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

J. G. LIESE1*, S. A. SILFVERDAL2, C. GIAQUINTO3, A. CARMONA4, J. H. LARCOMBE5, J. GARCIA-SICILIA6, A. FUAT7, M. GARCES-SANCHEZ8, M. L. ARROBA BASANTA9, E. MUÑOZ HIRALDO10, L. CANTARUTTI11, W. KROENIGER12, J. VOLLMAR12, K. HOLL13, J. Y. PIRÇON13 and M. R. ROSENLUND13,14

1Department of Paediatric Infectious Diseases and Immunology, University Children’s Hospital, Würzburg, Germany; 2Department of Clinical Sciences, Pediatrics, Umeå University, Umeå, Sweden; 3Department of Paediatrics, University of Padova, Italy and PEDIANET Project; 4Instituto Hispalense de Pediatría, Sevilla, Spain; 5Harbinson House Surgery, Sedgefield, County Durham, and Centre for Integrated Health Care Research, University of Durham, UK; 6Hospital Materno-Infantil La Paz, Madrid, Spain; 7Durham University, County Durham and Carmel Medical Practice, County Durham, UK; 8Department of Paediatrics, Nazaret Health Center, Valencia, Spain; 9CS Pozuelo Universidad Autónoma de Madrid, Madrid, Spain; 10Department of Pediatrics, Health Centre Dr Castroviejo, Madrid, Spain; 11Family Paediatrician ‘Pediomet Project’, Padova, Italy; 12GlaxoSmithKline Vaccines, Munich, Germany; 13GlaxoSmithKline Vaccines, Wavre, Belgium; 14Centre for Pharmacoepidemiology, Unit for Clinical Epidemiology, Department of Medicine, Karolinska Institutet, Sweden

Received 11 February 2013; Final revision 29 August 2013; Accepted 4 October 2013; first published online 13 December 2013

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-typable 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...
can be safely used in most AOM cases [9–11]. A recent study from The Netherlands found 50% of patients have recurrences of AOM [12]. Data from clinical practice in the UK have shown that 15% of children with AOM present with ear discharge [13], while severe infections, such as mastoiditis, are infrequent (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, petrositis, 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:

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

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), \( e_i \) 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, \( e_i \) 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.
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).

Signs, symptoms and complications of AOM

At least one sign or symptom was documented in the medical chart during at least one visit for 87·6% (1205/1376) of episodes. The most common sign or symptom was redness of the tympanic membrane, reported for 52·8% (727/1376) of episodes, and ear pain, reported for 48·4% (666/1376) of episodes. Ear discharge was reported for 14·4% (198/1376) of episodes and varied by country from 2·6% in Germany to 9·1% in Italy, 15·2% in Spain, 18·2% in the UK, and 26·5% in Sweden. No differences were observed in documented symptoms of AOM by age group. Complications occurred in <1% of episodes (7/1376): sepsis (n=1), hospitalization due to unknown reason (n=1), dehydration (n=1), otitis media with effusion (n=2) and unspecified (n=2).

Table 1. Demographic characteristics at enrolment of children aged 0–5 years in five European countries

| Characteristic          | Germany (N=1258) | Italy (N=1267) | Spain (N=1189) | Sweden (N=1243) | UK (N=807) | Total (N=5764) |
|-------------------------|------------------|---------------|---------------|----------------|-----------|---------------|
| Age (months), mean±S.D. | 32·0±20·8        | 31·5±21·0     | 31·2±21·0     | 33·5±19·7      | 28·1±21·4 | 31·5±20·8     |
| 0–2 years age group, n (%) | 652 (51·8)      | 695 (54·8)    | 641 (53·9)    | 701 (56·4)     | 489 (60·6) | 3178 (55·1)  |
| 3–5 years age group, n (%) | 606 (48·2)      | 572 (45·2)    | 548 (46·1)    | 542 (43·6)     | 318 (39·4) | 2586 (44·9)  |
| Gender, n (%)           |                  |               |               |                |           |               |
| Female                  | 632 (50·2)       | 615 (48·5)    | 554 (46·6)    | 609 (49·0)     | 396 (49·1) | 2806 (48·7)  |
| Male                    | 626 (49·8)       | 652 (51·5)    | 635 (53·4)    | 634 (50·1)     | 411 (50·9) | 2958 (51·3)  |

Data presented here are for the children included in both the retrospective and prospective periods of the study, and do not include the 12 children who participated only in the retrospective study.

Table 2a. Number of confirmed and probable acute otitis media episodes in children aged 0–5 years in five European countries as diagnosed by a physician and documented in the medical chart during the 12-month (2007–2008) retrospective study period

|          | Confirmed | Probable | Total medically diagnosed |
|----------|-----------|----------|--------------------------|
| Germany  | 74 (23·9%)| 235 (76·1%)| 309                      |
| Italy    | 24 (12·1%)| 174 (87·9%)| 198                      |
| Spain    | 86 (21·4%)| 316 (78·6%)| 402                      |
| Sweden   | 73 (23·3%)| 240 (76·7%)| 313                      |
| UK       | 19 (12·3%)| 135 (87·7%)| 154                      |
| Total    | 276 (20·1%)| 1100 (79·9%)| 1376                   |

The study protocol was reviewed and approved by both local and national ethics committees.
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.

Table 2b. Number of confirmed, probable and suspected acute otitis media episodes in children aged 0–5 years in five European countries as diagnosed by a physician or reported by the parents during the 12-month (2008–2010) prospective study period

|               | Confirmed | Probable | Total medically diagnosed | Suspected (parent-reported) |
|---------------|-----------|----------|---------------------------|----------------------------|
| Germany       | 142 (44.0%) | 181 (56.0%) | 323                       | 193                        |
| Italy         | 101 (42.1%) | 139 (57.9%) | 240                       | 59                         |
| Spain         | 106 (28.3%) | 268 (71.7%) | 374                       | 47                         |
| Sweden        | 113 (37.4%) | 189 (62.6%) | 302                       | 156                        |
| UK            | 33 (18.3%)  | 147 (81.7%) | 180                       | 145                        |
| Total         | 495 (34.9%) | 924 (65.1%) | 1419                      | 600                        |

Twelve children included in the retrospective period of the study (Table 2a) did not have follow-up information available and are therefore not included in the prospective study (Table 2b).

Fig. 1. Percentage of children aged 0–5 years in five European countries with 1, 2, 3, or ≥4 acute otitis media (AOM) episodes as diagnosed by a physician during (a) the 12-month (2007–2008) retrospective study period, and (b) the 12-month (2008–2010) prospective study period in children aged 0–5 years in five European countries.
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

| Country | 0–2 years | Incidence (95% CI) | 3–5 years | Incidence (95% CI) |
|---------|-----------|--------------------|-----------|--------------------|
| Germany | 182       | 311 (267–359)      | 134       | 218 (183–258)      |
| Italy   | 119       | 193 (160–232)      | 113       | 197 (162–237)      |
| Spain   | 223       | 392 (342–447)      | 148       | 263 (223–309)      |
| Sweden  | 204       | 344 (298–394)      | 98        | 174 (141–212)      |
| UK      | 108       | 247 (203–298)      | 66        | 202 (156–257)      |
| Total   | 836       | 299 (279–320)      | 559       | 212 (195–230)      |

CI, Confidence interval.

Table 3. Incidence of acute otitis media (per 1000 person-years) as diagnosed by a physician during the 12-month prospective study period (2008–2010) in children aged 0–5 years in five European countries
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 underreported 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.

ACKNOWLEDGEMENTS

The authors thank Dr Franziska Feldl (GlaxoSmithKline), Dr Andrea Streng (University Children’s Hospital Würzburg), Dr Peter Helm (Scottish Medicines for Children Network), Pilar García Corbeira (GlaxoSmithKline), Juan A. García Martínez (GlaxoSmithKline), Saúl Robles (GlaxoSmithKline), Dr Manuel Martínez Pons – C.S. República Argentina (Valencia, Spain), Dr Mª Luisa Arroba – C.S. Pozuelo-Estación (Madrid, Spain), Dr Fuente, Dr Acosta, Dr García Bernabeu, Dr Amil, Dr Tellez, Dr Peralta, Dr Casani, Dr Vazquez, Dr Riquelme, Dr Rivas, Dr Muñoz, Dr Alvarez de Laviada Mulero (Valencia, Spain), Dr García López (Valencia, Spain), Dr Peris Vidal (Valencia, Spain), Dr Liras, Dr Cantarutti and Dr Tichmann for their contributions throughout the study. They also thank Dr Anna Dow (independent medical writer c/o GlaxoSmithKline Vaccines) for scientific writing support and Dr Barbara Pelgrims and Dr Véronique Mouton (XPE Pharma & Science, c/o GlaxoSmithKline Vaccines) for editorial assistance and manuscript coordination.

GlaxoSmithKline Biologicals SA funded all costs associated with the development and the publishing of this paper. All authors contributed to the study, were involved in writing and reviewing the paper and approved the final version. All authors had full access to the data and the corresponding author had final responsibility for submission of the manuscript.

DECLARATION OF INTEREST

J.L. received fees for participating in review activities from GlaxoSmithKline group of companies. He received institutional grants from GlaxoSmithKline group of companies for epidemiological studies on varicella/herpes zoster and influenza. He received payment for participating in advisory board from GlaxoSmithKline group of companies, Novartis,
Sanofi Pasteur MSD and AstraZeneca. He received payment for consultancy from GlaxoSmithKline group of companies and AstraZeneca. He received lectures fees from GlaxoSmithKline group of companies, Sanofi Pasteur MSD, AstraZeneca, Abbott and Pfizer. He received travel grant support for participation in congresses on infectious diseases from GlaxoSmithKline group of companies, Sanofi Pasteur, Pfizer and CSL Behring. S.A.S. received institutional grant from GlaxoSmithKline group of companies for travel to attend scientific meeting. He received payment from GlaxoSmithKline group of companies for giving a lecture on pneumococcal disease. He received payment from GlaxoSmithKline group of companies and AstraZeneca for participation in advisory boards. C.G. received payment from GlaxoSmithKline group of companies for consultancy, for given lectures and for participating in advisory board. He also received institutional grants from GlaxoSmithKline group of companies. J.H.L. received institutional payment from the National Institute for Health Research (NIHR) to support costs related to recruitment of subjects and data collection. J.G.S. received institutional grant from GlaxoSmithKline group of companies. M.G.S. received payment from GlaxoSmithKline group of companies for expert testimony and for participating in advisory boards. She received payment from GlaxoSmithKline group of companies and Sanofi Pasteur MSD for giving lectures and for development of educational presentations. M.L.A. received payment and institutional grants from GlaxoSmithKline group of companies. She received travel grant from GlaxoSmithKline group of companies for participation as a speaker at 60th Congress of the Spanish Association of Paediatrics, Valladolid, 16–18 June 2011. W.K. is employed by GlaxoSmithKline group of companies and has stock options. J.V. is employed by GlaxoSmithKline group of companies and has stock options. K.H. is employed by GlaxoSmithKline group of companies. J.Y.P. is employed by GlaxoSmithKline group of companies. M.R.R. was employed by GlaxoSmithKline group of companies at the time the study was conducted. He had stock options and now has shares from GlaxoSmithKline group of companies.

REFERENCES

1. Klein JO. Otitis media. Clinical Infectious Diseases 1994; 19: 823–833.

2. Casey JR, Pichichero ME. Changes in frequency and pathogens causing acute otitis media in 1995–2003. Pediatric Infectious Disease Journal 2004; 23: 824–828.

3. Leibovitz E, Jacobs MR, Dagan R. Haemophilus influenzae: a significant pathogen in acute otitis media. Pediatric Infectious Disease Journal 2004; 23: 1142–1152.

4. Sierra A, et al. Non-typeable Haemophilus influenzae and Streptococcus pneumoniae as primary causes of acute otitis media in colombian children: a prospective study. BMC Infectious Diseases 2011; 11: 4.

5. Cáceres Udina MJ, et al. Incidence, air pollution and risk factors of acute otitis media in the first year of life: a prospective study [in Spanish]. Anales de Pediatría 2004; 60: 133–138.

6. Cohen R, Levy C, Boucherat M. Epidemiologic survey of acute otitis media in urban pediatric practices [in French]. Médecine et Enfance 1996; 6: 27–31.

7. McGaig LF, Hughes JM. Trends in antimicrobial drug prescribing among office-based physicians in the United States. Journal of the American Medical Association 1995; 273: 214–219.

8. Riquelme Pérez M, et al. Acute otitis media in a pediatric primary care unit [in Spanish]. Anales de Pediatría 2004; 61: 408–412.

9. McCormick DP, et al. Nonsevere acute otitis media: a clinical trial comparing outcomes of watchful waiting versus immediate antibiotic treatment. Pediatrics 2005; 115: 1455–1465.

10. Grevers G. Challenges in reducing the burden of otitis media disease: an ENT perspective on improving management and prospects for prevention. International Journal of Pediatric Otorhinolaryngology 2010; 74: 572–577.

11. Venekamp RP, et al. Antibiotics for acute otitis media in children. Cochrane Database of Systematic Reviews 2013; 1: CD000219.

12. Damoiseaux RA, et al. Long-term prognosis of acute otitis media in infancy: determinants of recurrent acute otitis media and persistent middle ear effusion. Family Practice 2006; 23: 40–45.

13. Smith L, et al. Ear discharge in children presenting with acute otitis media: observational study from UK general practice. British Journal of General Practice 2010; 60: 101–105.

14. Thompson PL, et al. Effect of antibiotics for otitis media on mastoiditis in children: a retrospective cohort study using the United Kingdom general practice research database. Pediatrics 2009; 123: 424–430.

15. García-Sánchez M, et al. Epidemiology and burden of acute otitis media in Valencia (Spain) [in Spanish]. Anales de Pediatría 2004; 60: 125–32.

16. Melegaro A, et al. The current burden of pneumococcal disease in England and Wales. Journal of Infection 2006; 52: 37–48.

17. Ziebold C, et al. Epidemiology of pneumococcal disease in children in Germany. Acta Paediatrica (Suppl.) 2000; 89: 17–21.

18. Schnabel E, et al. Burden of otitis media and pneumonia in children up to 6 years of age: results of the LISA
19. Joki-Erkkilä VP, Laippala P, Pukander J. Increase in paediatric acute otitis media diagnosed by primary care in two Finnish municipalities – 1978–9. *Epidemiology and Infection* 1998; 121: 529–534.

20. Labout JA, et al. Risk factors for otitis media in children with special emphasis on the role of colonization with bacterial airway pathogens: the Generation R study. *European Journal of Epidemiology* 2010; 26: 61–6.

21. Eskola J, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. *New England Journal of Medicine* 2001; 344: 403–409.

22. Liese J, et al. The effect of paediatric acute otitis media in children on parents’ quality of life: development and validation of a questionnaire implemented in a prospective observational cohort study in Europe. *International Society for Pharmacoeconomics and Outcomes Research, 14th Annual European Congress* 2011; 14 (A233–AS10): A509.

23. Liese J, et al. The clinical and economic burden of acute otitis media: a large prospective observational cohort study in Europe. *International Society for Pharmacoeconomics and Outcomes Research, 14th Annual European Congress* 2011; 14 (A233–AS10): A508–509.

24. World Health Organization. Statistics by countries (http://www.who.int). Accessed 16 July 2013.

25. Ulm K. A simple method to calculate the confidence interval of a standardized mortality ratio (SMR). *American Journal of Epidemiology* 1990; 131: 373–375.

26. Fireman B, et al. Impact of the pneumococcal conjugate vaccine on otitis media. *Pediatric Infectious Disease Journal* 2003; 22: 10–16.

27. François M. The incidence of acute otitis media in France in children aged 0-6 years [in French]. Réunion Interdisciplinaire de Chimiothérapie Anti-infectieuse, Paris, France, 4–5 December 2008 (Abstract 382).

28. Garcés-Sánchez MD, et al. Epidemiology of community-acquired pneumonia in children aged less than 5 years old in the Autonomous Community of Valencia (Spain) [in Spanish]. *Anales de Pediatría* 2005; 63: 125–130.

29. Wolleswinkel-van den Bosch JH, et al. The health care burden and societal impact of acute otitis media in seven European countries: results of an Internet survey. *Vaccine* 2010; 28 (Suppl. 6): G39–52.

30. Vernacchio L, et al. Validity of parental reporting of recent episodes of acute otitis media: a Sloan Center Office-Based Research (SCOR) Network study. *Journal of the American Board of Family Medicine* 2007; 20: 160–163.