more likely to bring their child in for suspected AOM. These findings are supported by a previous study which reported that parents in Spain were more likely to consult a physician during a child’s illness compared to parents in the UK [29]. It is important to note that it is possible that not all of the parent-reported suspected episodes of AOM were truly episodes of AOM. While parent-reported AOM data have been shown to accurately reflect medical records [30], it does not necessarily mean that all suspected cases would meet the criteria for probable or confirmed AOM if the child were to be examined by a physician. However, the incidence of suspected cases still provides a valuable estimate of the burden of disease which may be missed when focusing solely on physician-diagnosed AOM.

Differences in healthcare-seeking behaviour by country may also explain some variation in frequency of spontaneous perforation of the tympanic membrane and ear discharge by country. For example, in parts of Sweden access to physicians is geographically limited, and there is a policy in place not to admit patients during the night for earache unless the child is aged <1 year or is septic. A delay in treatment due to either of these country-specific factors could contribute to the higher frequency of spontaneous perforation and ear discharge seen in Sweden in this study. It is also possible that there are ecological differences in bacterial colonization by country. For
example, the later introduction of PCV7 vaccination in Sweden may be associated with more aggressive pneumococcal strains than are seen in other countries where the vaccine was introduced earlier. A limitation of the data on spontaneous perforation of the tympanic membrane is the potential misclassification which may have occurred. As spontaneous perforation of the tympanic membrane is accompanied by ear discharge, and therefore ear discharge is often considered an indication of perforation, it is possible that there were investigator-specific differences in data recording surrounding ear discharge and perforation. As ear discharge was noted more frequently than spontaneous perforation, perforation may be underestimated in the study. Based on the available data, it is not possible to know if these differences in recording practices were variable by country. Differences in healthcare system-related characteristics and healthcare-seeking behaviour which may impact documentation, consulting and diagnostic behaviour between countries are an unavoidable limitation for this study which should be considered in interpreting results. Another limitation of this study is that the study population may have differed from the general population because of the recruitment approach. Recruited children could have been healthier due to attending regularly scheduled visits, or alternatively, they could have been more ill and therefore more likely to go to the doctor, increasing the chances of being enrolled. However, that was not the case for Sweden, where mailing was used, and AOM incidence in Sweden was consistent with other countries. Moreover, despite efforts to document all available information regarding visits to other medical facilities for AOM during follow-up, it is possible that some visits were not included and that this resulted in an underestimate of the incidence of AOM. However, parent-reported AOM episodes should not be affected by this bias, since parents were instructed to report all AOM episodes.

In conclusion, this study demonstrates the importance of a public health perspective, by capturing and reporting all suspected, probable, and confirmed episodes using different sources including medical charts, follow-up, and parental reports, to better understand the public health burden of AOM. Differences in incidence of spontaneous perforation of the tympanic membrane by country should be examined in parallel with data on ear discharge, and may represent a combination of true differences and variability in healthcare-seeking behaviour and in diagnostic procedures by country. Although it is often believed that retrospective reviews of medical charts are associated with underestimation of the burden of AOM, the comparability of incidence results based on chart review vs. those based on data collected through follow-up visits suggests that a thoroughly performed chart review can deliver reliable AOM incidence results. As the burden of disease is high within Europe, there is a case for promoting preventative strategies for AOM such as immunization.

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