A Population-Based Study of Childhood Respiratory Morbidity after Severe Lower Respiratory Tract Infections in Early Childhood

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Objectives To estimate the risk of childhood chronic respiratory morbidity among those hospitalized for severe lower respiratory tract infection (LRTI) in early childhood, and to determine whether severe LRTI is an independent predictor.

Study design The population-based Régie de l'Assurance Maladie du Québec datasets were used to identify LRTI hospitalizations before age 2 years in a birth cohort from 1996-1997 and a comparison cohort of children without an LRTI hospitalization. The incidence rate and incidence rate ratio of chronic respiratory morbidity before age 10 years were calculated, and multivariable logistic regression was performed to estimate the impact of LRTI hospitalization on chronic respiratory morbidity. Population-attributable risks of chronic respiratory morbidity due to severe LRTI were estimated, and similar analyses were performed for respiratory syncytial virus LRTI.

Results Among the birth cohort, 7104 patients (4.9%) were hospitalized for LRTI before age 2 years. By age 10 years, 52.5% of the LRTI cohort and 27.9% of the nonhospitalized cohort had developed chronic respiratory morbidity; the incidence rate ratio was 1.81 (95% CI, 1.76-1.86) for males and 1.91 (95% CI, 1.84-1.99) for females. The OR for chronic respiratory morbidity based on LRTI hospitalization before age 2 years was 2.79 (95% CI, 2.66-2.93). The population-attributable risk of chronic respiratory morbidity due to any LRTI was approximately 25%, and that for respiratory syncytial virus LRTI was similar.

Conclusions Hospitalization of young children for LRTIs is associated with two-fold increased risk of childhood chronic respiratory morbidity, demonstrating the ongoing impact of LRTI in infancy. *(J Pediatr 2014;165:123-28)*.

Childhood chronic respiratory conditions, such as asthma and recurrent wheezing, are responsible for a substantial clinical and economic burden worldwide.[1] In addition to environmental and genetic risk factors, severe lower respiratory tract infections (LRTIs) in infancy, especially those due to respiratory syncytial virus (RSV), may play a contributing role.[2-4] Severe LRTIs are themselves a leading cause of hospitalization among infants,[5] especially for those born premature, with bronchopulmonary dysplasia (BPD), or with congenital heart disease (CHD).[6]

Although it is generally agreed that severe LRTIs are associated with childhood chronic respiratory morbidity,[2-4,7] whether that role is causal or whether the propensity to severe LRTIs and asthma share a common distal source remains a topic of debate.[8-11] Unlike many other asthma risk factors, severe LRTIs may be preventable, and thus it is prudent to carefully evaluate the association between chronic respiratory morbidity and LRTIs to understand the potential impact of their prevention.

Although results from smaller prospective cohorts consistently show an increased risk of chronic respiratory morbidity associated with severe LRTI, the magnitude of risk estimate varies, because estimates are derived from studies with different samples, designs, sizes, durations, and outcomes.[2-4,6,12] A recent systematic review confirmed the significant association between severe RSV LRTI in infancy and subsequent childhood asthma, although their conclusions were limited by the methodological variability of the studies reviewed.[12] No large population-based study of the association between severe LRTIs in infancy and childhood chronic respiratory morbidity, or the associated attributable risk, has been reported to date.

The objective of the present study was to estimate the risk of childhood chronic respiratory morbidity among children hospitalized for severe LRTI before age 2 years. Secondary objectives included assessing whether the risk of chronic respiratory morbidity was higher in children at high risk for severe LRTI, and to determine whether severe LRTI is an independent predictor of childhood chronic respiratory morbidity.

BPD	Bronchopulmonary dysplasia
CHD	Congenital heart disease
CLD	Chronic lung disease
ICD-9	*International Classification of Diseases, Ninth Revision*
IRR	Incidence rate ratio
LRTI	Lower respiratory tract infection
RAMQ	Régie de l'Assurance Maladie du Québec
RSV	Respiratory syncytial virus

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Sponsored by AbbVie. K.G. and P.V. are employees of AbbVie. S.S. and E.K. are employees of ICON plc, and A.L. and P.B. are paid consultants to ICON plc. The other authors declare no conflicts of interest.

Portions of the study were presented as a poster at the Excellence in Pediatrics meeting, Istanbul, Turkey, December 1-3, 2011.

http://dx.doi.org/10.1016/j.jpeds.2014.02.053

Methods

This retrospective population-based study followed a birth cohort to estimate the impact of severe LRTI (defined as hospitalization during the RSV season, October to April[13]) before age 2 years on the incidence of chronic respiratory morbidity before age 10 years. The study was conducted using patient-level administrative data from the Régie de l'Assurance Maladie du Québec (RAMQ) physician billing and MED-ECHO hospital discharge abstract databases. The RAMQ insures all provincial health plan registrants in Quebec (99% of 7 731 600 residents in 2006) for medical and hospital services, and their databases include claims from the approximately 92% of Quebec physicians who work on a fee-for-service basis, as well as all acute care hospital discharge abstracts in the province.[14] Ethical approval of the protocol and data release was provided by the Commission d'acces à l'information du Québec.

The study cohort included all children born in 1996-1997 with a valid birth date on a newborn hospital discharge abstract who did not move out of the province during the first 2 years of life (n = 145 430). From the birth cohort, the LRTI cohort comprised all infants with a primary or secondary *International Classification of Diseases, Ninth Revision* (ICD-9) hospital discharge diagnostic code for LRTIs within the RSV season (**Table I**; available at www.jpeds.com) before age 2 years. The RSV cohort comprised the subset of the LRTI cohort with an ICD-9 diagnostic code indicating RSV infection (466.11). The third cohort, the nonhospitalized comparison, comprised all children not hospitalized for LRTI before age 2 years.

Selected clinical risk factors for severe LRTI—BPD (chronic lung disease [CLD] of infancy), CHD, and preterm birth—were identified from physician billing or hospital discharge abstracts from the first 2 years of life. Any of the relevant ICD-9 codes presented in **Table I** were used to classify CHD and BPD, and gestational ages on newborn discharge abstracts were used to classify children born preterm.

Chronic respiratory morbidity was identified by physician billing or hospital discharge abstract ICD-9 codes (**Table I**) according to the following subgroups: asthma, chronic wheezing, chronic bronchitis, or CLD.[15,16] An aggregate category of any chronic respiratory morbidity was generated based on any of the aforementioned diagnoses. A sensitivity analysis focused on those with more severe disease, defined as hospitalization for chronic respiratory morbidity.

Statistical Analyses

Demographic characteristics and distributions of risk factors for severe LRTI were tabulated by cohort. Cohort-specific incidences of childhood chronic respiratory morbidity were estimated, stratified by chronic respiratory morbidity subgroup and age (from 2 to <10 years or from 2 to <5 years vs from 5 to <10 years).[17] Age-specific denominators were adjusted for children who died or moved out of the province. Differences in rates of chronic respiratory morbidity in the LRTI, RSV, and nonhospitalized comparison cohorts were used to calculate the population-attributable risk of chronic respiratory morbidity due to LRTI.[18] Incidence rate ratios (IRRs) with 95% CIs were used to compare the age-specific risk of diagnosis or hospitalization for chronic respiratory morbidity in childhood among the LRTI cohort and RSV cohorts relative to the nonhospitalized comparison cohort.

The incidence of childhood chronic respiratory morbidity was estimated in children in the LRTI and nonhospitalized comparison cohorts at high risk for severe LRTI (considering children with any measured clinical risk factor or, individually, those with CHD or born preterm). IRRs were used to estimate excess risk by comparing incidence rates in children with the clinical risk factor who were hospitalized for LRTI before age 2 years, children with the clinical risk factor not hospitalized for LRTI before age 2 years, and the nonhospitalized comparison cohort. These analyses were not performed for the RSV cohort because of small sample sizes.

The importance of severe LRTI for predicting childhood chronic respiratory morbidity was assessed using logistic regression. Univariate analyses were conducted with potential predictors including sex, hospitalization for severe LRTI, and the clinical risk factors for severe LRTI (BPD, CHD, and preterm birth). The validity of including these clinical factors in the model was assessed after confirming the significant association between each of these factors and childhood chronic respiratory morbidity in patient populations not hospitalized for LRTI. All variables from the univariate analyses and interactions between variables significant at $P < .20$ that remained significant at $P \leq .05$ on multivariable analysis—male sex, prematurity, diagnosis of CHD or BPD, and hospitalization for LRTI before age 2 years—were included in the final model. The results are presented as ORs with 95% CIs of chronic respiratory morbidity based on the presence of the selected covariate. In sensitivity analysis, predictors of hospitalization for childhood chronic respiratory morbidity were assessed as well. Similar analyses were performed focusing on RSV LRTI. Statistical analyses were performed with Stata 10 for Windows (StataCorp, College Station, Texas).

Results

Of the 145 430 children in the birth cohort, 70 801 (48.7%) were male, 8300 (5.7%) were born preterm, 3223 (2.2%) were diagnosed with CHD, and 291 (0.2%) were diagnosed with BPD within the first 2 years of life (**Table II**). The most frequent diagnostic codes identifying entry into the LRTI cohort (n = 7104; 4.9%) were those for acute bronchitis or bronchiolitis (64.2%), followed by unspecified pneumonia (20.3%); almost 97% of LRTIs during the RSV season did not have the causal agent specified. A total of 230 children (0.2% of the birth cohort and 3.2% of the LRTI cohort) were hospitalized for severe RSV LRTI (RSV cohort). The nonhospitalized comparison