Respiratory syncytial virus (RSV) is the most important cause of lower respiratory tract disease among infants and children worldwide.1,2 Almost all children have been infected with RSV by age 2 years.3 Although reinfection throughout life is common, a child’s initial RSV infection typically is the most severe and the most likely to involve the lower respiratory tract.3,4 Severe RSV disease, as gauged by the requirement for hospital admission, is most common among infants aged 1 to 3 months.3,5

The hallmark of RSV infection is bronchiolitis, a disease of infancy characterized by wheezing, lung hyperexpansion, and hypoxia. Other lower respiratory tract illnesses, especially pneumonia, are also common manifestations of RSV infection. In studies of hospitalized children in temperate countries, RSV infection has been associated with 43% to 74% of bronchiolitis cases6-12 and with 19% to 54% of pneumonia cases.6-12 During the 1985-1994 winter seasons in Rochester, NY, RSV was associated with 30% to 60% of pneumonia hospitalizations and with 19% to 54% of pneumonia hospitalizations.6-12

The only national estimates of hospitalizations attributable to RSV infection were made by the Institute of Medicine in 1985.13 By estimating that 0.5% of children younger than 5 years infected with RSV would require hospitalization, and assuming that 60% of RSV-associated hospitalizations would occur among infants younger than 1 year, the Institute of Medicine projected that 54,697 infants younger than 1 year and 36,465 children aged 1 year and 36,465 children aged 1 to 3 years would require hospitalization for RSV bronchiolitis. In 1988-1996, the estimate of the number of infants younger than 6 months and 81% among those younger than 1 year. Among children younger than 1 year, annual bronchiolitis hospitalization rates increased 2.4-fold, from 12.9 per 1000 in 1980 to 31.2 per 1000 in 1996. During 1988-1996, infant hospitalization rates for bronchiolitis increased significantly (P for trend <.001), while hospitalization rates for lower respiratory tract diseases excluding bronchiolitis did not vary significantly (P for trend = .20). The proportion of hospitalizations for lower respiratory tract illnesses among children younger than 1 year associated with bronchiolitis increased from 22.2% in 1980 to 47.4% in 1996; among total hospitalizations, this proportion increased from 5.4% to 16.4%. Averaging bronchiolitis hospitalizations during 1994-1996 and assuming that RSV was the etiologic agent in 50% to 80% of November through April hospitalizations, an estimated 51,240 to 81,985 annual bronchiolitis hospitalizations among children younger than 1 year were related to RSV infection.

Conclusions During 1980-1996, rates of hospitalization of infants with bronchiolitis increased substantially, as did the proportion of total and lower respiratory tract hospitalizations associated with bronchiolitis. Annual bronchiolitis hospitalizations associated with RSV infection among infants may be greater than previous estimates for RSV bronchiolitis and pneumonia hospitalizations combined.

See also Patient Page.
bronchiolitis among infants.

Recent progress in 2 areas warrants updating national RSV-associated hospitalization estimates. First, the Food and Drug Administration recently licensed palivizumab, a humanized murine RSV monoclonal antibody for monthly intramuscular administration among high-risk children during RSV seasons to prevent lower respiratory tract disease hospitalizations. Palivizumab is easier to deliver and less expensive than the previously available prophylactic antibody preparation, RSV-enriched human immunoglobulin, which must be intravenously administered. Recommendations from the American Academy of Pediatrics regarding use of both products among high-risk infants are available. Second, advances in the development of safe subunit and live attenuated RSV vaccine candidates have been reported recently. To update hospitalization estimates, we examined temporal trends in hospitalizations among US children associated with bronchiolitis, the most specific RSV-associated illness. We estimated recent RSV-associated hospitalizations by using discharge data for bronchiolitis and used bronchiolitis and pneumonia hospitalizations to estimate RSV-associated morbidity among infants.

METHODS

Hospital discharge data from 1980 through 1996 were obtained from the National Hospital Discharge Survey (NHDS) through the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC). The NHDS is a representative sample of patient discharge records from short-stay, nonfederal, general and children's hospitals in the United States. Hospitalizations were weighted using NCHS procedures to obtain national estimates. NHDS records do not contain individual identifiers; therefore, the unit of analysis was a hospitalization.

All discharge records from children younger than 5 years with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for any respiratory illness (codes 460-519) among the as many as 7 discharge diagnoses listed were selected for study. A bronchiolitis-associated hospitalization was defined as a discharge with acute bronchiolitis (code 466.1) listed anywhere on the record. Use of this strategy detected hospitalizations for which a bronchiolitis-associated complication (eg, respiratory failure) might be coded first and those associated with nosocomially acquired bronchiolitis, which may represent a substantial proportion of RSV-associated bronchiolitis among hospitalized infants. Severe bronchiolitis was defined as a discharge listing an ICD-9-CM procedure code for endotracheal intubation (code 96.04) or for receipt of continuous mechanical ventilation (codes 96.72 or 96.71 [1992-1996]; 93.92 [1988-1991]; or 93.90 [1980-1987]).

Hospitalizations were stratified by patient age: younger than 6 months, 6 through 11 months, 12 through 23 months, or 24 through 59 months. For approximately 1.0% of bronchiolitis hospitalizations, age data were missing; these records were not included in analyses. Hospitalizations were also stratified by sex, length of stay, and census geographic region (Northeast, Midwest, South, and West). Because data on race/ethnicity were missing from 23% of discharge records examined, we made no comparisons by ethnicity. Temporal trends in hospitalizations were examined by discharge month and year. From 1988 through 1996, aggregate estimates of discharges by month were made using only records sampled from hospitals fully responding for that year (I. M. Shimizu, PhD, NCHS, written communication, November 16, 1998). Bronchiolitis and pneumonia hospitalizations attributable to RSV were estimated using winter RSV recovery rates among children hospitalized with bronchiolitis (50% to 80%) or pneumonia (30% to 60%). Only hospitalizations occurring from November through April were used in estimating disease likely attributable to RSV infection.

To determine whether changes in diagnostic coding practices during the study period influenced the number of bronchiolitis-associated hospitalizations, other lower respiratory tract disease hospitalizations were also examined. Discharges associated with lower respiratory tract diseases other than bronchiolitis were defined by the following ICD-9-CM codes: acute and chronic/ unspecified bronchitis (466.0, 490-491); pneumonia (480-486); influenza (487); asthma (493); bronchiectasis (494); pneumonitis (507); respiratory conditions due to unspecified external agents (508); emphysema (492); empyema (510); pleurisy (511); and other diseases of the lower respiratory system (512-519). Conditions specifically noted on discharge records included pneumonia, organism unspecified (486), bronchopneumonia (485), RSV pneumonia (480.1), other specified viral infection (078.9), otitis media (382.9), congenital heart disease (743-747), chronic respiratory distress arising in the perinatal period (770.7), and a history of perinatal problems (V13.7).

Hospitalization rates were calculated using denominators derived from US census data for children younger than 5 years or from US natality data for children younger than 1 year. Population estimates of children age 1 through 4 years for each calendar year were made by subtracting natality figures from census figures. Rates were expressed as the number of estimated hospitalizations per 1000 children of the corresponding age group.

The NHDS was redesigned in 1988, when new methods of sampling hospitals and collecting data were introduced; however, most estimates obtained using the old and the new methods have not been substantially different. SUDAAN software was used to calculate annual SEs during 1988-1996 to account for the stratified sampling techniques used during this period. Overall SEs for the entire study period were estimated using NCHS pro-
Denominators obtained from vital records data were considered free from sampling error. Statistical tests for rate comparisons were performed only with 1988-1996 hospitalization data because of the 1988 changes in survey design. Comparisons were made by period and demographic characteristics with 2-sided $t$ tests incorporating weighted variance estimates. A weighted least squares regression method was used as a test for trend with data obtained from 1988 through 1996.

RESULTS

Bronchiolitis Hospitalizations

From 1980 through 1996, an estimated 1,648,281 (SE, 121,129) hospitalizations associated with bronchiolitis occurred among US children younger than 5 years. Eighty-one percent (1,334,566; SE, 105,396) of these hospitalizations occurred among children younger than 1 year and 57% (946,358; SE, 83,309) among children younger than 6 months. As expected for an illness frequently associated with RSV infection, bronchiolitis hospitalizations peaked annually during the winter months, usually in January or February (Figure 1). Among children younger than 5 years, 81% of bronchiolitis hospitalizations occurred from November through April, and among children younger than 1 year, 83% occurred during these months.

During the study period, we estimated that bronchiolitis hospitalizations accounted for 7.0 million inpatient days (SE, 575,554). The median length of stay was 3 days per hospitalization (interquartile range, 2-5 days). Length of stay did not vary substantially by age in months, by sex, or by calendar year (data not shown).

Although the annual number of bronchiolitis hospitalizations fluctuated, they increased among children in each age group during the study period (Figure 2). The most dramatic rise in hospitalizations occurred among children younger than 6 months, for whom bronchiolitis hospitalizations increased by 239% from 1980 to 1996.

Among children aged 1 through 4 years, the bronchiolitis hospitalization rate increased gradually, from 1.3 per 1000 in 1980 to 2.3 per 1000 in 1996 (+77%). Among children younger than 1 year, rates increased more rapidly during this period, from 12.9 per 1000 to 31.2 per 1000 (+152%).

Bronchiolitis hospitalization rates increased proportionately among males and females. Among infant males, the rate increased from 24.9 per 1000 during 1988-1990 to 38.4 per 1000 during 1994-1996 (+54%; $P = .01$); among infant females the rate increased from 15.1 to 24.4 per 1000 (+62%; $P = .02$) during these periods. Males were 1.6 times more likely to be hospitalized with bronchiolitis than females, irrespective of age group or calendar year.

Bronchiolitis hospitalization rates among infants increased in each of the
4 regions of the United States. However, the only statistically significant increase took place in the South, where the annual average hospitalization rate increased from 19.0 per 1000 in 1988-1990 to 33.4 per 1000 in 1993-1995 (+75.8%; P = .03).

**Hospitalization Rates for Lower Respiratory Tract Diseases**

From 1980 through 1996, bronchiolitis was responsible for increasing proportions of lower respiratory tract disease and total hospitalizations among children younger than 1 year. The proportion of total hospitalizations among children younger than 1 year associated with bronchiolitis increased from 5.4% to 16.4%; for lower respiratory tract diseases, the proportion diagnosed with bronchiolitis increased from 22.2% to 47.4% (Table).

To determine whether bronchiolitis hospitalization rates were influenced by temporal trends in diagnostic coding practices, we examined hospitalization rates for other lower respiratory tract diseases. Hospitalization rates among children younger than 1 year for all lower respiratory diseases increased by 13% during the study period, from 58.1 per 1000 in 1980 to 65.8 per 1000 in 1996 (Figure 3). Pneumonia hospitalization rates declined from 28.5 per 1000 in 1980 to 23.9 per 1000 in 1988, while bronchiolitis hospitalization rates increased from 12.9 to 17.3 per 1000. The increase in bronchiolitis rates during 1980-1988 may have resulted, in part, from a trend to diagnose bronchiolitis instead of pneumonia among children younger than 1 year. However, bronchiolitis hospitalization rate increases after 1989 among children younger than 1 year were not accompanied by concomitant rate decreases for either pneumonia or asthma (Figure 3). Finally, hospitalization rates for bronchiolitis and all lower respiratory tract diseases increased significantly during 1988-1996 (P for trend <.001 for each comparison), while hospitalization rates for all lower respiratory tract diseases except for bronchiolitis did not vary significantly (P for trend = .20).

**Recent Patterns in Bronchiolitis Hospitalizations**

Specific diagnoses and procedures associated with bronchiolitis discharges were examined in detail during 1994-1996 to determine the most recent hospitalization patterns. Bronchiolitis was the first-listed diagnosis in 83% of records. Pneumonia, organism unspecified (4.5%), RSV pneumonia (2.9%), asthma (1.9%), and bronchopneumonia (1.1%) were other common first-listed diagnoses. The most frequent underlying conditions recorded for bronchiolitis-associated discharges were congenital heart disease (2.4%), chronic respiratory distress arising in the perinatal period (2.0%), and a history of perinatal problems (1.4%). Severe bronchiolitis was uncommon during the entire study period, but it may have become more prevalent in recent years. Among children younger than 1 year during the entire study, 1980-1996, bronchiolitis-associated discharges were recorded with the following diagnoses: acute bronchiolitis (466.1); acute and chronic or unspecified bronchitis (466, 490-491); pneumonia (480-486); influenza (487); asthma (493); bronchiectasis (494); pneumonitis (507); respiratory conditions due to unspecified external agents (508); emphysema (492); empyema (510); pleurisy (511); and other diseases of the lower respiratory system (512-519).

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1.0% of bronchiolitis hospitalizations were coded for endotracheal intubation or receipt of continuous mechanical ventilation. However, during 1994-1996, the discharges of 1.7% of children younger than 1 year hospitalized with bronchiolitis were coded for endotracheal intubation or for receipt of continuous mechanical ventilation.

Procedures frequently coded for the discharges of children younger than 1 year with a 1994-1996 bronchiolitis-associated hospitalization included nebulization therapy (17.2%), receipt of supplemental oxygen (8.6%), lumbar puncture (4.8%), and antibiotic injection (1.3%).

Estimates of RSV-Associated Hospitalizations

To provide current estimates of RSV-associated morbidity, we averaged bronchiolitis hospitalizations among children younger than 1 year and 5 years during 1994-1996. An average of 123,471 bronchiolitis hospitalizations occurred annually among children younger than 1 year and 154,365 among children younger than 5 years during this 3-year period. Assuming that 50% to 80% of bronchiolitis hospitalizations occurring during November through April were attributable to RSV, we estimated that 51,240 to 81,985 children younger than 1 year and 62,518 to 100,029 children younger than 5 years were hospitalized during each of these years for RSV-associated bronchiolitis.

We also estimated the contribution of RSV to pneumonia hospitalizations among children younger than 1 year. Assuming that 30% to 60% of November through April pneumonia hospitalizations in 1994-1996 were RSV-related, 22,160 to 44,321 infant pneumonia hospitalizations annually were attributable to RSV infection.

COMMENT

Our study is the first to examine temporal trends in bronchiolitis hospitalizations and estimate RSV-associated hospitalizations by using nationally representative data. Our finding that bronchiolitis hospitalizations have increased substantially during the 17 years studied was not expected. We found that infant bronchiolitis hospitalization rates increased significantly from 1988 through 1996, while hospitalization rates for other lower respiratory tract diseases did not vary significantly. Among infants, bronchiolitis currently is associated with approximately 47% of lower respiratory tract disease discharges and with 16% of total discharges.

In 1985, the Institute of Medicine estimated that 91,162 hospitalizations for bronchiolitis and pneumonia associated with RSV occurred annually among US children younger than 5 years. For bronchiolitis alone, we estimate that 62,500 to 100,000 RSV-associated hospitalizations occur annually among children younger than 5 years. The Institute of Medicine appeared to underestimate the RSV-associated disease burden among infants younger than 1 year because they assumed that 60% of RSV hospitalizations among children younger than 5 years would occur among infants. We found that 81% of bronchiolitis hospitalizations occurred among infants. Our estimate of 51,200 to 82,000 annual infant hospitalizations for RSV-associated bronchiolitis is similar in magnitude to the 1985 Institute of Medicine projection of 54,700 RSV-associated infant hospitalizations for bronchiolitis and pneumonia combined. Currently, we estimate that 73,400 to 126,300 annual hospitalizations among US infants for bronchiolitis or pneumonia may be attributable to RSV infection, considerably more than the 1985 projection.

The etiology of the increase in bronchiolitis hospitalization rates is probably multifactorial. Trends in childcare practices, changes in the criteria for hospitalization of children with lower respiratory tract disease, decreasing mortality among premature and medically complex infants at high risk for RSV-associated hospitalization, changes in RSV strain virulence, modifications in the NHDS, or alterations in diagnostic coding practices during the study period are potential reasons for the increases.

Several of these factors are unlikely to contribute substantially to increasing bronchiolitis hospitalization rates. Although RSV strains vary in virulence and strain differences may account for variation in the severity of RSV outbreaks, documented RSV strain circulation patterns do not suggest that increasing strain virulence is responsible for the national temporal trends we found. A predominant national RSV outbreak strain or strains have not been documented. Instead, the pattern of outbreak strains vary.
bronchiolitis hospitalization rates. This study has several limitations. First, NHDS-based hospitalization estimates are generated by using a complex, nationally representative sample of discharges, which in 1996 were amassed from 480 responding hospitals.21 Thus, the weighted estimates have more variability than might be expected from the magnitude of the numbers presented. We have presented SEs where appropriate so that this variability can be assessed. Second, the NHDS does not include hospitalizations occurring in federal facilities providing pediatric care, particularly Indian Health Service hospitals—and the highest US hospitalization rate for RSV disease ever reported was among Alaska Native infants in the southwestern part of the state (100/1000).46 Third, data that may relate to socioeconomic status, such as race/ethnicity and insurance coverage, are incompletely recorded in NHDS records, precluding examination of these factors. Infants born to low-income urban families have increased admission rates for acute lower respiratory tract disease compared with those born to middle-income families.31-34 Socioeconomic factors need to be examined in relation to temporal trends in bronchiolitis hospitalizations. Finally, lack of a specific ICD-9-CM code for RSV-associated disease forced us to use a proportion of bronchiolitis hospitalizations occurring from November through April as the primary proxy for RSV-associated hospitalizations. We believe this approach is reasonable. Many studies have documented that RSV is responsible for the majority of winter bronchiolitis hospitalizations.6-13 and annual RSV detections in the National Respiratory and Enteric Virus Surveillance System correlate closely with annual peaks of bronchiolitis hospitalizations in NHDS data (CDC unpublished data, 1990-1996).22-23 In those years with a particularly prominent mid-winter peak in bronchiolitis hospitalizations, it is likely that a greater proportion of bronchiolitis hospitalizations are associated with RSV infection; however, we were not
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able to document this possibility, as no virologic data were abstracted for NHDS records.

In summary, nationally representative data suggest that the current number of RSV-associated bronchiolitis and pneu-
monia hospitalizations among infants is approximately 1.5 to 2 times greater than previously estimated. From 1980 through
1996, bronchiolitis hospitalization rates and the proportion of hospitalizations associated with bronchiolitis increased
substantially among infants. Finally, despite the availability of prophylactic antibody preparations to reduce RSV-associated
hospitalizations among children with conditions placing them at high risk for serious disease,13,16 the majority of US in-
fants hospitalized with bronchiolitis are not concurrently diagnosed with prematurity or underlying lung disease. A safe
and effective RSV vaccine is needed to reduce bronchiolitis hospitalizations.

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