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Sequelae of Severe Respiratory Syncytial Virus Infection in Infancy and Early Childhood Among Alaska Native Children

Rosalyn J. Singleton, MD*‡; Greg J. Redding, MD§; Toby C. Lewis, MD‖; Patricia Martinez, MD¶;
Lisa Bulkow, MS*; Barbara Morray, RN§; Helen Peters, RN*‡; James Gove, RN*; Carol Jones, RN#;
David Stamey, RT§; Deborah F. Talkington, PhD**; Jeffrey DeMain, MD‡‡; John T. Bernert, PhD§§;
and Jay C. Butler, MD*

ABSTRACT. *Objective.* In 1993–1996, we conducted a nested case-control study to determine risk factors for hospitalization with respiratory syncytial virus (RSV) infection among Alaska Native infants and young children. In the current study, we returned to former RSV case-patients and their control subjects during 1999–2001 to determine whether children who are hospitalized with RSV at <2 years of age are more likely to develop chronic respiratory conditions.

Methods. For each former RSV case-patient and control subject from remote villages in southwest Alaska, we reviewed medical records, interviewed parents, performed physical examinations and spirometry, collected sera, and analyzed chest radiographs. Case-patients were identified through surveillance for RSV hospitalization, and matched control subjects without lower respiratory infection (LRI)-related hospitalization were identified.

Results. Hospitalization for RSV infection was associated with a significant increase in wheezing, LRIs, and asthma diagnosis during the first 4 years of life. The association decreased with age and was no longer significant by 5 years of age. However, hospitalization for RSV infection was associated with increased respiratory symptoms and increased chronic productive cough at 5 to 8 years of age. Children who were hospitalized with RSV were not more likely at follow-up to have allergies, eczema, or a positive family history of asthma.

Conclusions. Severe RSV infection in infancy may produce airway injury, which is manifested in chronic productive cough with or without wheezing and recurrent LRIs. Although the association of RSV infection with wheezing seems to be transient, children remain at higher risk for chronic productive cough at 5 to 8 years of age. RSV prevention modalities may prevent sequelae that occur early and later in childhood. *Pediatrics* 2003; 112:285–290; *Alaska Native, respiratory syncytial virus, asthma.*

Respiratory syncytial virus (RSV) infection is responsible for approximately 126 300 hospitalizations[1] and 510 deaths[2] among children in the United States each year. Follow-up studies show that infants are hospitalized with RSV wheeze more than control subjects for the first 5 years of life; however, in most studies, there is no significant difference in recurrent wheezing after 5 years.[3–9] The presence of atopy in general does not differ between children with RSV and control children.[3,5,7,9,10]

Alaska Native children have extremely high rates of hospitalization for RSV infection, especially in the Yukon Kuskokwim (YK) Delta of southwestern Alaska (156 per 1000 children younger than 1 year).[11,12] Chronic respiratory conditions, including asthma, chronic bronchitis (chronic productive cough), persistent infiltrates, recurrent pneumonia, and bronchiectasis, are also common among Alaska Native children.[13] In Washington State, asthma hospitalization rates were similar for American Indians and Alaska Natives older than 1 year compared with all children; however, hospitalization rates for asthma and bronchiolitis in American Indians and Alaska Natives younger than 1 year were 2 to 3 times higher.[14] Of 466 YK children interviewed in 1997 as part of the International Study on Asthma and Allergies in Childhood (ISAAC), 8% reported a physician diagnosis of asthma, and another 12% reported asthma-like symptoms.[13] A novel finding was the large proportion (19%) who reported a chronic productive cough (expectoration of mucus with cough occurring more than occasionally but without a diagnosis of asthma or asthma-like symptoms). Bronchiectasis, rare in other US populations, is still relatively common in the YK Delta, where the prevalence remains 11 to 20 per 1000 births for the past 5 decades, despite control of tuberculosis and vaccine-preventable diseases.[15] Eighty-three percent of these bronchiectasis cases in the 1980s were preceded by lower respiratory infection (LRI), suggesting a link

between acute infection and chronic respiratory disease. No data are available on long-term effects of RSV infection or the contribution of RSV infections to high rates of chronic lung conditions in Alaska Native children.

In 1993–1996, we conducted a case-control study among YK Delta children who were younger than 3 years and hospitalized with RSV infection to determine factors associated with RSV disease.[16] In the current study, we returned to the former RSV case-patients and their controls during 1999–2001 to determine whether Alaska Native children who are hospitalized with RSV during infancy are more likely to develop chronic respiratory conditions.

METHODS

The original case subjects were recruited from participants in a prospective, hospital-based, laboratory surveillance study of children who were from the YK Delta and were hospitalized with acute respiratory infections during the first 3 years of life.[12,16] The original study was conducted over 3 RSV seasons (1993–1996) during which time there were 930 acute respiratory hospitalizations, 431 of which were RSV positive by rapid antigen or culture. For the purpose of the case-control study,[16] a case was defined as an illness leading to the first hospitalization with laboratory confirmation of RSV infection among children younger than 3 years. Age- and village-matched control subjects were recruited during the same season, using caliper matching on the basis of the case-patient's date of birth and village/subregion of residence. Potential control subjects were excluded from consideration when they had been hospitalized for any respiratory infection.

The current study was approved by the YK Health Corporation Health Board and Human Studies Committee, the Alaska Area Native Health Research and Publications Committee, and the Centers for Diseases Control and Prevention Institutional Review Board. Case-patients were children who were hospitalized with RSV when they were younger than 2 years and enrolled in the 1993–1996 study, and control subjects were the respective age- and village-matched control subjects from the earlier study. For the current study, a research nurse contacted parents of case-patients and control subjects (now 5–8 years of age), obtained assent to participate, and arranged a village visit. Village visits were conducted between September 1999 and September 2001 by an investigative team consisting of a pediatric pulmonologist or pediatrician, a respiratory therapist, and a nurse. We selected villages with the most potential participants and invited all potential children in a village to participate. Subjects were evaluated in their home village clinic with the majority of subjects evaluated during September 1999, 2000, or 2001. After obtaining informed consent, a nurse interviewed parents regarding the subject's medical history (including medical conditions, family history, household characteristics, and respiratory symptoms) using a standardized questionnaire. Nurses asked questions about respiratory symptoms from the standardized ISAAC questionnaire,[17] questions about cough in the past year ("In the past year, has your child had: daily cough, cough with mucous, cough >3 months, cough at night, cough with exercise, 4 or more illness with cough?"), and questions about doctor-diagnosed asthma.

The evaluation included a physical examination, pulmonary function testing, blood draw, and throat swab. Physical examination included measurements of height and weight, head and neck examination, inspection of the skin, auscultation of the heart and lungs, and the ability to cough and expectorate mucous. Pulmonary function testing (spirometry) was performed on each patient using the Schiller spirometer (Schiller America, Tustin, CA). This pneumotach-based portable digital spirometer meets American Thoracic Society guidelines for the measurement of forced vital capacity, forced expiratory volume at 1 second, and average flow between 25% and 75% of expired vital capacity.[18] Serum cotinine was analyzed by the Centers for Disease Control and Prevention, National Center for Infectious Diseases, Tobacco Exposure Biomarkers Laboratory (Atlanta, GA), using a high-performance liquid chromatography atmospheric pressure chemical ionization

tandem mass spectrometry.[19,20] This method has a nominal detection limit of 0.050 ng/mL.

Clinic visit and respiratory hospitalizations were reviewed using a standard form at village clinics, YK Delta Regional Hospital in Bethel, and Alaska Native Medical Center in Anchorage. Information abstracted from the record included respiratory examination findings (wheezing, crackles, etc), chest radiograph results, and medications prescribed. Chest films since birth were reviewed by 2 of us (G.J.R., T.C.L.), both pediatric pulmonologists, using a scoring sheet adapted from the Wisconsin chest radiograph scoring system for cystic fibrosis.[21] When chest films were unavailable, the original radiologist report was reviewed.

Definitions

Study participants who were control subjects in the original study but were subsequently hospitalized with RSV at <2 years of age were considered cases in the current analysis. Intermediate outcomes between ages 2 and 6 years, evaluated by chart review, included wheezing noted on physical findings during outpatient visits, diagnoses of LRIs (pneumonia, bronchiolitis), and reactive airway disease or asthma noted on outpatient encounters or hospitalization discharge.

We assessed the cohort for 3 current outcomes at the time of study examination: current wheezing, chronic bronchitis, and bronchiectasis. Current wheezing was defined as wheezing in the past year determined by interview with parent, review of outpatient visits in the medical record, or wheezing on study examination. Chronic bronchitis was defined as cough productive of mucous by interview plus 1 of the following chronic respiratory symptoms during the past year: daily cough, cough lasting >1 month, or ≥4 illnesses with cough. We defined bronchiectasis on the basis of chest radiographs at 2 years of age or later showing saccular changes or cylindrical outlines of airways that widened as airways extended into the periphery.

Statistical Methods

This study was a cohort study, following 2 previously defined groups of children and examining them at 5 to 8 years of age. Therefore, comparisons between former RSV case-patients and control subjects were made using a relative risks (RR) with Taylor series 95% confidence intervals (CI). Possible confounders were controlled using a Mantel-Haenszel test. For comparisons between children with and without identified respiratory outcomes at 5 to 8 years of age, odds ratios (OR) and Cornfield 95% CI were calculated. P values of dichotomous variables were calculated with a χ^2 test or Fisher exact test as appropriate. Differences in continuous variables were examined using a t test for means and a Wilcoxon rank sum test where medians are reported.

RESULTS

Between October 1993 and September 1996, 204 hospitalized RSV case-patients were recruited and matched with 338 control subjects in the RSV case-control study. The current follow-up study includes 95 RSV-hospitalized case-patients and 113 control subjects who were younger than 2 years at the time of the RSV infection. There was a higher proportion of premature infants among case-patients than among control subjects in the original and current study (Table 1). Demographic characteristics of patients and control subjects in the initial study and in the current follow-up study were similar except that follow-up study participants were less likely to live with a cigarette smoker and more likely to have running water in the house (Table 1).

Outcomes

By chart review, RSV case-patients had significantly more visits with wheezing than control subjects at ages 2 to 4 years, but the mean number of wheezing visits decreased each year, and at 5 to 6 years, there was no difference from control subjects

TABLE 1. Comparison of the RSV Case-Patients With Control Subjects Included in the Current Study

	Original Case-Control Study, 1993-1996			Current Cohort Follow-up Study, 1999-2001		
	Case-Patients	Control Subjects	P Value	Case-Patients	Control Subjects	P Value
No. of subjects	204	338		95	113	
Male gender	53%	47%	.183	56%	50%	.442
Age (mean, min, max)	0.65 y (0.02, 2.90)	0.69 (0.02, 2.90)	.496	6.39 (4.87, 8.09)	6.42 (4.87, 7.94)	.705
Bethel residence	9%	9%		15%	19%	
Premature	10%	2%	<.001	14%	3%	.004
No. in house (mean)	7.2	6.6	.007	7.1	6.2	.003
Smoker in household	68%	59%	.024	47%	44%	.653
Running water	31%	36%	.325	41%	47%	.396

min indicates minimum; max, maximum.

* Among participants in the follow-up study, the proportion living in a household with a smoker has decreased significantly ($P < .001$) and the proportion with running water in the household has increased ($P < .001$).

(Fig 1). Case-patients also experienced significantly more clinic visits for LRIs at ages 2 and 4 years (Fig 2). Last, case-patients were 3 times more likely to have had a diagnosis of reactive airway disease or asthma at ≥2 years of age (27%) than control subjects (9%; RR: 3.09; 95% CI: 1.57–6.08).

At the time of study examination, formerly hospitalized RSV case-patients were significantly more likely than control subjects to have chronic bronchitis but not more likely to have current wheezing alone (Table 2). On the basis of chest radiograph findings at ≥2 years of age, 10 (11%) of the 95 RSV patients and 11 (10%) of the 113 control subjects had evidence of bronchiectasis (RR: 1.08; 95% CI: 0.48–2.44). Similar findings exist when analyses are controlled for factors such as history of breastfeeding, prematurity, or presence of household smoker, which were significantly associated with RSV hospitalization in the original case-control study.

Twenty-eight percent (12 of 43) of former cases and 17% (9 of 53) of control subjects (RR: 1.64; 95% CI: 0.76–3.53) had an forced expiratory volume at 1 second/forced vital capacity <85%. On study examination, case-patients were more likely than control subjects to have productive cough (11% vs 3%) and increased chest diameter (11% vs 2%), but not more

likely to have wheezing or crackles (Table 3). Several respiratory symptoms (including cough >1 month of duration, cough at night, productive cough, and wheezing with exercise and shortness of breath) were more common in the past year in case-patients than in control subjects. There was no difference between patients and control subjects in median cotinine level (0.31 vs 0.29; rank sum, $P = .999$).

Other Factors Affecting Final Outcomes

Among potential confounding factors (smoker in house, animals in house, wood stove, median number in house, number of rooms in house, place of residence, median cotinine level, gender, and age at follow-up), only the presence of a dog in the house was marginally associated with current wheezing (OR: 2.21; 95% CI: 0.99–4.97) and chronic bronchitis (OR: 2.35; 95% CI: 0.89–6.11). Children with current wheezing, regardless of RSV history, were more likely to have a family history of asthma (31% vs 18%; OR: 2.11; 95% CI: 1.04–4.30) and to have a history of allergies by interview (32% vs 16%; OR: 2.19; 95% CI: 1.07–4.47) but were not more likely to have eczema (16% vs 17%; OR: 0.89; 95% CI: 0.39, 2.00), compared with children without current wheezing.
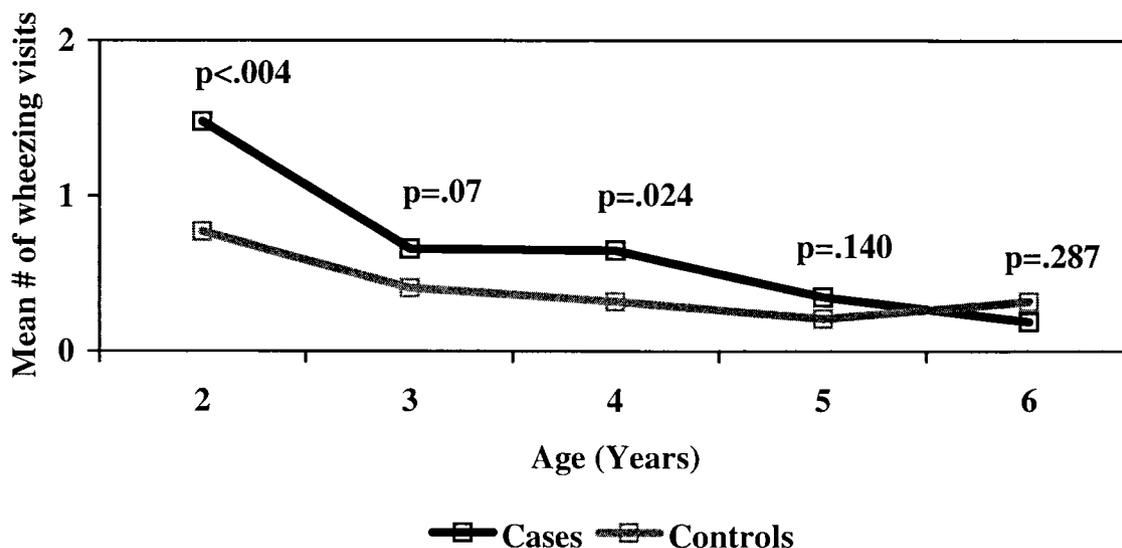

Fig 1. Mean number of visits with wheezing on examination per child by year of age from 2 years to the study age in former RSV patients compared with control subjects.
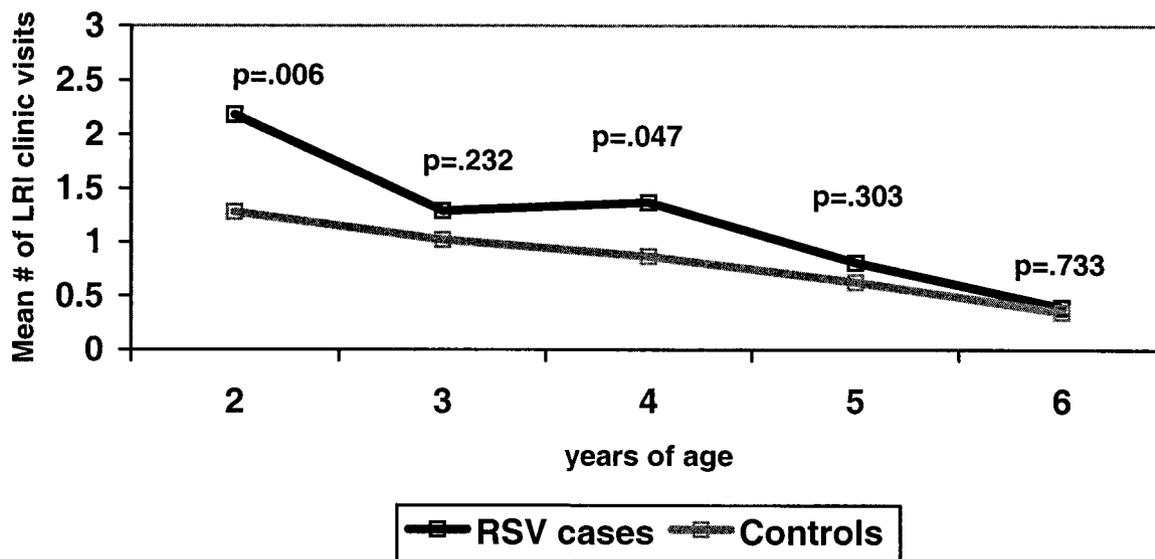
Fig 2. Mean number of clinic visits with an LRI diagnosis per child by year of age in former RSV patients compared with control subjects.

TABLE 2. Respiratory Outcomes at 5 to 8 Years of Age in Children Hospitalized at Age <2 Years With RSV Infection, Compared With Nonhospitalized Control Subjects

	RSV Case-Patients (N = 95; n [%])	Control Subjects (N = 113; n [%])	Relative Risk (95% CI)			
			Unadjusted	Adjusted for Breastfeeding	Adjusted for Household Smoking	Adjusted for Prematurity
Current wheezing	41 (43%)	41 (36%)	1.19 (0.85–1.66)	1.17 (0.83–1.64)	1.10 (0.77–1.55)	1.10 (0.77–1.57)
Chronic bronchitis	21 (22%)	12 (11%)	2.08 (1.08–4.01)	1.97 (1.02–3.83)	1.84 (0.94–3.58)	2.10 (1.03–3.94)
Bronchiectasis ≥2 y	10 (11%)	11 (10%)	1.08 (0.48–2.44)	0.96 (0.43–2.18)	1.05 (043–2.59)	1.21 (0.51–2.84)

TABLE 3. Respiratory Symptoms, Signs, and Treatments in the Past Year in Former RSV Case-Patients Assessed at 5 to 8 Years Compared With Control Subjects

	RSV Case-Patients (N = 95; n [%])*	Control Subjects (N = 113; n [%])*	Relative Risk (95% CI)
Symptoms			
Albuterol in last year	28/92 (30%)	10/112 (9%)	3.41 (1.75–6.64)
Cough lasting >1 mo	10 (11%)	2 (2%)	5.95 (1.34–26.5)
Cough at night	49 (52%)	36/112 (32%)	1.60 (1.15–2.24)
Productive cough	41/90 (46%)	30/110 (27%)	1.67 (1.14–2.44)
Wheeze with exercise†	12/63 (19%)	3/74 (4%)	4.70 (1.39–15.9)
Shortness of breath	16/92 (17%)	7/110 (6%)	2.73 (1.18–6.36)
Daily cough	18/91 (20%)	15/110 (14%)	1.45 (0.78–2.71)
≥4 illnesses with cough	20/94 (21%)	12/99 (12%)	1.76 (0.91–3.39)
Physical findings			
Wheezing	5 (5%)	4 (4%)	1.48 (0.41–5.38)
Crackles	6 (6%)	4 (4%)	1.78 (0.52–6.14)
Wheezing or crackles	10 (11%)	6 (5%)	1.98 (0.75–5.25)
Cough productive of sputum	10 (11%)	3 (3%)	3.96 (1.12–14.0)
Increased AP chest size	10 (11%)	2 (2%)	5.95 (1.34–26.5)
Laboratory			
FEV$_1$/FVC <85%	12/43 (28%)	9/53 (17%)	1.64 (0.76–3.53)
Cotinine ng/mL (median)	0.31 (n = 75)	0.29 (n = 96)	Rank sum (P = .999)

FEV$_1$ indicates forced expiratory volume in 1 second; FVC, forced vital capacity.
* Percentage is of total denominator unless otherwise noted.
† Questions added during course of study, not asked of earlier participants.

DISCUSSION

We have shown that hospitalization for RSV infection among Alaska Native children younger than 2 years was associated with a significant increase in wheezing, LRIs, and asthma diagnoses during the first 4 years of life. The association decreased with age and was no longer significant by 5 years of age.

However, hospitalization for RSV infection was associated with increased respiratory symptoms, including cough, and increased chronic bronchitis at 5 to 8 years of age.

As in our study, most published follow-up studies of infants who were hospitalized with RSV infections or bronchiolitis have found increased wheezing for

the first 4 to 5 years of life, which rapidly subsides, with no significant difference from control subjects after 5 to 10 years of life. In Kneyber's[3] quantitative review of controlled follow-up studies of patients who were hospitalized with bronchiolitis, wheezing was more common in children who had RSV bronchiolitis compared with control subjects for 1 to 5 years after the episode (40% vs 11%; $P < .001$) but not for 5 to 10 years after the episode (22% vs 10%; $P = .19$). The presence of either a personal and/or a family history of either atopy and/or asthma did not differ between the 2 groups.

The factors that contribute to increased risk of subsequent wheezing after RSV bronchiolitis or pneumonia may be multifactorial. First, RSV infections could promote allergic sensitization; however, studies to determine whether RSV enhances allergy in humans have yielded conflicting results.[22,23] Second, the severe lower airway inflammation produced by RSV and other infections could affect lung development, initiate airway remodeling, or produce scar after injury.[24] Third, it is possible that children with severe RSV infections may have ineffective antiviral responses that predispose them to subsequent viral infections.[25] Fourth, atopic children or children with reactive airways may be more vulnerable to more severe RSV infection. In our study, there is no evidence that RSV infections enhance allergies in YK Delta children; however, children with RSV infections were more likely to have wheezing and LRIs during the first 4 years of life, suggesting that either RSV produces airway damage or that increased airway reactivity may have resulted in RSV hospitalization initially. The high rate of RSV recurrence in YK Delta children (19% of all children hospitalized with RSV during 1993–1996 had >1 RSV-positive hospitalization)[12] suggests that ineffective antiviral responses may play a role in subsequent LRIs and produce cumulative airway injury over time.

The most important risk factors for current wheezing in our cohort were family history of asthma, history of allergies, and presence of animals in the house. Sigurs et al[26] also found that family history of asthma in 1 or 2 parents and presence of indoor furred animals were important risk factors for "any wheezing" at 7.5 years of age. Smokers in the household and serum cotinine levels were not positively associated with wheezing, chronic bronchitis, or cough in the past year in our study. The percentage of households with smokers in our study (45%) was similar to that found in a national survey,[27] in which approximately 44% of children aged 4 to 11 were reportedly subject to smoke exposure in the home. Median serum cotinine levels measured in the children in the YK Delta approximated the 75th percentile of nonsmokers aged 3 to 19 observed in a national survey (0.32 ng/mL).[28] Thus, the children who were exposed to household cigarette smoke in our study may have had more intense exposure relative to current national values, although the exposure levels were similar in both the case and control children and in currently wheezing and nonwheezing children.

A unique aspect of our study is the high propor-tion of study children with chronic bronchitis, defined as chronic productive cough. Chronic productive cough is a very prevalent symptom among these rural Alaska Native children. In an ISAAC survey study[13] conducted in 1997 on sixth- to ninth-grade YK children, children were classified into 4 mutually exclusive, hierarchical categories: asthma, asthma-like symptoms (wheezing in the last 12 months without diagnosis of asthma), productive cough (mucus with cough more than occasionally), and asymptomatic. Of the 466 adolescents, 8% had asthma, 12% had asthma-like symptoms, and 19% had productive cough.

Seear and Wensley[29] described children in his Canadian pediatric pulmonary practice with chronic productive cough associated with increased frequency of lower respiratory infections but not with atopy, which he also designated as "chronic bronchitis." Children in this category were more likely to be of Native Indian parentage, have chronic otitis media, live in poor social conditions, and have mothers who smoked. In Australian aboriginal children, chronic productive cough is reported in a high proportion of children and is associated with bronchiectasis.[30,31] In aborigines, chronic bronchitis was diagnosed on the basis of productive cough, with associated ausculatory findings in some and pneumonia or recurrent chest infections in most.[30] In our study, RSV former case-patients were more likely to have chronic bronchitis at 5 to 8 years of age than were control subjects. Our data support the assertion that chronic bronchitis with or without wheezing exists as a unique respiratory phenotype.[29,30,32] Unlike atopic asthma, respiratory symptoms associated with chronic bronchitis develop earlier in life and are associated with recurrent lower respiratory infections. Because our study design included children who had already been hospitalized with RSV, we cannot determine whether RSV hospitalization itself leads to greater respiratory morbidity or whether unknown factors that initially predisposed the children to be hospitalized in infancy also affected outcome.

CONCLUSIONS

Infants in rural southwest Alaska experience an extremely high rate of RSV hospitalization. We found that children with RSV in infancy have higher rates of respiratory morbidity through 5 to 8 years of age. Reducing the overall burden of respiratory illness in infancy[33] could prevent additional pulmonary illness later in childhood.

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Perez-Pena R. Medical study finds many procedures, not as much practice. *New York Times.* February 10, 2003

Submitted by Student

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