

Severe Respiratory Syncytial Virus Infection in Preterm Infants and Later Onset of Asthma

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Background: Respiratory syncytial virus (RSV) is the leading cause of viral lower respiratory tract infections in infants. Preterm infants are at increased risk for hospitalization with RSV (RSV-H), but there are few data on the relationship between RSV-H and asthma in preterm infants, or any data stratified by gestational age, and most studies have short follow-up periods. We sought to evaluate the relationship between serious RSV illness and onset of asthma up to 5 years of age in a cohort of preterm children and to quantify this association.

Methods: A retrospective birth cohort of preterm infants (29 weeks 0 days to 35 weeks 6 days gestational age) was constructed from a provincial population-based database, and children were followed forward for 5 years. Incidence rates of RSV-H and asthma were determined. In a Cox proportional hazards model, controlled for putative confounding factors for asthma, the hazard ratio and 95% CI of asthma in children with and without RSV-H was evaluated.

Results: Among 3916 premature children, the incidence rate of RSV-H was 25/1000 infants. The cumulative incidence rate of asthma at 5 years of age in children with RSV-H was 57.9/1000 person-years compared with 36.7 in those without RSV-H; the adjusted hazards ratio for asthma in RSV-H infants was elevated at 1.58 (95% CI: 1.03–2.41).

Conclusions: In prematurely born children, there is a moderate association between severe RSV infection, as measured by RSV-H in the first year of life, and asthma up to 5 years of age.

Key Words: respiratory syncytial virus, hospitalization, asthma, prematurity, lower respiratory tract infections

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Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infection in infants and young children worldwide, and severe infections result in hospitalization, morbidity and mortality.^{1–3} Preterm infants are at elevated risk of hospitalization with RSV (RSV-H) compared with those born at term.⁴ Respiratory infection in early life with rhinovirus and RSV has been associated with increased risk of childhood asthma,⁵ but this has not a consistent finding in all settings.^{6–8} The association is thought to be multifactorial and include genetic factors and exposure to environmental triggers.^{5,9} A better understanding of the nature of the association

between early RSV exposure and asthma is needed, and this could be obtained by diverse study designs from various settings. In particular, there are few data on preterm infants or any data stratified by gestational age (GA),^{3,4} and most studies have short follow-up periods.¹⁰

The availability of a maternal-perinatal population-based health database in our jurisdiction provided the opportunity to assemble a retrospective birth cohort to determine if severe RSV infection, as measured by hospitalization in the first year of life, increased risk of subsequent asthma in premature children. We report here the incidence of RSV-H in the first year of life and evaluate the relationship between asthma and preceding RSV-H in a preterm infant cohort followed until 5 years of age.

METHODS

Study Design and Population

This was a retrospective cohort study of live-born infants ≥ 29 weeks, 0 days to 35 weeks, 6 days gestation who were followed to the age of 5 years, 0 days. Eligible infants were born to women who were residents of Nova Scotia (NS), Canada, between July 1, 1998 and December 31, 2009, and survived until at least 12 months of age. Infants were excluded if GA information was not available, if birth occurred outside of a hospital or if birth occurred in NS but the child lived in another province. The other exclusionary criteria were infants with chronic lung disease/bronchopulmonary dysplasia, congenital heart disease, or immunodeficiency, as these children are known to be at increased risk of complicated RSV infection¹¹ and are offered palivizumab prophylaxis in this jurisdiction. Children with Down syndrome, cystic fibrosis and neuromuscular disorders are not eligible for palivizumab in our jurisdiction. Chronic lung disease was diagnosed by a neonatologist and congenital heart disease by a pediatric cardiologist.

The cohort was assembled by linking all eligible premature children in the Nova Scotia Atlee Perinatal Database (NSAPD) to pre-determined respiratory coded illness events in the Canadian Institutes of Health Research Discharge Abstract Database (CIHI-DAD) to capture RSV and asthma-associated hospitalizations and to the Nova Scotia Medical Services Insurance Database to capture service encounters for asthma rendered by a physician. In NS, everyone is eligible for a health card and health care if they can provide proof of citizenship or immigration.

Data Collection

The NSAPD contains information on all pregnancies in the province and is collected by health care professionals during care using standardized forms and on health records. The database is evaluated regularly for accuracy and reliability. The NSAPD includes information on perinatal health, deliveries, maternal and newborn diagnoses and morbidity and mortality. The Nova Scotia Palivizumab Utilization Program database was used to identify palivizumab receipt. The CIHI-DAD includes administrative, clinical and demographical information on hospital discharges in Canada. The Medical Services Insurance Database records all physician claims for health care provision in the province of NS and was used to identify outpatient visits for asthma. The Nova Scotia Vital

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Statistics Database was used to identify deaths during the study period.

The primary exposure variable, RSV-H, was captured in the CIHI-DAD using International Classification of Diseases (ICD), 9th and 10th revisions, Clinical Modification codes. An RSV-H was defined as a minimum of 1 hospital admission during the infant's first year of life with the RSV-specific ICD codes: RSV-bronchiolitis (466.11, J21.0), RSV-bronchitis (J20.5), RSV-pneumonia (480.1, J12.1) or RSV-unspecified (079.6, B97.4). RSV hospitalizations included 1 or more RSV-specific ICD codes that were either the primary reason for the admission or a secondary diagnosis.

The primary outcome was asthma. Children were followed forward until 5 years of age, or to a diagnosis of asthma, and were censored if they left the province or died. The asthma outcome was met if there was either 1 hospitalization for asthma or 2 outpatient physician visits for asthma within a 3-year period. Case verification studies on pediatric asthma diagnoses in secondary data in Canada demonstrate high accuracy for population-level asthma surveillance.⁸The following ICD (ICD, 9th and 10th revisions, Clinical Modification) codes for asthma were used: extrinsic (493.00, 493.01), intrinsic (493.10), chronic obstructive (493.20), other forms (J45.00, 45.01) and unspecified asthma. When the asthma outcome was met by 2 outpatient physician visits, the date of diagnosis was taken as the first of the 2 physician visits. Infants diagnosed with asthma before an RSV-H diagnosis were censored at the time of asthma diagnosis and were considered not to have RSV-H in the analysis. If an infant was hospitalized with RSV and diagnosed with asthma on the same day, the case was not considered to have had asthma after an RSV-H.

We controlled for potential confounders that could influence the onset of asthma, as well as be associated with RSV. These were chosen based on a literature review and variables available in the NSAPD: sex, GA in weeks, birth month, Appearance, Pulse, Grimace, Activity, Respiration scores (1 and 5 min), mode of delivery (vaginal or cesarean), marital status of the mother, and small for GA birth weight (greater than or less than or equal to the 10th percentile for GA). Infants who received at least 1 dose of palivizumab were considered as having had this intervention (palivizumab prophylaxis). Three proxy variables were created based on NSAPD data: “preschool-age siblings,” “household crowding” and “exposure to tobacco smoke.” Preschool-aged siblings, defined as children under 5 years of age, was created by totaling the previous maternal birth records from the NSAPD of siblings who were of preschool age during the study period. Household crowding, defined as >5 persons in the home, was created based on the number of previous births of children ≤18 years of age to determine the number of household siblings and the marital or common law status of the mother to determine if an adult partner lived in the home. “Exposure to tobacco smoke” was considered positive if any 1 of 3 variables in the NSAPD were present: maternal smoking pre-pregnancy or smoking at the first and 20-week prenatal visits or smoking at the time of the delivery admission. The socioeconomic status of the family was estimated using the Quintile of Annual Income Per Person Equivalent, a measure based on the mother's postal code linked to Canadian census data on neighborhood income quintiles.

Statistical Analysis

The background demographic and baseline characteristics of the cohort were described. The incidence rate of RSV-H was calculated by dividing the number of new RSV-Hs occurring during the infant's first year of life by the total study population at risk for RSV-H, with 95% CIs. The attack rate of RSV in each GA range (week) was reported. The cumulative incidence rate of asthma was calculated by dividing the number of new asthma cases diagnosed

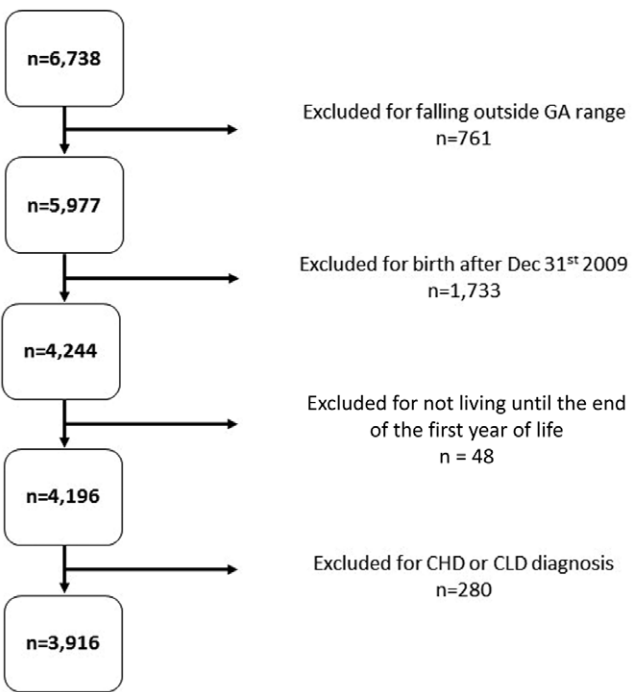


FIGURE 1. Final study cohort. CHD, congenital heart disease, CLD, chronic lung disease, GA, gestational age.

during the study period by the total population of infants at risk for asthma development using person-year units.

In a preliminary analysis, unadjusted for risk factors, the incidence of asthma in children with and without RSV-H was compared by dividing the RSV-exposed rate by the unexposed rate with 95% CIs.

The association between RSV-H and subsequent asthma development was evaluated using a Cox proportional hazard (PH) regression model while accounting for different lengths of participant follow-up. Bivariate analysis was used to independently assess the association between covariates and asthma development. Variables found to be significant (at a $P < 0.15$ level) were eligible for

TABLE 1. Demographic Characteristics of the Infant Cohort

Characteristic	N=3916	%
Male [N (%)]	2098	53.6
Socioeconomic status quintile		
Highest	621	15.9
Upper-middle	858	21.9
Middle	821	21.0
Lower-middle	786	20.1
Lowest	795	20.3
Birth weight < 2500 g	2483	63.4
Birth weight for GA <10 th percentile	365	9.2
Delivery by cesarean section	1681	42.9
Living in a household with		
Maternal smoking	1055	26.9
≥ 5 Individuals/household	211	5.4
Preschool-aged siblings (≤ 5 years of age)	1845	47.1
Low APGAR Score (0–6)		
1 min	1028	26.2
5 min	175	4.5
Palivizumab receipt	259	6.6

APGAR indicates Appearance, Pulse, Grimace, Activity, Respiration score.

TABLE 2. Hospitalization With RSV in the First Year of Life in a Cohort of Premature Infants, by Gestational Age

Gestational Age Range (Weeks + Days)	Cohort Size (n, %)	RSV-H (n/%)	RSV-H/1000 Infants (95% CI)	
			Excluding Infants Receiving Palivizumab*	Total Population
29 to 29+6	103 (2.6)	0 (0)	0 (0)	0 (0)
30 to 30+6	152 (3.9)	<5	10.3 (1.4–7.0)	6.6 (0.9–45.5)
31 to 31+6	219 (5.6)	7 (7.5)	49.7 (23.8–100.7)	32.0 (15.3–66.0)
32 to 32+6	344 (8.8)	<5	14.0 (5.3–36.7)	11.6 (4.4–30.6)
33 to 33+6	515 (13.1)	22 (20.4)	43.9 (29.1–65.8)	42.7 (28.3–64.1)
34 to 34+6	922 (23.6)	25 (26.9)	27.1 (18.4–39.8)	27.1 (18.4–39.8)
35 to 35+6	1661 (42.5)	37 (40.0)	22.2 (16.2–30.7)	22.2 (16.2–30.6)
Total	3916 (100)	96 (100)	26.3 (21.5–32.0)	24.5 (20.1–29.9)

<5: due to privacy legislation, data values less than 5 may not be shown.

*Overall, 6.6% (n = 259) of the cohort received palivizumab.

inclusion in the multivariable Cox PH model and were subsequently removed if found not to be a confounder (ie, RSV-H hazard ratio did not change by more than 10%). Tests for effect modification between RSV-H and independent variables significant from the bivariate analysis were conducted by comparing the likelihood ratios from a model with and without the interaction term to see if the interaction term was statistically significant. A test of the proportional hazards assumption was conducted using Schoenfeld global test to ensure the 2 hazard functions were statistically proportional.

Kaplan-Meier curves were used to visually display the time to asthma diagnosis in both the RSV-H and comparison groups. A log rank-sum test was used to compare the estimated Kaplan-Meier survival curves.

All analyses were conducted using STATA software for Windows version 15, StataCorp 2017 College Station, TX.

Approval to conduct the study was obtained from the Research Ethics Board of the IWK and the Privacy office of the Government of Nova Scotia Department of Health and Wellness.

RESULTS

Of 5977 infants born between 29 weeks 0 days to 35 weeks 6 days GA, 3916 were eligible (Fig. 1). At birth, the cohort was 53.6% male, and most were late preterm GA (34 weeks 0 days–35 weeks 6 days GA; 66%) with 63.4% at a birth weight under 2500 g (Table 1). Delivery by cesarean section was common (42.9%).

Incidence of RSV Hospitalization and Asthma

The overall incidence of RSV-H during the first year of life was 24.5 per 1000 infants (95% CI: 20.1–29.9); in children not given palivizumab, the incidence was 26.3/1000 infants (21.5–32.0) (Table 2). Infants born at 31 weeks GA not receiving palivizumab had the highest RSV-H rate (49.7/1000 infants) (Table 2), but CIs were overlapping with other GA groups. Bronchiolitis was the most common RSV-associated diagnostic ICD code (90.6%) among those with RSV-H.

During the 5-year follow-up period, 655 infants were diagnosed with asthma, with a cumulative incidence rate of 37.1 per 1000 person-years (95% CI: 34.4–40.1).

Relationship Between RSV-H and Asthma

Seven variables significantly associated with childhood asthma in the bivariate analysis were entered into the multivariable analysis: RSV-H, male sex, maternal cigarette smoking during pregnancy, a low Appearance, Pulse, Grimace, Activity, Respiration score 1 minute after birth, living with ≥ 1 preschool-aged

siblings in the household and GA 29 weeks, 0 days to 30 weeks 0 days and upper-middle socioeconomic status were associated with increased risk of asthma (Table 3). There were no cases of asthma in the palivizumab-prophylaxed group, so this exposure could not be considered in the multivariate model. The model included 91 infants with RSV-H and 3825 infants without RSV-H; 5 infants were diagnosed with asthma before RSV-H and were censored.

The rate of asthma in infants with RSV-H was 57.9 per 1000 person-years (95% CI: 38.8–88.0) and in those without RSV-H, was 36.7 per 1000 person-years (95% CI: 33.9–39.6). RSV-H was independently associated with the development of childhood asthma (hazard ratio: 1.58, 95% CI: 1.03–2.41, $P = 0.036$) (Fig. 2). The Cox PH model met the proportionality assumption (Schoenfeld global test $P = 0.074$). No independent variables evaluated in the multivariable model met the criteria for being a significant confounder, and no statistically significant interaction effects were observed.

DISCUSSION

In this retrospective population-based birth cohort study of infants born at 29 weeks, 0 days to 35 weeks, 6 days and followed for 5 years, hospitalization with RSV-associated lower respiratory tract illness was associated with later physician-diagnosed asthma. The increased risk of asthma in RSV-hospitalized preterm children was relatively small, about one and a half times higher in children with an RSV-H. A systematic review estimated the risk of later asthma after RSV infection to be increased by odds ratios of 2.07 to 12.7,⁵ but some studies have found no association.^{6–8} Differences in study findings may be because of sample variation or to the variable influences of the many concurrently acting host and environmental factors that together, with viral infection, increase risk. These factors include the genetic profile regulating innate and adaptive immunity and the inflammatory response to RSV infection, the nature of the child's microbiome, exposure to environmental toxins such tobacco smoke or particulate matter, or to allergens,^{5,9} the early neonatal adaptation period¹² and interactions between these factors. We suggest that because there are undoubtedly many etiologic factors that increase the risk of asthma, a multifaceted approach to prevent asthma in addition to preventing RSV infection is needed.

The incidence of RSV-H in these preterm children not receiving anti-RSV monoclonal antibody, 2.5%, is at the lower end of rates found in many settings, which ranged from 2.3 to 10% in a systematic review.⁴ The lower estimate is similar to an earlier study in our population¹³ and in Canada as a whole.¹⁴ In a systematic review, Stein et al³ found the global incidence of RSV-associated

TABLE 3. Cox PH Bivariate Analysis of Possible Covariates for Asthma Development

Predictive Variable	% Asthma	Hazard Ratio		P Value
		Estimate	95% CI	
RSV-H				
Yes	24.2 (22/91)	1.58	1.03–2.41	0.036
No	16.6 (633/3823)	1.00	—	—
Sex				
Male	18.9 (397/2098)	1.38	1.18–1.61	<0.001
Female	14.2 (258/1818)	1.00	—	—
GA				
29 weeks + 0 days–29 weeks + 6 days	8.7 (9/103)	0.49	0.25–0.96	0.037
30 weeks + 0 days–30 weeks + 6 days	11.8 (18/152)	0.68	0.42–1.10	0.114
31 weeks + 0 days–31 weeks + 6 days	13.2 (29/219)	0.77	0.53–1.13	0.181
32 weeks + 0 days–32 weeks + 6 days	14.8 (51/344)	0.87	0.65–1.17	0.358
33 weeks + 0 days–33 weeks + 6 days	19.4 (100/515)	1.17	0.93–1.47	0.172
34 weeks + 0 days–34 weeks + 6 days	18.1 (167/922)	1.08	0.89–1.31	0.416
35 weeks + 0 days–35 weeks + 6 days	16.9 (281/1661)	1.00	—	—
Socioeconomic status				
Highest	18.2 (113/621)	0.96	0.75–1.23	0.746
Upper-middle	13.8 (118/858)	0.72	0.56–0.91	0.007
Middle	15.8 (130/821)	0.83	0.66–1.05	0.123
Lower-middle	17.4 (137/786)	0.93	0.73–1.17	0.510
Lowest	18.7 (149/795)	1.00	—	—
Missing data	22.9 (8/35)	1.25	0.61–2.55	0.538
Siblings < 5 (preschool age)				
≥ 1 sibling	15.7 (290/1845)	0.89	0.76–1.04	0.136
0 siblings	17.6 (365/2071)	1.00	—	—
Siblings < 18				
≥ 1 sibling	16.6 (358/2150)	1.00	0.86–1.16	0.983
0 siblings	16.8 (297/1766)	1.00	—	—
APGAR score at 1 minute				
Low score 0–6	18.2 (187/1028)	1.13	0.96–1.34	0.150
Normal score 7–10	16.2 (465/2869)	1.00	—	—
Missing data	15.8 (3/19)	1.01	0.33–3.15	0.981
APGAR score at 5 minutes				
Low score 0–6	14.9 (26/175)	0.88	0.59–1.30	0.522
Normal score 7–10	16.8 (625/3717)	1.00	—	—
Missing data	16.7 (4/24)	1.01	0.38–2.69	0.988
Mode of delivery				
C-section	16.0 (269/1681)	0.92	0.79–1.07	0.285
Vaginal	17.3 (386/2235)	1.00	—	—
Household crowding (≥ 5 individuals/household)				
Yes	15.6 (33/211)	0.94	0.66–1.34	0.743
No	16.8 (597/3549)	1.00	—	—
Missing Data	16.0 (25/156)	0.96	0.64–1.43	0.842
Birth weight for gestational age				
≤ 10 th percentile	18.6 (68/365)	1.13	0.89–1.46	0.310
> 10 th percentile	16.6 (586/3537)	1.00	—	—
Missing data	7.1 (1/14)	0.42	0.59–3.00	0.389
Smoke exposure during pregnancy				
Yes	18.5 (195/1055)	1.16	0.98–1.37	0.085
No	16.2 (450/2778)	1.00	—	—
Missing Data	12.1 (10/83)	0.72	0.38–1.35	0.304
Palivizumab prophylaxis				
Yes	0.0 (0/259)	—	—	—
No	17.9 (655/3657)	—	—	—

Cohort includes 655 infants diagnosed with childhood asthma and 3261 who did not develop asthma.

Significant variables ($P < 0.15$ considered as covariates in the bivariate analysis to be tested in the multivariable model) are in bold. APGAR indicates Appearance, Pulse, Grimace, Activity, Respiration score.

acute respiratory illness hospitalization was, at 6.4%, about 3 times greater than that for term children. However, medically attended as well as hospitalization children were included in that study.

There are several limitations to our study. The retrospective study design meant that potential confounders not present in the dataset could not be measured or controlled for in the analysis. We are confident that a high proportion of children hospitalized with RSV would have been captured as it was common practice to obtain a nasal swab for diagnosis if a child required hospital care.

The incidence of RSV-H could be underestimated if some children did not have laboratory confirmation or if physicians' admitting practice varied across the province. All hospitals had the capability to test for RSV during the study, although diagnostic methods changed over time from antigen-based tests to polymerase chain reaction. Only RSV-specific codes were included in the analysis to minimize misclassification bias and ensure only true RSV-cases were included. Another potential limitation could be misclassification of asthma in children under 5 years. However, validation

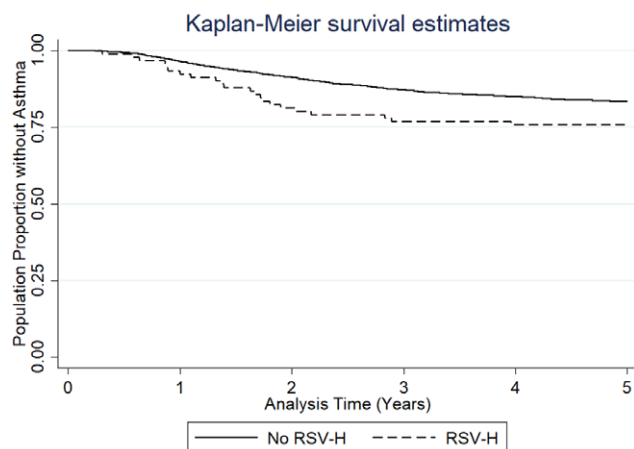


FIGURE 2. Survival analysis of premature children RSV-H and not RSV-H (no RSV-H) in the first year of life and the diagnosis of asthma up to 5 years of age. Survival in the Kaplan-Meier analysis is the time without the development of asthma. Children who had RSV-H (dotted line) had a higher incidence of asthma diagnosis.

studies of the asthma definition used in this study report high accuracy for population surveillance.⁸ In children over five years of age asthma diagnosis can be established using spirometry but this is not possible in younger children.¹⁵

Increased recognition of the significant burden of illness associated with RSV in infancy worldwide has led to renewed efforts to prevent infection. Proposed preventive strategies include maternal and childhood vaccines, monoclonal antibodies and improved therapeutics.^{16–18} In this study, we found an association in preterm children without significant heart or lung disease, between severe RSV illness in the first year of life, as measured by hospitalization, and later physician-diagnosed asthma. Ongoing research should consider the multiple influences that together increase the risk for respiratory virus-exposed infants to develop asthma.

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