Impact of Early-Onset Acute Otitis Media on Multiple Recurrences and Associated Health Care Use

Marieke L. A. de Hoog, PhD[1], Alexandre C. Fortanier, MSc[1], Henriette A. Smit, PhD[1], Cuno S. P. M. Uiterwaal, MD, PhD[1], Cornelis K. van der Ent, MD, PhD[2], Anne Schilder, MD, PhD[1,3,4], Roger A. M. J. Damoiseaux, MD, PhD[1], Roderick P. Venekamp, MD, PhD[1,3], and Patricia Bruijning-Verhagen, MD, PhD[1,5]

Objective To quantify the critical age period of first episode of acute otitis media (AOM) and its consequences for AOM recurrences and AOM health care use.

Study design Children enrolled in the Wheezing-Illnesses-STudy-LEidsche-Rijn cohort with at least 1 episode of AOM documented in their primary care health record before 2 years of age were followed until 6 years of age. Data on episodes of AOM and associated primary care consultations, antibiotic prescriptions, and specialist referrals were retrieved. Regression models assessed the presence and shape of the associations between age of first AOM and subsequent episodes of AOM and health care use.

Results A total of 796 of 2026 children (39%) experienced a first AOM before 2 years of age. Each month decrease in age at first AOM in the first 2 years of life increased the risk of developing recurrent AOM (≥3 AOM episodes in 6 months or ≥ 4 in 1 year) linearly by 6% (adjusted risk ratio: 1.06; 95% CI: 1.02-1.10). For first AOM occurring before 9 months, the cumulative 6-year primary care consultation rate increased by 8% (adjusted incidence rate ratio: 1.08; 95% CI: 1.03-1.15) and the associated specialist referral increased by 16% (adjusted risk ratio: 1.16; 95% CI: 1.07-1.27) for each month decrease in age. No associations were found between age at first AOM and total AOM episodes or antibiotic prescriptions.

Conclusions The association between earlier age of first AOM and recurrent AOM as well as total health care use during childhood is particularly strong before 9 months of age. *(J Pediatr 2016;177:286-91).*

Acute otitis media (AOM) is a prime reason for health care consultations and antibiotic use in children.[1-3] In high-income countries, the incidence of AOM in children aged 0-5 years ranges from 136 to 273 per 1000 child-years,[4-7] with a peak incidence in the first 2 years of life.[7] Typically, children experience a first episode of AOM between the age of 6 and 11 months.[8] Although symptoms of AOM resolve spontaneously in most cases, these infections have a significant impact on child and family life and carry a considerable health care and economic burden.[9-11]

Early-onset AOM has been suggested as a risk factor for subsequent episodes of AOM, otitis media with effusion, and atopic diseases during early childhood[12-15] and may consequently increase the use of health care resources. It has long since been recognized that early-onset AOM is associated in more AOM episodes in the first 3 years of age.[8,13,16] Genetic, immunologic, and environmental factors have been postulated to contribute to this phenomenon[17-23]; however, results have not been confirmed when longer follow-up periods are studied.[24,25] Furthermore, previous studies did not always adjust for possible confounding and did not study the relationship between early-life AOM and associated health care use later in life. More importantly, these studies were unable to establish an exact critical age below which the risk for AOM recurrences was greater.

Identifying this critical age-period and quantifying the long-term consequences of early-onset AOM can be important to optimize management and prevention programs aiming to reduce the burden of AOM allowing for risk-stratified approaches. Therefore, our study investigated the association between age at first AOM in the first 2 years of life and AOM recurrences and associated

AOM	Acute otitis media
ICPC	International Classification of Primary Care
IRR	Incidence rate ratio
PCV	Pneumococcal vaccination
SES	Socioeconomic status
RR	Risk ratio
WHISTLER	Wheezing-Illnesses-STudy-LEidsche-Rijn

From the [1]Julius Center for Health Science and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; [2]Department of Pediatric Pulmonology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands; [3]Department of Otorhinolaryngology, University Medical Center Utrecht, Utrecht, The Netherlands; [4]evidENT, Ear Institute, University College London, London, United Kingdom; and [5]Center for Infectious Diseases Control, National Institute of Public Health and the Environment (RIVM), Bilthoven, The Netherlands

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health care use, including primary care consultations, antibiotic prescriptions, and specialist referrals, up to 6 years of age. We hypothesize that age at first AOM is a risk factor for AOM recurrences and future health care use.

Methods

This study is part of the Wheezing-Illnesses-STudy-LEidsche-Rijn (WHISTLER) study, a prospective birth-cohort study on perinatal and infant risk factors for wheezing illness. The WHISTLER study enrolled healthy newborns born between December 2001 to December 2012 living within a large residential area of Utrecht (Leidsche Rijn), The Netherlands. Study design and rationale of the WHISTLER study are described in detail elsewhere.[26,27] To summarize in brief, after obtaining written informed consent from both parents, we enrolled infants within the first 2 months of life. Exclusion criteria at baseline were gestational age <36 weeks, major congenital abnormalities, and neonatal respiratory disease. The medical ethical committee of the University Medical Center Utrecht, The Netherlands, approved the study.

At baseline, data on prenatal risk factors and parental characteristics were collected by a questionnaire. Data on postnatal risk factors, such as daycare attendance and duration of breastfeeding, were collected prospectively by monthly questionnaires during the first 12 consecutive months.

Follow-up of participants included extraction of 6 years of relevant medical data, or until lost-to-follow-up status, from the child's primary care electronic health records using the International Classification of Primary Care (ICPC) and the Anatomical Therapeutical Chemical coding systems. Specifically, primary care AOM diagnoses (ICPC H71), antibiotic prescriptions (Anatomical Therapeutical Chemical code J01), and AOM-related specialist referral to secondary health care were retrieved from the primary care electronic health records. All participating family physicians are trained according this system and use strict criteria for ICPC code H71 based on the Dutch family physician AOM guidelines.[28,29] In the Netherlands, family physicians serve as gatekeepers for the health care system, both during and outside the office hours. Specialist referrals are issued by family physicians and required for health care visits to secondary or tertiary care.

Definition of Outcomes

The primary outcome variable was defined as the number of family physician-diagnosed AOM (ICPC H71) episodes during the first 6 years of life. A new AOM episode was documented after an interval without any AOM-related primary care consultations of at least 28 days. Recurrent AOM was defined as having 3 or more AOM episodes in 6 months or 4 or more episodes in 1 year.[30] For each episode of AOM, the number of primary care consultations, antibiotic prescriptions, and specialist referrals were extracted.

Definition of Exposure and Confounders

The exposure variable of interest was age (in months) at first AOM within the first 2 years of life (continuous). Additional characteristics such as sex, season of birth, duration of exclusive breastfeeding, age of daycare entrance in the first year of life, parental education level, presence of older siblings, household smoking, and pneumococcal vaccination (PCV) status were considered as confounders. Duration of exclusive breastfeeding was divided into 4 categories, no breastfeeding, 1 to 3 months, 4-6 months, and more than 6 months of breastfeeding. Age of entry to out-of-home childcare was defined as the age of initial start of out-of-home childcare for at least one-half day per week in the first year of follow-up. Age of entry was divided into 4 categories, no out-of-home childcare in first year of follow-up, start of out-of-home childcare before 3 months of age, from 3 to 5 months of age, and 6 to 12 months of age. Educational level was categorized as high if one or both parents had completed at least vocational or university education and low-middle otherwise. Household smoking was defined as number of months exposed to household tobacco smoke for at least 1 day a week in the first year of life. PCV vaccination status was divided into 3 categories; no PCV vaccination (children born before April 2006), PCV-7 vaccination (children born from April 2006 to February 2011), and PCV-10 (children born from March 2011 until present).

Statistical Analyses

We studied the associations between age of the first AOM and several measures of AOM-related disease burden in the first 6 years of life, including recurrent AOM, related specialist referral, number of AOM episodes related to primary care consultations, and antibiotic prescriptions.

To study occurrence of recurrent AOM and specialist referral, both outcomes were defined as a dichotomous variable. Poisson regression analysis with robust standard errors was used to calculate risk ratios (RRs).[31] To study the number of AOM episodes, related primary care consultations, and antibiotic prescriptions, negative binomial regression analyses was used to calculate incidence rate ratios (IRRs). The negative binomial function was chosen because distributions were strongly overdispersed. In both the Poisson and negative binomial regression analysis, the natural log of follow-up duration was used as the offset variable to indicate exposure time. Follow-up duration was estimated as the time from the first AOM until the last known date of follow-up from the child's primary care electronic health records or until age 6 years.

To investigate the shape of the age-association, all associations were tested for possible nonlinearity with a quadratic function of age. If the result for a given model indicated that a linear model provided an adequate fit (Wald test *P*-value for squared age >.05), results from a linear model were reported, else, the nonlinear association was fitted in a graph.

All regression models were adjusted for potential confounders, including sex, parental education level, presence of older siblings, household smoking, duration of exclusive breastfeeding, first-year daycare attendance, season of birth, and PCV vaccination status.

Because of missing values in parental and child-related factors we imputed missing values using the Multivariate Imputation by Chained Equations (MICE) procedure in SPSS, version 20.0