ORIGINAL RESEARCH

Trends in Chronologic Age and Infant Respiratory Syncytial Virus Hospitalization: an 8-Year Cohort Study

Jon P. Fryzek · William J. Martone · Jessie R. Groothuis

ABSTRACT

Introduction: Respiratory syncytial virus (RSV) is a major cause of lower respiratory tract infections in infants and young children and the leading cause of hospitalization in infants aged <1 year. *Methods:* We examined trends in RSV hospitalization (RSVH) among infants from 1998 to 2006, using the United States (US) National Hospital Discharge Survey (NHDS) database. RSVH was defined by the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes 079.6 (RSV), 466.11 (acute bronchiolitis due to RSV), and 480.1 (pneumonia due to RSV). Age at the time of hospitalization was determined using NHDS birth records; RSVH rates were analyzed for infants grouped into three age cohorts (<3 months, 3 to 6 months, and >6 to <24 months). Trends in hospitalization rates were evaluated using linear regression. Relative rates (RR) and 95% confidence intervals (CI) were computed to compare average RSVH rates for infants across age-specific groups. The annual proportion of RSVH by age group was also calculated. *Results:* Approximately 1.1 million (90,000-147,000 per year) RSVHs in predominantly term children aged <24 months were analyzed. Compared with children aged >6 to <24 months, rates for RSVH were significantly higher among infants aged <3 months (RR, 7.38; 95% CI, 7.35-7.41) and infants aged 3 to 6 months (RR, 5.28; 95% CI, 5.26-5.29). The proportion of RSVH in the first year of life was lowest among infants aged <1 month (0.9%). The greatest proportion of RSVH was observed in children aged 3 to 6 months (14%-23% RSVH per year; chi-square *P*<0.0001). When the definition of RSVH was expanded to include unspecified hospitalizations for acute bronchiolitis, similar results were observed. *Conclusion:* RRs were highest among the <3- month and 3- to 6-month age groups. The highest proportion of RSVH was among the 3- to 6-month age group. Analysis of the impact of RSV season, clinical practices, and other factors on these trends is warranted.

Keywords: age; hospitalization; respiratory syncytial virus; young infants

Jon P. Fryzek · William J. Martone · Jessie R. Groothuis (✉)
One MedImmune Way, Gaithersburg, MD 20878, USA.
Email: GroothuisJ@MedImmune.com

INTRODUCTION

Respiratory syncytial virus (RSV) is recognized as the leading cause of serious lower respiratory tract disease in infants and young children.[1-3] RSV in infants and children accounts for approximately 50%-80% of winter bronchiolitis and 30%-60% of winter pneumonia hospitalizations in the United States (US).[1] As many as 125,000 infants and young children are hospitalized in the US each year owing to severe RSV disease, and approximately 80% of hospitalizations involve term infants.[3-5] Palivizumab was licensed in 1998 for the prevention of RSV disease in high-risk infants. We analyzed data from the US National Hospital Discharge Survey (NHDS) to examine temporal trends in RSV hospitalizations (RSVH) among children <2 years of age. Although the NHDS does not have information on treatment or prophylaxis, we were interested in exploring trends in RSVH after 1998, following the introduction of palivizumab.

MATERIALS AND METHODS

Data from the US NHDS, a nationally representative cohort of inpatient RSVHs in children aged <24 months, were analyzed to examine trends in RSVH rates by chronologic age (CA) from 1998 (the launch of palivizumab) to 2006. The proportion of RSVHs out of all hospitalizations was calculated for each year between 1998 and 2006 to examine the burden that RSVH imposes on the US healthcare system. Infants and children were stratified into three mutually exclusive CA groups: <3 months, 3 to 6 months, and >6 to <24 months. Because testing for RSV is not consistently performed in the hospital setting, we repeated the analyses with an expanded definition of RSV, to include unspecified acute bronchiolitis (AB).

NHDS

Administered annually since 1965, the NHDS is the largest available nationally representative survey of inpatient hospitalizations in nonfederal acute care hospitals. Patient discharge records from hospitals with ≥6 beds for inpatient use were included in the survey. A three-stage probability design based on geographic area, hospital, and discharge data was used to select sample data. Data were weighted to produce national estimates. Variables collected at each discharge included patient demographics (age, sex, race, marital status); hospital characteristics (geographic location, number of beds); inpatient hospitalization characteristics (up to seven International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM]-coded diagnoses); days of hospitalized care; patient disposition; month, day, and year of discharge; primary and secondary expected source of payment; and type of admission and procedures. Patient identifiers were removed to ensure patient anonymity.[6]

Hospitalization Due to RSV

An RSVH was defined as including ≥1 RSV-related ICD-9-CM code among up to seven discharge diagnosis codes in the hospital discharge record. For this study, RSV-related ICD-9-CM codes included 079.6 (RSV), 466.11 (AB due to RSV), or 480.1 (pneumonia due to RSV), in the hospital discharge records. The current study analyzed data from 1998, as RSV codes were first introduced in 1996, thus allowing a 2-year period to ensure nationwide hospital adoption of the new codes.

RSV and AB

Testing for RSV is often not consistently performed in the hospital setting, and presumptive RSV

lower respiratory infections may frequently be coded as unspecified AB. We therefore expanded our definition of RSVH to include unspecified AB hospitalizations (ABH) and conducted additional analyses based on this expanded definition of the disease (RSVH/ABH). Specifically, a hospital discharge with at least one diagnosis code of 079.6 (RSV) 466.XX (AB, unspecified), or 480.1 (pneumonia due to RSV) was considered as RSVH/ABH.

Age

The birth month, day, and year were abstracted from the hospital records. Age at hospitalization was calculated by subtracting the birth date from the hospital admission date. For purposes of analyses, CA was categorized into three groups (<3 months, 3 to 6 months, and >6 to <24 months). Age categories were chosen based on the American Academy of Pediatrics guidance for RSV prophylaxis use.[7]

Statistical Methods

Analyses were limited to children <24 months. Hospital admissions related to birth were excluded. Simple descriptive statistics were calculated. All analyses were stratified by age categories (<3 months, 3 to 6 months, and >6 to <24 months). All statistical analyses were performed using Statistical Analysis Software version 9.1 (SAS Institute Inc., Cary, NC, USA).

Incidence Calculations

Incidence rates of RSVH were calculated as the estimated number of new RSVHs per 1000 children for each year and age category of interest. The number of RSVHs was determined by summing the weighted values for each observation in the NHDS;

denominator values were estimated by the number of live births for children using the natality data for the corresponding year. Thus, the number of children aged 0 to <3 months and 3 to 6 months were each estimated by taking the annual estimate of live births and multiplying by 0.25. The number of children aged >6 to <24 months was estimated by taking the annual estimate of live births and multiplying by 1.5. Trends were calculated using linear regression.

Relative Rates

Crude regression models were built to compare the incidence of RSVH in older children (>6 to <24 months of age) with younger children (<3 months, and 3 to 6 months of age). Relative rates (RR) and associated 95% confidence intervals (CI) were reported.

Annual Proportions

The annual proportion of hospitalizations due to RSV was calculated to estimate the burden that RSV imposes on the healthcare system for the three age categories. Annual proportions of RSVH were calculated by dividing the number of RSVHs (as defined above) by the total hospitalizations for that year for each of the age categories of interest. Incidence rates, RR, and annual proportion analyses were repeated for RSVH/ABH as the outcome of interest.

RESULTS

Hospitalization Due to RSV

There were 1,102,293 (90,000-147,000 per year) hospitalizations due to RSV in children <24 months of age identified between 1998 and 2006. Most children were <3 months (40%), male (57%), and white (61%) and lived in the southern

region of the US (37%; Table 1). Compared with children aged >6 to <24 months, rates for RSVH were significantly higher for infants aged <3 months (RR, 7.38; 95% CI, 7.35-7.41) and infants aged 3 to 6 months (RR, 5.28; 95% CI, 5.26-5.29). However, the incidence of RSVH showed a nonsignificant decrease for all age groups from 1998 to 2006 (–0.4 per 1000 children per year; P=0.784). Between 2000 and 2006, RSVH decreased at a faster rate (age <3 months, –3.5 per 1000 children per year; age 3 to 6 months, –3.3 per 1000 children per year; age >6 to <24 months, –0.35 per 1000 children per year), with the most significant decrease (P=0.026) for children <3 months of age (Figure 1).

Between 1998 and 2006, the annual proportion of RSVHs varied from 8% to 12% per year for children aged <3 months, and 6% to 10% per year for children aged >6 to <24 months. The highest proportion of hospitalizations due to RSV (14% to 23% per year) occurred in children aged 3 to 6 months (chi-square, P<0.0001; Figure 2). We also examined the proportion of hospitalizations by CA (in months) for all study years combined (1998 to 2006) to explore the appropriateness of the age groups analyzed (ie, <3 months, 3 to 6 months, >6 to <24 months). Approximately 9% of hospitalized infants aged ≤1 month had RSV. In contrast, approximately 20% of hospitalized infants aged 2 to 4 months had RSV, and approximately 16% of hospitalized children aged 5 to 8 months had RSV. After 8 and 12 months of age, the proportion of hospitalized children with RSV fell to approximately 10% and 7%, respectively (Figure 3).

Hospitalizations Due to RSV and AB

When the definition of RSVH was expanded to include unspecified ABH, the total number of hospitalizations for children aged <24 months between 1998 and 2006 increased to 1,928,520. Results for RR, annual incidences, and annual proportions by CA were similar

**Table 1**. Characteristics of children aged <24 months with RSV hospitalizations* from 1998 to 2006.

Characteristic	RSV hospitalizations, n (%)
Age, months	
<3	436,921 (40)
3 to 6	312,088 (28)
>6 to <24	353,284 (32)
Sex	
Male	629,361 (57)
Female	472,932 (43)
Race	
White	677,510 (61)
Black	142,690 (13)
Other	282,093 (26)
Region	
Northeast	139,024 (13)
Midwest	227,465 (21)
South	408,907 (37)
West	326,897 (30)

RSV= respiratory syncytial virus. *Newborn hospitalizations were excluded.

Figure 1. RSV hospitalization rates by age group for children <24 months: 1998-2006. RSV=respiratory syncytial virus.
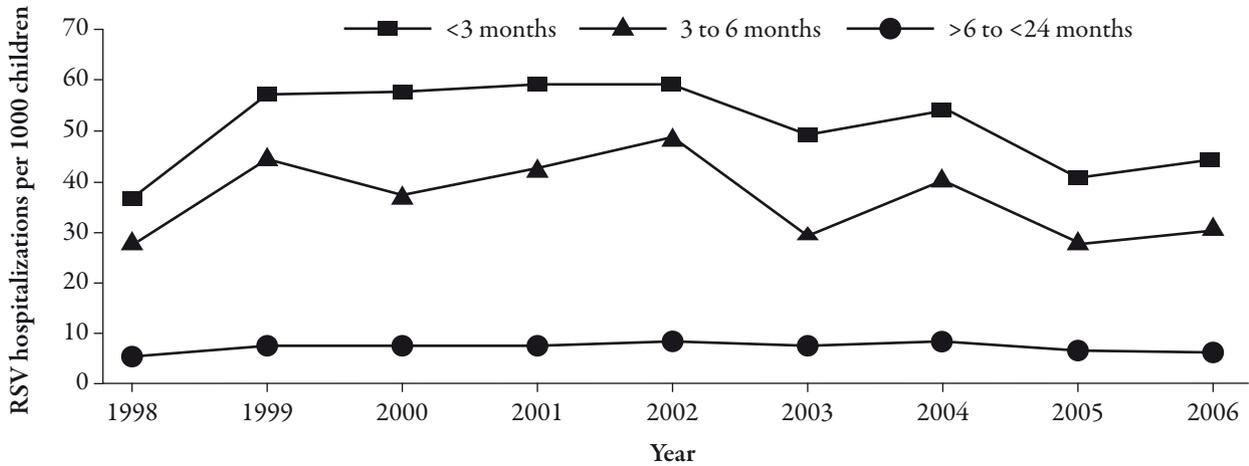
Figure 2. Proportion of RSV hospitalizations among all hospitalizations stratified by age group: 1998-2006. RSV=respiratory syncytial virus.
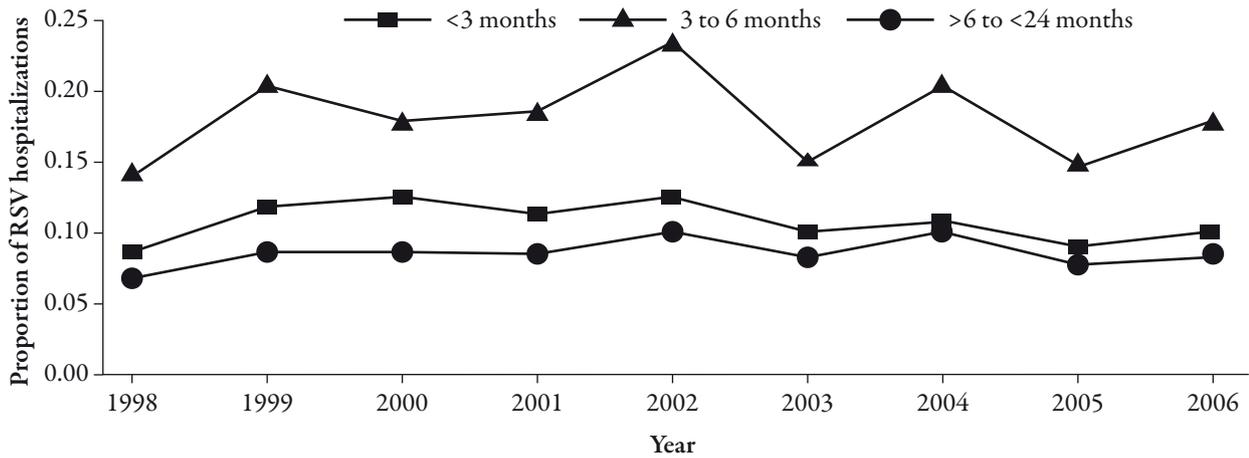
Figure 3. Proportion of RSV hospitalizations by chronologic age: 1998-2006. RSV=respiratory syncytial virus.
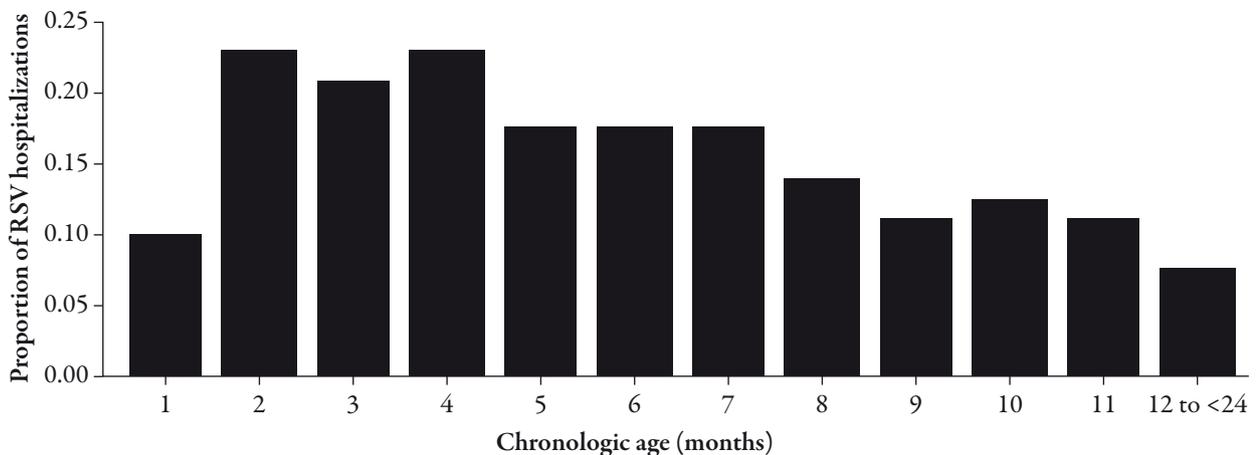
for RSVH and RSVH/ABH. Rates for RSVH/ABH were significantly higher for infants aged <3 months (RR, 5.45; 95% CI, 5.43-5.47) and infants aged 3 to 6 months of age (RR, 5.11; 95% CI, 5.10-5.13), compared with children aged >6 to <24 months. As with RSVH, RSVH/ABH rates declined faster after the year 2000 for children aged <3 months (–5.3 per 1000 children per year; P=0.008) and children aged 3 to 6 months (–7.0 per 1000 children per year; P=0.028) compared with children aged >6 to <24 months (0.03 per 1000 children per year; P=0.446); the percentage of RSVHs/ABHs was greatest for those aged 3 to 6 months (30% to 40% of total annual hospitalizations, compared with 14% to 20% of annual hospitalizations in the other two age categories), and for those with a CA of 2 to 8 months (27% to 37% of total annual hospitalizations; data not shown).

DISCUSSION

RSV lower respiratory tract infection remains the most important cause of rehospitalization in infants and young children.[1,5] Consistent with results from other studies,[1-5] we found that RR of RSVH were significantly higher (P<0.001) in children ≤6 months of age compared with children with a CA of >6 months. The incidence of RSVH appeared to decrease in a nonsignificant fashion among children of all ages from 1998 to 2006. The only significant decrease in hospitalization rates was observed in infants with a CA of <3 months (P=0.026). This may reflect greater protection due to the implementation of the 3-month maternity leave and increased awareness of the importance of protection from RSV in this very young age group. The overall decreasing trend for RSVH in all infants and children may also be a reflection

of the shift towards outpatient management of RSV disease.[4]

This study also assessed annual proportions by month of CA as an estimate of the burden imposed by RSVH. The proportion of RSVH in the first year of life was lowest in infants with a CA of <1 month (0.9%). We speculate that this may be due to a combination of diminished exposure to RSV, and high maternal antibody levels.[8,9] The largest proportion of RSVH occurred in children with a CA of 2 to 4 months (20%) and 5 to 8 months (16%). Additional RSVH risk factors in these groups may include immunologic vulnerability to severe RSV illness due to the nadir in circulating maternal immunoglobulin G antibody[9] and increased RSV exposure of older infants in situations such as day care.[8] The proportion of RSVH remained high for children through the first year of life: 13% at a CA of 8 months, and 10% at 11 months.

It has been reported that RSV testing is not performed in up to 30% of suspected cases.[4] We therefore expanded our definition of RSVH to include unspecified AB and reanalyzed the data using the expanded definition of the disease. For all analyses, results were similar. We found no evidence that potential misclassification of RSV or frequency of RSV testing played an important role in the trends we observed.

The strengths of this study include its large sample size, records-based data collection, broad geographic scope, and prolonged period of surveillance (eight RSV seasons). However, a number of study limitations exist. RSV testing was not routinely employed. Furthermore, we could not validate the type of RSV test used for those who were tested. This study was also historical in nature, and the hospital discharge data used could have included coding errors.

We believe that the findings from this study are an important step in the further delineation of those infants and children at highest risk for

RSVH. Further studies are warranted, as such information could have important implications for future development of guidelines for RSV immunoprophylaxis and vaccines.

REFERENCES

1. Hall CB. Respiratory syncytial virus. In: Feigen RD, Cherry JD, eds. Textbook of Pediatric Infectious Diseases. Philadelphia, PA: WB Saunders; 1987:1653-1675.

2. Hall CB. Respiratory syncytial virus and parainfluenza virus. N Engl J Med. 2001;344:1917-1928.

3. Shay DK, Holman RC, Newman RD, et al. Bronchiolitis-associated hospitalizations among US children, 1980-1996. JAMA. 1999;282:1440-1446.

4. Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med. 2009;360:588-598.

5. Leader S, Kohlhase K. Recent trends in severe respiratory syncytial virus (RSV) among US infants, 1997 to 2000. J Pediatr. 2003;143:S127-S132.

6. Dennison C, Pokras R. Design and operation of the National Hospital Discharge Survey: 1988 redesign. Vital Health Stat 1. 2000;39:1-42.

7. American Academy of Pediatrics Committee on Infectious Diseases and Committee of Fetus and Newborn. Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. Pediatrics. 2003;112:1442-1446.

8. Holberg CJ, Wright AL, Martinez FD, et al. Risk factors for respiratory syncytial virus-associated lower respiratory illnesses in the first year of life. Am J Epidemiol. 1991;133:1135-1151.

9. Yeung CY, Hobbs JR. Serum-gamma-G-globulin levels in normal premature, post-mature, and "small-for-dates" newborn babies. Lancet. 1968;1:1167-1170.