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Respiratory Syncytial Virus Infection in Navajo and White Mountain Apache Children

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ABSTRACT. *Objective.* **The hospitalization rate for bronchiolitis of any cause among US children younger than 1 year is estimated at 31.2 per 1000. No data exist on respiratory syncytial virus (RSV)-specific hospitalization rates among high-risk Native Americans other than Alaska Natives, for whom the incidence of RSV hospitalization was estimated at 150 per 1000 among infants younger than 1 year. We aimed to estimate RSV hospitalization rates among Navajo and White Mountain Apache children younger than 2 years.**

Methods. **We conducted prospective population-level hospital-based surveillance to determine RSV hospitalization rates among Navajo and White Mountain Apache children younger than 2 years. From 1997 to 2000, all children who were admitted for acute lower respiratory tract infection between October 1 and March 31 had a nasopharyngeal aspirate obtained and tested for RSV by commercial enzyme immunoassay kits. We reviewed charts of children who tested positive for RSV antigen to determine disease severity.**

Results. **During 3 RSV seasons (1997–2000), 51.3% of 1837 admissions for acute lower respiratory tract infection among children younger than 2 years were attributed to RSV infection. The overall seasonal RSV hospitalization rate among children younger than 2 years was 63.6 per 1000 and 91.3 per 1000 among children younger than 1 year. In a univariate analysis, predictors of severity included age <6 months (relative risk: 6.8; 95% confidence interval: 3.1–17.0).**

Conclusions. **Navajo and White Mountain Apache children are at high risk for RSV disease requiring hospitalization. A lower threshold for hospitalization or underlying chronic conditions that predispose to severe RSV disease do not seem to explain high RSV hospitalization rates in this population.** *Pediatrics* **2002;110(2). URL: http://www.pediatrics.org/cgi/content/full/110/2/e20;** *respiratory syncytial virus, American Indian, hospitalization, lower respiratory tract infection, bronchiolitis, surveillance.*

R espiratory syncytial virus (RSV) is a leading cause of lower respiratory tract disease and hospitalization among young children throughout the world.[1,2] The rates of hospitalization for bronchiolitis of any cause among US children younger than 1 year are estimated to be between 31 and 41 per 1000 children by studies of *International Classification of Diseases, Ninth Revision* discharge codes.[3,4] During the past 2 decades, RSV attributable hospitalization rates among young US children have increased from 12.9 per 1000 to 31.2 per 1000.[3] Known risk factors for serious RSV infection include congenital heart disease (CHD), chronic lung disease of prematurity (CLD), prematurity, immunodeficiency, male gender, crowding, passive smoke exposure, lack of breastfeeding,[4,5–14] and low titers of passively acquired RSV-neutralizing antibody.[8]

American Indian and Alaska Natives have been documented to have higher rates of various infectious diseases (eg, *Haemophilus influenzae, Streptococcus pneumoniae,* and hepatitis A) compared with the general US population.[15–18] These populations also have high rates of mortality and morbidity from acute lower respiratory tract infections (ALRIs). However, the data on which the latter characterization is based are limited. In 1994 to 1996, 4% of all infant deaths among American Indians and Alaska Natives were caused by pneumonia and influenza compared with only 1% of infant deaths in the general US population.[19] In addition, a retrospective analysis of United States Indian Health Service (IHS) discharge records revealed that the Navajo Area had the highest hospitalization rate for bronchiolitis (estimated to be 96.3 per 1000 among children younger than 1 year[6]) among American Indians and Alaska Natives. Alaska Natives have documented rates of RSV-specific hospitalization of 150 per 1000 among children younger than 1 year; these rates are 4 to 5 times those of the general US population.[5,20]

We sought to assess accurately the burden of RSV disease among the Navajo and White Mountain Apache children who live on these reservations. The Navajo Nation is the largest reservation in the United States and is located in the Four Corners area of the American Southwest. The White Mountain Apache reservation, also located in Arizona, is smaller. To our knowledge, there are no reports of RSV-specific hospitalization rates on Navajo and White Mountain Apache reservations. In addition, the severity of RSV

infection has not been previously described in this population. Recent progress in the development of RSV vaccines and the availability of an RSV monoclonal antibody warrant estimating the burden of RSV disease in this potentially high-risk population.

METHODS

Study Site

This study was conducted on the Navajo and White Mountain Apache reservations. The IHS, an agency of the US Department of Health and Human Services, administers health care on the reservations. Because this health care is provided to tribal members without charge to them individually, the vast majority of tribal members receive both inpatient and outpatient care at IHS facilities. The White Mountain Apache reservation has a single IHS hospital and the Navajo reservation has 5 IHS hospitals that provide inpatient services. The current study was conducted at 3 of the 5 Navajo hospitals and at the White Mountain Apache hospital.

Surveillance

We conducted prospective, hospital-based surveillance among children who were younger than 2 years and admitted for respiratory symptoms or apnea between October 1 and March 31 of 1997 through 2000. Nasopharyngeal (NP) aspirates were collected from all children who were hospitalized with an ALRI or apnea at the 4 participating hospitals. Study personnel were available to collect aspirates from 9 to 5, Monday through Friday. Nasal aspirates collected within 72 hours before and after the admission date were used to indicate the RSV status of the child at admission. Children who were hospitalized for ALRI on weekends and holidays had an NP aspirate tested on the next business day when they were still hospitalized.

Ethics

This study was approved by the institutional review boards of the Johns Hopkins University, the Navajo Nation, the Phoenix Area IHS, the National IHS, and the White Mountain Apache Tribe. Written informed consent was obtained from parents for collection and testing of NP aspirate and chart review of those children who were found to be infected with RSV.

Laboratory Methods

NP aspirates were tested within 2 hours of collection using commercial RSV-specific enzyme immunoassay kits. NP aspirates collected between October 1997 and March 1999 were tested using the Abbot EIA Test Pack (Abbott, Oak Park, IL). This kit was not commercially available during the 1999 to 2000 season; therefore, the Directigen kit (Becton-Dickinson, Franklin Lakes, NJ) was used instead.

Assessment of Disease Severity

We reviewed the charts of children whose NP aspirates were positive for RSV antigen to collect information on severity of infection, demographics, and underlying chronic conditions. To avoid a subjective assessment of disease severity, we used a previously published severity index.[21] According to this index, 1 point each was assigned for apnea, pH <7.35, Pco_2 >45, Sao_2 <87%, and length of stay >5 days, and 2 points were assigned for mechanical ventilation. The severity index for each subject was the sum of the points (the total possible score was 7). A score of ≥3 was categorized as severe disease.[21] Underlying condition was defined as the presence of 1 of the following: CHD, CLD of prematurity, reactive airway disease, 2 or more previous hospitalizations for respiratory infection, history of mechanical ventilation, or immunodeficiency. Prematurity was defined as gestational age <36 weeks. Disease severity was compared with that of children who were younger than 2 years and admitted to the Johns Hopkins Hospital (JHH; Baltimore, MD) between October 1, 1993, and September 30, 1996. These data were generated from a reanalysis of a previously published study in which the surveillance methods are described.[20]

Hospitalization Rates

Hospitalization rates per 1000 children were calculated using denominators derived from annual births reported by IHS facilities under surveillance. There were 6833 births from 1997 through 1999 at the 4 IHS sites at which RSV surveillance was conducted. For purposes of the study, births were assumed to be evenly distributed throughout the year. Only the first admission for RSV infection for each child was used for rates calculations.

Statistical Analysis

We categorized RSV disease episodes as severe (score >3) or nonsevere (score <3). Potential predictors of severe disease included prematurity, underlying chronic conditions, gender, and age. Infants who had an underlying condition were analyzed separately from premature infants. Demographic factors analyzed included gender and age at time of hospitalization (<1 month, followed by 2 months age interval categories).

Simple and multivariate logistic regression analyses were used to examine the risk factors for disease severity while controlling for other potential confounders. Crude and adjusted odds ratios (ORs) are reported. The colinearity of the covariates was assessed by using variance inflation factors fitting the child's medical record number as the response variable. Pearson's goodness-of-fit test was used to check the fit of the logistic model. Stata7.0 (Stata Corp, College Station, TX) software program was used to perform statistical computing.

RESULTS

Disease Rates

During 3 RSV seasons, 1997 to 2000, there were 1837 admissions for ALRI among children younger than 2 years at the Navajo and White Mountain Apache Service Units under surveillance; of these, 1322 were among those younger than 1 year. Overall, 913 (49.7%) and 642 (48.6%) ALRI hospitalizations were attributed to RSV infection among all those younger than 2 years and those younger than 1 year, respectively. A small proportion of admissions attributed to RSV were among children who had previously been admitted for RSV-associated ALRI, 4.8% (44) and 2.8% (18), among those younger than 2 years and younger than 1 year, respectively. The average seasonal RSV-associated hospitalization rate was 63.6 per 1000 and 91.0 per 1000 among those younger than 2 years and those younger than 1 year, respectively. The average seasonal RSV-associated hospitalization rate for White Mountain Apache children younger than 1 year was at least twice the rate for Navajo children, 164.3 per 1000 and 78.1 per 1000, respectively. Hospitalization rates among children younger than 2 years showed a similar trend, 164.3 per 1000 and 78.1 per 1000 for White Mountain Apache and Navajo children, respectively. Gender was not reported for 78 (4.2%) of all hospitalized children. Among those for whom gender information was collected, girls younger than 2 years had higher rates of RSV hospitalization when compared with boys (66 vs 51 per 1000 respectively; relative risk: 1.1; 95% confidence interval: 1.0–1.3), although boys had more severe disease. Age-specific hospitalization rates for RSV infection by season are shown in Fig 1. The highest documented rate of RSV-associated hospitalization was 159.9 per 1000 among children younger than 6 months during the 1999 to 2000 season. Approximately 35% (302 of 869) of RSV-associated hospitalizations occurred among 6- to 12-month-old Navajo and White Mountain Apache infants.

Fig 1. RSV-associated seasonal hospitalization rates by age and calendar year among Navajo and White Mountain Apache children younger than 2 years, 1997 to 2000. ■, 1997 to 1998 season; □, 1998 to 1999 season; ▨, 1999 to 2000 season.
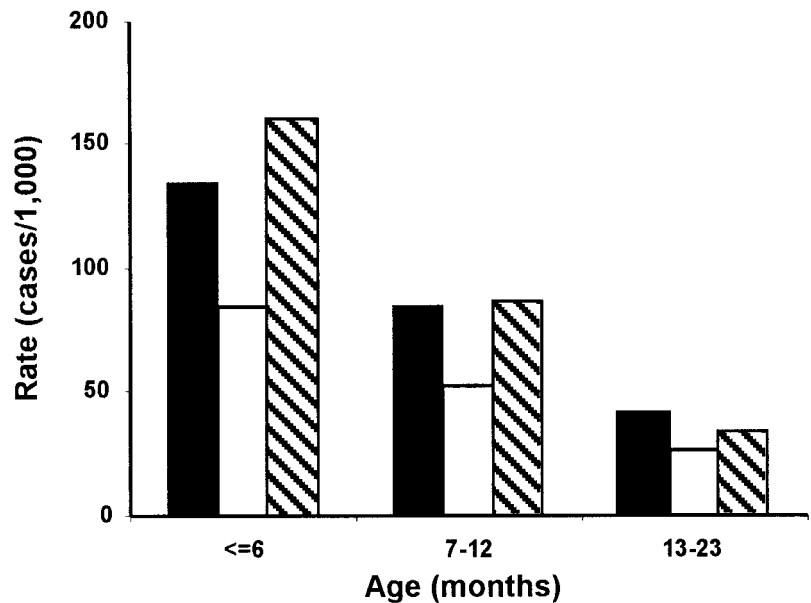
Severity of Disease

Of the 913 RSV-associated hospitalizations among children younger than 2 years, 876 (96%) had chart reviews completed for assessment of disease severity and the presence of underlying conditions. Of these, 4% had arterial blood gas results and 99% had oxygen saturation results documented. Only a small number of children were born prematurely or had recognized underlying conditions (prematurity [63 (7%)], CLD [3 (0%)], CHD [11 (1%)], reactive airway disease or 2 or more previous hospitalizations for respiratory infection [49 (6%)]). Of the 876 admissions that had a chart review completed, 23 required ventilatory support. The duration of hospital stay for the 876 children ranged from 0 to 31 days, with a mean of 4.1 days (95% confidence interval: 3.8–4.3) and a median of 3 days. The mortality rate from RSV infection was low at 0.1% (1 of 876).

Figure 2 shows the percentages of hospitalized children who were between 0 and 24 months of age and developed severe RSV disease, stratified into 2-month intervals. Severe RSV disease occurred most frequently in very young infants: hospitalized infants younger than 1 month were at least 5 times more likely to develop severe RSV disease than those 5 to 6 months of age. Overall, severe disease was documented among 45 (5%) children; of those, 82% (37 of 45) were younger than 6 months.

Risk Factors for Severe Disease

The crude and adjusted ORs for severe RSV disease are summarized in Table 1. Age younger than 6 months, prematurity, and male gender conferred elevated ORs for severe disease, although only age younger than 6 months reached statistical significance. Crude and adjusted ORs gave similar point estimates for each explanatory variable. The possibility of effect modification among gender, prematurity, and underlying condition was explored by using interaction terms. However, no statistically significant effect was observed (data not shown).

To evaluate whether elevated rates of RSV hospitalization were attributable to a low threshold for admission, we compared the proportion of Navajo and White Mountain Apache children with various disease severity measures with those from children who were younger than 2 years and admitted to JHH (Table 2). The JHH data represent a reanalysis of data

Fig 2. Percentage of Navajo and White Mountain Apache children who were hospitalized for RSV infection and had severe disease during 1997 to 2000, by age.
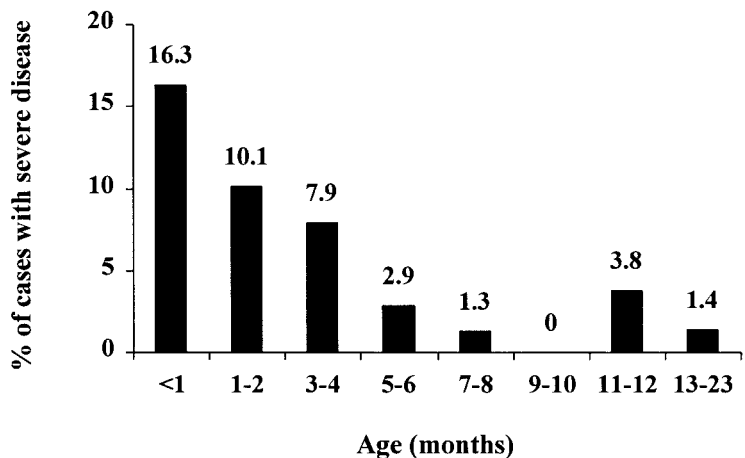
TABLE 1. Risk Factors for Severe RSV Disease Among Navajo and Apache Children Younger Than 2 Years Hospitalized for RSV Infection, 1997 to 2000

Risk Factor	Severe Disease		Crude OR (95% CI)	Adjusted OR (95% CI)
	Yes	No		
All infants	45	831	Reference	Reference
Age <6 mo	37	337	6.8 (3.1–17.0)	6.6 (3.0–14.4)
Prematurity	5	58	1.7 (0.5–4.5)	1.8 (0.7–5.1)
Underlying condition*	1	62	0.3 (0.0–1.7)	0.5 (0.1–3.5)
Male gender	25	418	1.2 (0.6–2.3)	1.2 (0.6–2.2)

CI indicates confidence interval.
* Underlying condition was defined as having at least 1 of the following: CHD, CLD of prematurity, reactive airway disease, 2 or more previous hospitalizations for respiratory infection, history of mechanical ventilation, or immunodeficiency.

TABLE 2. Severity of RSV Disease in Non–High-Risk Children Younger Than 2 Years

	N/WMA (N [%])	JHH (N [%])
All admissions	813	192
Median severity index	1	0
Median low O_2	85	91
Sao$_2$<87%	576 (71)*	26 (14)
Patients receiving assisted ventilation	22 (3)*	16 (8)
Age <2 mo	148 (18)†	67 (35)
Length of stay >5 d	189 (23)^{NS}	51 (27)

N/WMA indicates Navajo/White Mountain Apache; SaO$_2$, oxygen saturation; NS, not statistically significant. Non–high-risk children had no underlying condition that might predispose to severe RSV disease (as defined in the text and Table 1) and were not premature (<36 weeks' gestation). Data from JHH was previously published[20] and was reanalyzed to exclude children younger than 24 months.
* $P < .0001$, χ^2 test.
† $P < .0000$, χ^2 test.

previously published.[20] Although fewer Navajo and White Mountain Apache children required ventilation (3% vs 8%), a much larger proportion was hypoxemic (71% vs 14%) and a similar proportion had prolonged hospitalization (23% vs 27%).

DISCUSSION

Of all bronchiolitis cases, approximately 50% to 80% are attributable to RSV.[13] We report the age-adjusted RSV-specific hospitalization rates among Navajo and White Mountain Apache children younger than 1 year of 91.3 per 1000, which is 3 times the rates reported for similarly aged children in the general US population[3] and more than twice the rate of inner-city Medicaid children (40.8/1000).[4] Between 1989 and 1993, the RSV-specific hospitalization rate for US Medicaid children who were younger than 1 year and considered to be at high risk for severe RSV disease was 388 per 1000 for those with CLD, 92 per 1000 for those with CHD, and 70 per 1000 for those born at <28 weeks' gestation.[4] Thus, the RSV hospitalization rates for Navajo and White Mountain Apache children are in the range of the RSV hospitalization rates for similarly aged high-risk US children. In addition, we compared severity indices in Navajo and White Mountain Apache children who were not at high risk of severe disease with reanalyzed published data from similarly aged children who were not at high risk and were admitted for RSV infection at JHH.[20] That comparison sug-

gests that a lower threshold for hospitalization does not explain high RSV-specific hospitalization rates on the Navajo and White Mountain Apache reservations.

Our data provide RSV-specific disease burden data among the Navajo and White Mountain Apache infants and toddlers regardless of the final discharge diagnosis. Most of the previously reported estimates of RSV disease are based on the diagnosis of bronchiolitis. However, approximately 50% to 90% of bronchiolitis among hospitalized children is attributable to RSV, and approximately 5% to 40% of RSV is not coded as bronchiolitis.[22] Hence, a discharge diagnosis of bronchiolitis may not be sufficiently sensitive or specific to ascertain true hospitalization rates for RSV disease. Lowther et al[6] reported all-cause bronchiolitis-associated infant hospitalization rates on the Navajo reservation of 96.3 per 1000 between January 1, 1990, and December 31, 1995. The reasons for higher RSV-associated hospitalization rates in our study when compared with this previous report are several-fold. First, we included all clinical syndromes known to be caused by RSV. Second, during the last 2 decades, a 2.4-fold increase of bronchiolitis hospitalizations among US children younger than 1 year was documented.[3] It is possible that RSV hospitalization rates have continued to rise on Navajo and White Mountain Apache reservations during the 5 to 6 years between the earlier study and this study. Therefore, both the prospective, pathogen-specific surveillance conducted in this population and increased RSV hospitalization rates in recent years may have contributed to the higher RSV hospitalization rates among Navajo and White Mountain Apache children documented in this study.

The overwhelming majority of Navajo and White Mountain Apache children hospitalized with RSV were healthy children born at term: only 14% had recognized underlying risk factors for severe RSV disease (Table 1). By contrast, a recent study of RSV-specific hospitalizations among the general US population younger than 3 years, 27% of children had a chronic condition that predisposed them to severe RSV disease.[4] This finding is perhaps not surprising, because the rates of premature births and associated complications are lower in the Navajo than in the general US population: 5.8% versus 7.3%.[19] In addition, during the time this study was conducted, palivizumab was in general use among premature

Navajo and White Mountain Apache infants in accordance with the recommendations of the American Academy of Pediatrics.[23] The data from the JHH admissions were collected at a time when neither palivizumab nor hyperimmune RSV immunoglobulin was in use. The findings from this study, like those of others, indicate that young age is an important risk factor for hospitalization as a result of RSV.[4–5,8,10,19,20]

This study had limitations. First, comparison of disease severity with another population was done using historical data. Second, NP aspirates were not collected on weekends and holidays. Although we tested all children who were hospitalized for ALRI on weekends and holidays on the next business day, we may have missed children who had short hospital stays; this would have led to an underestimation of the RSV hospitalization rate. We believe that the proportion of children who were hospitalized for ALRI and not tested is small because only 15% (129 of 876) of children in our study had a length of hospitalization <2 days. In addition, RSV hospitalizations were evenly distributed throughout the week; therefore, only 4% of children would be expected to be admitted on the weekend and be discharged before Monday (data not shown). Finally, RSV infection was detected by rapid antigen testing only, which could lead to either an underestimation or an overestimation of rates of infection, depending on the percentage of false-negative or false-positive results. The assays used in this study are reported to have sensitivity and specificity of 91% and 83%, respectively, for the Abbott RSV ELISA test and 93% to 97% and 90% to 99%, respectively, for the Directigen RSV ELISA assay. It is therefore possible that children with RSV infection were missed using antigen detection (false-negatives) and that children without true RSV infection were erroneously included (false-positives). However, the reported sensitivities and specificities suggest that it is unlikely that the use of these assays would lead to an overestimation of the rates of hospitalization for RSV disease.

The reasons for the high RSV hospitalization rates in the Navajo and White Mountain Apache population are unknown but are most likely to be multifactorial. High RSV hospitalization rates have been associated with low socioeconomic status,[8] environmental smoke exposure through wood- or coal-burning stoves,[13,14] crowding,[10,24] and a lack of breastfeeding.[25] American Indians constitute one of the poorest US populations: 46.8% of the Navajo Nation families have incomes below the poverty level, which is 3.6 times higher than the US population as a whole.[19] In addition, approximately 50% to 60% of homes have wood/coal-burning stoves. Therefore, low socioeconomic status and environmental smoke exposure could contribute to high RSV hospitalization rates in this population. In contrast, breastfeeding rates are high on Navajo and White Mountain Apache reservations. Fifty-one percent of 4- to 6-month-old Navajo infants were breastfed, compared with 29% of similarly aged US infants[26] (Dr Chris Percy, personal communication, March 21, 2001). Therefore, the high RSV-associated hospital-

ization rates are not explained by low rates of breastfeeding.

White Mountain Apache children were hospitalized for RSV disease nearly twice as often as Navajo children. The reasons for this are unknown. However, the households of White Mountain Apache families tend to be closer to each other and the families migrate less often than do Navajo families. The Navajo children live in sparsely populated areas, where the family compounds might be many miles away from each other and therefore less prone to rapid transmission of RSV.

A recent case-control study among young Finnish children indicated an association between the surfactant protein A (SP-A) 2 allele and severe RSV infection.[27] Although no data are available on the SP-A allelic distribution frequencies in the Navajo and White Mountain Apache populations, it is possible that this or other genetic characteristics play a role in the observed high rates of RSV disease. Future studies of risk factors for severe RSV disease could include evaluation of potential social, environmental, and genetic risk factors in this population at high risk for RSV hospitalization in early childhood.

CONCLUSION

Navajo and White Mountain Apache children have rates of RSV hospitalization 3 times those of the general US population. Only 14% of those hospitalized had conventional risk factors for severe RSV disease. We conclude that Navajo and White Mountain Apache children are at high risk of severe RSV infection and that effective preventive interventions are needed. Interventions that are effective at preventing disease in the first 6 months of life are most urgently needed because 82% of the children with severe disease were in this age group. However, to achieve maximum impact on RSV hospitalization in this highly susceptible population, a strategy that protects infants beyond 6 months of age will also be needed because half of the hospitalizations occurred in children who were older than 6 months.

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