DOI:10.1046/j.1365-2125.2003.02019.x

Acute otitis media in children: a retrospective analysis of physician prescribing patterns

Caroline Quach,[1,2] Jean-Paul Collet[3] & Jacques LeLorier[1]

[1]*Pharmacoepidemiology Unit, Research Institute, CHUM, Campus Hôtel-Dieu, University of Montreal, Montreal (QC), Canada,* [2]*Infectious Disease Division, Department of Pediatrics and Department of Medical Microbiology, McGill University Health Center, Montreal Children's Hospital, Montreal (QC), Canada, and* [3]*Department of Epidemiology and Biostatistics, McGill University, Montreal (QC), Canada*

Correspondence
Dr Jacques LeLorier,
Pharmacoepidemiology Unit Research Institute, CHUM, Campus Hôtel-Dieu, 3840, St-Urbain, Montreal (Qc) H2W 1T7, Canada.
Tel: + 1 514 890 8000, ext. 14080
Fax: + 1 514 412 7174
E-mail:
massicoa@courrier.umontreal.ca

Keywords
acute otitis media, antibiotic, drug utilization review, Régie de l'assurance maladie du Québec (RAMQ)

Received
11 May 2003
Accepted
1 October 2003

Background
Acute otitis media (AOM) is one of the most common infectious diseases of childhood and the most frequent indication for antibiotic use in children.

Aim
To better understand the prescribing patterns and appropriateness of AOM therapy.

Methods
We investigated a historical cohort of children aged ≤6 years who had a first AOM episode between June 1999 and June 2002, using the Régie de l'assurance maladie du Quebec (RAMQ) administrative databases. Conformity of prescription was based on the consensus guidelines on AOM treatment from the Drug-resistant *Streptococcus pneumoniae* Therapeutic Working Group. These recommendations suggested amoxicillin as the first-line drug, and amoxicillin-clavulanic acid or cefuroxime for children who had received antibiotics in the previous month. Data were analysed using descriptive statistics, χ^2 test and logistic regression.

Results
During the study period, 60 513 children ≤6 years of age experienced their first AOM episode with a mean age of 2.6 years. They were seen by 4708 physicians [87% general practitioners (GPs), 9% paediatricians, and 3% ENT specialists]. Amoxicillin was the antibiotic that was prescribed the most (43%), followed by cefprozil and azithromycin. Overall, 42% of physicians adhered to antibiotic guideline recommendations. Compared with GPs, paediatricians were almost as likely to prescribe in conformity with the consensus guidelines, whereas ENT specialists were 50% less likely to prescribe an antibiotic recommended by the guidelines.

Conclusion
Continuing medical education is necessary to ensure appropriate adherence to antibiotic guidelines.

Introduction

Antimicrobial resistance is increasing worldwide. Previous studies have shown a correlation between the total use of antibiotics at a local level and the prevalence of resistant respiratory tract pathogens [1–3]. In Sweden, a national initiative that targeted inappropriate antibiotic prescription in children with respiratory tract infection succeeded in stopping the progression of resistance among *Streptococcus pneumoniae* [4], a major cause of pneumonia, bacteraemia, meningitis, and otitis media in children (AOM) [5].

AOM, shown to be a frequent reason for consulting a

physician, is one of the most common infectious diseases of childhood [6, 7]. It is also the most common indication for antibiotic use in children [6, 7]. In a single year, 46.8% of children aged 13–24 months will be diagnosed to have AOM compared with 35.4% aged 25–36 months and 9.6% aged 7–13 years [8]. In the USA, AOM accounts for more than 20 million physician visits per year, with an average of 2.9 physician office visits per child [9]. Moreover, the US Food and Drug Administration reported an increase in the use of broader spectrum and more expensive antimicrobial agents between the years 1980 and 1992 [10]. The cost of such antibiotic prescribing to the health systems has been estimated to be between $US 3 and 4 billions per year [11, 12]. Nearly half of this expenditure is incurred in the treatment of children under 3 years of age. The per capita cost of AOM treatment in children aged between 1 and 3 years has been estimated to be $US 453 in 1992, due mainly to physician visits [13].

Although most AOM cases will resolve spontaneously, it is not possible to determine *a priori* which AOM will result in suppurative complications. The Canadian Pediatric Society [14], in a position statement issued in April 2002, suggested considering all AOM cases as candidates for antibiotics. Watchful waiting for 48–72 h before initiating antibiotics was considered as 'feasible in children over 2 years of age if good follow-up could be assured', and decision should be made on a patient-by-patient basis. Numerous antibiotics are available for AOM treatment. However, the Drug-resistant *Streptococcus pneumoniae* Therapeutic Working Group as well as the Canadian Pediatric Society recommended amoxicillin as the first-line drug, with amoxicillin-clavulanic acid or cefuroxime for children who had received antibiotics in the previous month [14, 15]. To understand better the prescribing patterns of physicians and the appropriateness of AOM therapy, we used the Régie de l'Assurance Maladie du Québec (RAMQ) administrative databases to identify retrospectively all children aged ≤6 years with a first-time diagnosis of AOM between the years 1999 and 2002. We were consequently able to ascertain the antibiotic prescription patterns of physicians, the factors associated with various antibiotics dispensed, the conformity of dispensed antibiotics with the consensus guidelines, and the factors associated with adherence to guideline recommendations.

Methods

Data source

We studied a historical cohort by reviewing antibiotics used for AOM treatment in Quebec children from June 1999 to June 2002. Canada has a universal public health insurance programme, which is under provincial responsibility. In the province of Quebec, the RAMQ is the government body that is responsible for medical insurance and all physicians work within this system. It insures all Quebec residents medically and also has a cost-sharing drug insurance plan that covers Quebec residents aged ≥65 years, welfare recipients along with their children, and other workers and their children who do not have access to private group insurance from other sources. Drugs prescribed to children covered under the RAMQ drug plan are free of charge. In 2001, the RAMQ insured medically 400 000 children <5 years, while approximately 25% of them were also covered by the RAMQ drug plan [16].

Patient records in the different RAMQ databases were linked using the unique patient identification numbers. In this study, we examined the medical and pharmaceutical claims databases and the database on familial links. The records database contains demographic variables (patient sex, date of birth), drug plan coverage eligibility periods as well as enrolment category, and information on siblings (date of birth, sex, number). The medical claims database includes information on date and type of service, diagnosis coded using the International Classification of Diseases, Ninth Revision (ICD-9) [17], and other medical procedures. The pharmaceutical claims database includes information on the date a drug was dispensed, together with formulation, dose, duration of treatment, quantity dispensed and cost, and information on the prescribing physician (type of practice, specialty). The prescription claims and the medical service databases have been validated and considered to be comprehensive and accurate [18, 19].

Study population

Inclusion criteria Children were included in the study if they were diagnosed between June 1999 and June 2002 to have AOM. The index AOM was defined as a medical service claim with an AOM diagnosis [ICD-9 codes: 382.0 (acute suppurative otitis media), 382.4 (unspecified suppurative otitis media), and 382.9 (unspecified otitis media)] [17], together with evidence of an antibiotic having been dispensed within the following 72 h for a maximum duration of 14 days. Antibiotics dispensed for more than 14 days were considered as being used for prophylaxis. The antibiotics selected as approved treatment for AOM were oral formulations of amoxicillin, amoxicillin-clavulanic acid, trimethroprim-sulfametoxazole, erythromycin-sulfisoxazole, cefaclor, cefuroxime axetil, cefprozil,

cefixime, ceftriaxone (i.v. or i.m.), erythromycin, clarithromycin, and azithromycin [20]. Children also needed continuous enrolment in the RAMQ drug plan for a period of 6 months prior to and until 4 weeks after the initial index diagnosis of AOM was made. Furthermore, the child was to be aged between 3 months and 6 years inclusively.

Exclusion criteria Children were excluded if they had a diagnosis of AOM in the past and if they received an antibiotic in the 6-month period prior to the index AOM without an associated diagnosis in the 72 h preceding the dispensation. These criteria were used to eliminate children with a possible history of previous otitis media.

Amoxicillin daily dosage calculation

Using the antibiotic reimbursement price divided by the price per unit as provided in the Liste des médicaments [21], we calculated the amoxicillin dosage in mg that was dispensed. We then divided the total amoxicillin dosage by the prescription duration. To obtain the dosage in mg kg^{-1} day^{-1}, we divided the daily dosage by mean weight for the patient's age and sex [22].

Conformity of dispensed antibiotic to published consensus guidelines

Conformity of the dispensed antibiotic was based on physician adherence to the consensus guidelines for AOM treatment from the Drug-resistant *Streptococcus pneumoniae* Therapeutic Working Group [15]. These consensus guidelines propose first-line treatment as well as alternatives when failure occurs. If the child received no antibiotic in the previous month, amoxicillin (usual or high dose ≥80 mg kg^{-1}) was the recommended treatment. On the other hand, if the child had received antibiotics in the previous month, recommended treatments were high-dose amoxicillin, high-dose amoxicillin-clavulanic acid, or cefuroxime axetil.

An antibiotic prescription was judged to be in adherence with recommendations if it was in agreement with the treatment recommendations proposed by Dowell *et al.* [16]. Since an important correlation was present between antibiotics dispensed by a single prescribing physician, we selected the physician as the unit of analysis. We selected one patient randomly per prescribing physician present in the database ($n = 4708$) and used logistic regression to determine predictors associated with conformity. We then calculated a conformity score for each physician who saw at least five eligible patients throughout our study period (number of prescriptions in conformity with the consensus guidelines/total number of prescriptions for a first AOM episode).

Statistical analysis

The data were first analysed using descriptive statistics, χ^2 test and Student's *t*-test. The determinants of amoxicillin, cefprozil, and azithromycin *vs.* all other antibiotics were identified by logistic regression (SAS Institute, v 8.0, CARY, NC, USA). Variables were kept in the final model if their coefficient was statistically significant, if they confounded variables already present in the model, or if they significantly improved the model fit as measured by log likelihood. All *P*-values were considered significant at 0.05 and were two-sided.

Results

Study population

Between June 1999 and June 2002, 60 513 children aged ≤6 years experienced a first AOM episode treated with antibiotics. This represents 45% of the total child population of this age covered by the RAMQ drug plan. Their mean age was 2.6 years (SD = 1.6 years). Fifty-two percent of the children were male, and the parents of 36% of the children were welfare recipients. Thirty percent of the children had no siblings, while 39% had one sibling, 19% had two siblings, and 12% had three siblings or more.

A total of 4708 physicians saw these children. Their specialty was general practitioner (GP) (87.3%), paediatrician (9.1%), and ENT specialist (2.5%). They saw an average of 12.9 patients each (SD = 19.6, range 1–338), while half of them saw at least seven patients. The physicians were mainly working in private offices (74.6%); the remainder worked in emergency rooms (22.4%) and outpatient clinics (2.2%). At the time of the study, 18 145 physicians were registered with RAMQ. Of all the registered physicians, 777 were paediatricians, 228 were ENT specialists, and 8442 were GPs.

Antibiotic utilization review

Table 1 lists the antibiotics prescribed for AOM first episodes. Among all specialties, amoxicillin was the most commonly prescribed antibiotic (42.8% of all antibiotics prescribed), followed by cefprozil (15.3%), and azithromycin (12.8%). Eighteen percent of patients were treated with suboptimal dosages based on weight. Of patients receiving amoxicillin, 71% were treated with a dosage of 40–70 mg kg^{-1} day^{-1}, while only 5% were given the high dose (80–90 mg kg^{-1} day^{-1}). Among the children followed in the study, 12.5% (7580) had received an antibiotic in the previous month associated with a diagnosis in the database and for reasons other than AOM.

Predictors associated with the prescription of different antibiotics are detailed in Table 2. Age was an important predictor of prescription of a given antibiotic. Multivariate analysis revealed that children aged <18 months were more likely to receive amoxicillin than any other antibiotic. The specialty of the prescribing physician was another important predictor. Compared with GPs, infectious disease specialists were twice as likely to prescribe amoxicillin, while ENT specialists were twice as likely to prescribe cefprozil. GPs were more likely to prescribe azithromycin compared with all other specialties. Patients whose parents were welfare recipients were more likely to receive amoxicillin than any other antibiotic. During the three study years (1999–2002), there was an increase in the prescription of newer, more expensive antibiotics: cefprozil, azithromycin, and clarithromycin were all given more often in the last year of the study in comparison with the first 2 years. Amoxicillin use throughout the study years was not significantly different.

Table 1
Description of antibiotics prescribed for first episodes of acute otitis media (AOM)

Antibiotics prescribed for first episodes of AOM	*n*	(%)
Amoxicillin	25873	(42.8)
Cefprozil	9258	(15.3)
Azithromycin	7771	(12.8)
Clarithromycin	5764	(9.5)
Cefaclor	3691	(6.1)
Trimethoprim-sulfamethoxazole	2724	(4.5)
Amoxicillin-clavulanic acid	2591	(4.3)
Erythromycin ethylsuccinate-sulfisoxazole acetyl	1778	(3.0)
Cefixime	750	(1.2)
Erythromycin	173	(0.3)
Cefuroxime axetil	128	(0.2)
Others	12	(0.0)

Conformity of antibiotic prescription

The conformity of antibiotics dispensed was analysed on the basis of the consensus guidelines for AOM treatment published in 1999 [15]. Overall, 42% of all physicians followed the consensus guidelines in their choice of antibiotic. When looking only at GPs working in emergency rooms, 53% adhered to the consensus guidelines, compared with 41% of all GPs (1686/4113). Forty-eight percent of paediatricians adhered to the consensus guidelines (206/427), 29% of ENT physicians (34/117), and 67% of infectious diseases physicians (4/6). Deviations from the recommended treatments were mainly due to dispensation of cefprozil or azithromycin (25% each) and clarithromycin (19%) in GPs; dispensation of cefprozil (39%) and azithromycin or clarithromycin (13% each) in paediatricians; and dispensation of cefprozil (33%) and clarithromycin (25%) in ENT physicians.

Children aged <18 months saw a 32% increase in their chances of receiving a prescription that was in

Table 2
Predictors associated with the prescription of various antibiotics in the treatment of acute otitis media (AOM) in children

	Antibiotics Amoxicillin		Cefprozil		Azithromycin		Clarithromycin	
Predictors	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Age ≥18 months	0.70	(0.68, 0.73)	1.13	(1.08, 1.19)	1.42	(1.34, 1.50)	1.40	(1.31, 1.49)
Number of siblings	1.05	(1.03, 1.06)	–	–	–	–	0.97	(0.95, 0.99)
Welfare recipients parents	1.18	(1.14, 1.23)	0.88	(0.84, 0.93)	0.90	(0.85, 0.95)	–	–
Antibiotic in previous month	0.24	(0.23, 0.26)	1.62	(1.52, 1.72)	1.44	(1.35, 1.54)	2.07	(1.93, 2.22)
AOM during winter	0.92	(0.88, 0.96)	1.10	(1.04, 1.17)	0.93	(0.88, 0.99)	1.12	(1.04, 1.20)
Physician's specialty (reference: general practitioner)								
Infectious disease	2.03	(1.35, 3.04)	0.06	(0.01, 0.40)	0.25	(0.09, 0.67)	0.18	(0.04, 0.72)
ENT	0.49	(0.40, 0.59)	2.16	(1.80, 2.61)	0.39	(0.28, 0.56)	1.09	(0.85, 1.40)
Paediatrics	1.23	(1.18, 1.28)	1.12	(1.06, 1.17)	0.62	(0.58, 0.66)	0.63	(0.59, 0.68)
Practising in private office	0.69	(0.67, 0.72)	1.18	(1.11, 1.25)	1.56	(1.46, 1.66)	1.17	(1.10, 1.26)
Year of study (reference 3rd year)								
1st year	–	–	0.61	(0.58, 0.64)	0.59	(0.55, 0.62)	0.83	(0.77, 0.89)
2nd year	–	–	0.82	(0.78, 0.87)	0.78	(0.74, 0.83)	0.91	(0.85, 0.98)

conformity with the consensus guidelines [odds ratio (OR) 1.32, 95% confidence interval (CI) 1.16, 1.49). Compared with GPs, paediatricians were more likely to conform to the consensus guidelines (OR 1.28, 95% CI 1.05, 1.57), whereas ENT specialists were 50% less likely than GPs to follow the consensus guidelines (OR 0.54, 95% CI 0.36, 0.81). Physicians working in private office were 40% less likely to follow the consensus guidelines that those working in hospitals (OR 0.60, 95% CI 0.53, 0.69). The distribution of conformity scores of physicians having five or more eligible patients showed that 14.3% of physicians were constantly using antibiotics not suggested in the consensus guidelines, while only 4.3% of physicians were constantly prescribing in conformity with the consensus guidelines.

Discussion

The study objective was to identify the pattern of antibiotic use for AOM treatment in children. Amoxicillin remained the most widely administered antibiotic and was prescribed most often at lower doses (40 mg kg^{-1} day^{-1}). This dosage is appropriate for AOM occurring in children without other risk factors for Penicillin Non-Susceptible *S. Pneumoniae* (PNSP) but the high dose (90 mg kg^{-1} day^{-1}) should be given when risk factors are present. An important risk factor for an infection caused by PNSP is the use of an antibiotic in the previous month. Interestingly, amoxicillin was less likely to be prescribed in such cases, with azithromycin, cefprozil and clarithromycin being more likely choices. Unfortunately, these drugs are not effective in the treatment of PNSP and high-dose amoxicillin alone or associated with clavulanic acid should be administered.

Another reported risk factor for PNSP was young age (< 24 months) [23], which may partially explain why children aged <18 months were 30% more likely to receive amoxicillin. On the other hand, the ease of administration of other molecules such as azithromycin and clarithromycin could also explain the decreased likelihood of amoxicillin dispensation for older children.

Children of welfare recipient parents were more likely to be dispensed amoxicillin. Children covered under the RAMQ drug plan do not need to pay any fees associated with a prescribed drug and therefore, drug cost should not influence the antibiotic choice. Working parents may request antibiotics that are easy to administer, such as azithromycin. The increasing knowledge about various antibiotics among parents may also explain the increased dispensation of azithromycin and clarithromycin in the last study year.

This study shows that a significant proportion of Quebec physicians did not follow the consensus guidelines on AOM treatment in children [15]. Overall, 58% of the prescriptions dispensed for the treatment of AOM were not in conformity with the consensus guidelines, compared with 47% of prescriptions by physicians working in emergency rooms. These numbers are higher than those published in a Spanish study, where only 23% of the prescriptions dispensed in emergency rooms were not appropriate [24]. However, the Spanish study was prospective and the physicians knew that they were being observed. Moreover, they considered fewer antibiotics as 'not appropriate' than we did. When looking at adherence levels by groups of physicians, it is striking to see that ENT physicians are the group with the lowest adherence to the consensus guidelines among all specialties (29% compared with approximately 40% in all other groups). Although ENT physicians would be more likely to see more severe AOM or its complications, it is surprising that their antibiotic choices are mainly cefprozil and clarithromycin, which are not recommended antibiotics for treatment of PNSP.

There are a number of limitations to the present study due to the retrospective and administrative nature of the data obtained from the RAMQ. Although the medical services database may be used to assess general health status, it is especially difficult in children to understand fully the past medical history of a given patient. In the elderly, medical conditions may be captured by a combination of diagnosis and prescriptions filled. It has been shown to be accurate and comprehensive in this population [18, 19], but has not been validated in paediatric subjects where conditions may be more difficult to assess because of the low rate of drug consumption. We assumed that the majority of our population was previously healthy. In fact, only 1.6% of our population was hospitalized prior to their first AOM, only 31 patients had a diagnosis of HIV (0.05%) and 26 patients had a diagnosis of trisomy-21 (otitis-prone conditions). Moreover, the use of this administrative, retrospective database did not allow us to identify patients allergic to penicillin for whom the prescription of macrolides could have been indicated. On the other hand, the reported incidence of penicillin allergy is usually low, between 1 and 9% [25, 26].

As with most retrospective drug claims databases, records relate only to drugs dispensed and do not take into account prescriptions given to parents but not filled, and assume that the entire amount of drug dispensed was administered.

In conclusion, continuing medical education is necessary to reinforce the antibiotic that should be used to

treat AOM. A better understanding by prescribing physicians of the pathogens involved in AOM and of the risk factors associated with the acquisition of a drug-resistant bacterium should enable them to choose the best antibiotic given the patient characteristics.

C.Q. was supported by a Clinical Pharmacology Fellowship from the Collège des médecins du Québec. J.-P.C. was supported by a senior Research Career Award from the Fonds de recherche en santé du Québec (FRSQ). J.L. has acted as a consultant and paid speaker for Abbott Laboratories, Bristol-Myers Squibb Canada, GlaxoSmithKline, and Pfizer Canada. The authors thank Mr Jacques Barry from the RAMQ for assistance with the data, and Mr Marc Dorais for assistance in cohort selection.

References

1 Arason VA, Kristinsson KG, Sigurdsson JA, Stefansdottir G, Molstad S, Gudmundsson S. Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? Cross sectional prevalence study. Br Med J 1996; 313: 387–91.

2 Melander E, Ekdahl K, Jonsson G, Molstad S. Frequency of penicillin-resistant pneumococci in children is correlated to community utilization of antibiotics. Pediatr Infect Dis J 2000; 19: 1172–7.

3 Bronzwaer SL, Cars O, Buchholz U et al. A European study on the relationship between antimicrobial use and antimicrobial resistance. Emerg Infect Dis 2002; 8: 278–82.

4 Molstad S, Cars O. Major change in the use of antibiotics following a national programme. Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance (STRAMA). Scand J Infect Dis 1999; 31: 191–5.

5 Musher DM. Streptococcus pneumoniae. In: Mandell, Douglas, and Bennett's principles and practice of infectious diseases, 5th edn, eds Mandell GL, Bennett JE, Dolin R. New York: Churchill Livingstone, 2000; 2128–47.

6 Froom J, Culpepper L, Grob P et al. Diagnosis and antibiotic treatment of acute otitis media: report from International Primary Care Network. BrMed J 1990; 300: 582–6.

7 Bergus GR, Levy BT, Levy SM, Slager SL, Kiritsy MC. Antibiotic use during the first 200 days of life. Arch Fam Med 1996; 5: 523–6.

8 Byrns PJ, Bondy J, Glazner JE, Berman S. Utilization of services for otitis media by children enrolled in Medicaid. Arch Pediatr Adolesc Med 1997; 151: 407–13.

9 Thompson D, Oster G, McGarry LJ, Klein JO. Management of otitis media among children in a large health insurance plan. Pediatr Infect Dis J 1999; 18: 239–44.

10 Bluestone CD. Role of surgery for otitis media in the era of resistant bacteria. Pediatr Infect Dis J 1998; 17: 1090–8.

11 Hoppe HL, Johnson CE. Focus on antimicrobial resistance and new treatment options. Am J Health Syst Pharm 1998; 55: 1881–97.

12 Takata GS, Chan LS, Shekelle P, Morton SC, Mason W, Marcy SM. Evidence assessment of management of acute otitis media. I. The role of antibiotics in treatment of uncomplicated acute otitis media. Pediatrics 2001; 108: 239–47.

13 Bondy J, Berman S, Glazner J, Lezotte D. Direct expenditures related to otitis media diagnoses: extrapolations from a pediatric medicaid cohort. Pediatrics 2000; 105: E72.

14 Infectious Diseases and Immunization Committee Canadian Paediatric Society. Antibiotic management of acute otitis media. Paediatr Child Health 1998; 3: 265–7. Reaffirmed April 2002.

15 McCracken GH Jr. Treatment of acute otitis media in an era of increasing microbial resistance. Pediatr Infect Dis J 1998; 17: 576–9.

16 Dowell SF, Butler JC, Giebink GS et al. Acute otitis media: management and surveillance in an era of pneumococcal resistance—a report from the Drug-resistant Streptococcus pneumoniae Therapeutic Working Group. Pediatr Infect Dis J 1999; 18: 1–9.

17 Régie de l'Assurance Maladie du Québec. Nombre d'adhérents selon le sexe, le groupe d'âge et la région sociosanitaire de la personne assurée, régime d'assurance médicaments, 2001. 2002; www.ramq.gouv.qc.ca/fr/statistiques/documents/2001/tab503.pdf.

18 World Health Organization. International classification of diseases, Ninth Revision (ICD-9). Geneva: World Health Organization, 1977.

19 Tamblyn R, Reid T, Mayo N, McLeod P, Churchill-Smith M. Using medical services claims to assess injuries in the elderly: sensitivity of diagnostic and procedure codes for injury ascertainment. J Clin Epidemiol 2000; 53: 183–94.

20 Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec. J Clin Epidemiol 1995; 48: 999–1009.

21 Klein JO, Bluestone CD. Otitis media. In Textbook of pediatric infectious diseases, 4th edn, eds Feigin RD, Cherry JD. Philadelphia: Saunders, 1998; 195–211.

22 Régie de l'Assurance Maladie du Québec. Liste de médicaments. Quebec (QC). 2002.

23 Clinical growth charts. Lawson Wilkins Pediatric Endocrine Society, 2003; http://lwpes.org/growth_curves/growth-curves.htm

24 Dagan R, Hoberman A, Johnson C et al. Bacteriologic and clinical efficacy of high dose amoxicillin/clavulanate in children with acute otitis media. Pediatr Infect Dis J 2001; 20: 829–37.

25 Solis G, Ochoa C, Perez MC. The variability and appropriateness of the antibiotic prescription of acute otitis media in childhood. The Spanish Study Group for Antibiotic Treatments. Int J Pediatr Otorhinolaryngol 2000; 56: 175–84.

26 Kerr JR. Penicillin allergy: a study of incidence as reported by patients. Br J Clin Pract 1994; 48: 5–7.

27 Bowrey DJ, Morris-Stiff GJ. Drug allergy: fact or fiction? Int J Clin Pract 1998; 52: 20–1.