Severe Respiratory Syncytial Virus Disease in Alaska Native Children

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Hospitalization rates for respiratory syncytial virus (RSV) infection range from 1 to 20/1000 infants. To determine the rate and severity of RSV infections requiring hospitalization for infants in the Yukon-Kuskokwim (YK) Delta of Alaska, a 3-year prospective surveillance study was conducted. The annual rate of RSV hospitalization for YK Delta infants <1 year of age was 53–249/1000. RSV infection was the most frequent cause of infant hospitalization. RSV disease severity did not differ among non–high-risk infants in the YK Delta and at Johns Hopkins Hospital (JHH). On average, 1/125 infants born in the YK Delta required mechanical ventilation for RSV infection. During the peak season, ~$1034/child <3 years of age was spent on RSV hospitalization in the YK Delta. In YK Delta infants <6 months old, RSV micro-neutralizing antibody titers <1200 were associated with severe disease (odds ratio = 6.2, \( P = .03 \)). In the YK Delta and at JHH, newborns may be at greater risk for severe RSV illness than previously thought.

Respiratory syncytial virus (RSV) is the most important cause of viral lower respiratory tract disease in infants and children worldwide [1] and accounts for ~91,000 hospitalizations and 5000 deaths in US children each year [2]. Reported hospitalization rates for RSV illness in developed countries range from 1 to 20 cases per 1000 infants <1 year of age [3–6].

Native children living in Arctic regions may be at particularly high risk for serious RSV disease. More than 25 years ago, respiratory infections were the most important cause of morbidity and mortality in native infants in southwestern Alaska [7]. RSV and influenza virus infections were associated with 75% of wintertime acute respiratory illness (ARI) in these children [8]. More recently, a report describing risk factors and outcomes in patients hospitalized with RSV in 7 Canadian medical centers showed that native children had more severe disease than nonnative children, although referral bias could not be excluded as a contributing factor [9].

A retrospective review of hospitalizations from 1991 to 1993 suggested that native infants from rural villages in the Yukon Kuskokwim (YK) Delta of southwestern Alaska had an unusually high rate of hospitalization for RSV infection (100/1000 infants), with a lower rate (33/1000) in an urban Alaska Native population [10]. Although this report [10] provided new information about RSV hospitalizations in YK Delta children, several issues were not addressed. First, the rate of RSV hospitalization may have been underestimated because specimens for RSV testing were not always obtained for children hospitalized with ARI. Second, the severity of the RSV-associated illness was not quantified. Since RSV infects nearly all children by age 2 years [11], it is possible that the high rates of hospitalization reflected a tendency to admit children with relatively mild illness rather than an increased incidence of severe disease. Finally, the impact of predisposing factors (high-risk conditions and level of maternally derived RSV neutralizing antibody) on disease severity was not assessed.

To address these issues, we conducted a 3-year prospective study to determine the incidence, age distribution, seasonality, and severity of RSV infections requiring hospitalization of Alaska Native children from the YK Delta and to assess the
effect of preexisting high-risk conditions and levels of cord RSV neutralizing antibody on disease severity. As a basis for comparison of disease severity, we reviewed hospitalizations for RSV disease at Johns Hopkins Hospital (JHH) during the same 3-year period.

Methods

Study population. The YK Delta encompasses 194,250 km² of coastal wetlands, tundra, and mountains (figure 1). A predominantly Yupik Eskimo population (~19,800) lives in the regional center, Bethel (population ~5000; figure 1), and in 52 Eskimo and Indian villages (populations ~200–1000) along the Yukon and Kuskokwim rivers and their tributaries. There are no roads between most villages, which are accessible only by small aircraft, snowmobile, or river boat. Because permafrost covers much of this region, indoor plumbing is only available in 30% of village homes. For purposes of describing the RSV epidemic, we divided the YK Delta into 10 subregions (figure 1) based on proximity and air taxi routes.

The Alaska Native population has increased by 55% in the past 20 years. Excluding Bethel, 48% of the population is <20 years of age. Few persons have graduated from high school, and unemployment exceeds 80%–90% in the villages. More than 60% of the families have incomes below the federal poverty line, and >40% receive Medicaid. Government jobs and subsistence or commercial fishing are the main sources of livelihood for those who are employed. Houses are small and underventilated.

The YK Delta Regional Hospital (YKDRH) in Bethel is a 50-bed general acute medical facility that provides inpatient care for the entire region. There are ~600 births annually in the YK Delta. Children are treated in village clinics by community health aides. All children requiring hospitalization are admitted to YKDRH but are transferred to one of three Anchorage hospitals (Alaska Native Medical Center [ANMC], Providence Alaska Medical Center [PAMC], or Columbia Alaska Regional Hospital [CARH]) if they are unstable, require intensive care, or if no pediatric beds are available at YKDRH.

Hospital-based surveillance. Alaska Native children from the YK Delta <3 years of age who were admitted with ARI to the YKDRH or to Anchorage hospitals between 1 October 1993 and 30 September 1996 were eligible for participation. Each subject had a nasopharyngeal aspirate (NPA) obtained for virus isolation and antigen studies. The NPA was immediately inoculated into transport medium and transported on ice to the hospital laboratory. NPAs were available for rapid antigen testing from 90% and for culture from 73% of children admitted with ARI. Cord blood from YK Delta newborns whose mothers gave consent was separated and frozen for future analysis.

Nosocomial RSV cases were defined as those occurring in children admitted with nonrespiratory disease or in those who were RSV-negative on admission but had a positive RSV test >7 days after admission or who were readmitted with an RSV infection <7 days after discharge for a non-RSV admission. Nosocomial cases were not included in the calculations of admission rates for RSV infection.

Assessment of the severity of respiratory illness. Patient hospitalization data were collected on a standardized form by chart review of all hospitalizations of YK Delta children <3 years of age. Disease severity was assessed for all patients hospitalized with ARI by use of an index developed to assess the relative severity of disease caused by RSV groups A and B [12, 13]. As in previous studies, severe disease was defined as an index ≥3 [13]. International Classification of Diseases (9th revision [ICD-9]) codes of discharge diagnoses were also collected. RSV-infected children were classified as having pneumonia if ICD-9 codes 480.1, 480.9, 485, or 486

Figure 1. Yukon-Kuskokwim Delta region (inset, location in southwestern Alaska). Region was divided into 10 subregions: A–I; regional center, Bethel (subregion Z).
appeared on their discharge summaries. All chest radiographs obtained in Alaska were evaluated by the same radiologist.

To determine whether YK Delta children hospitalized with RSV had less severe disease than children hospitalized elsewhere, we compared the severity of RSV disease in hospitalized YK Delta children to that in children hospitalized at JHH. We reviewed all available charts for children <3 years of age hospitalized at JHH with RSV disease between 1 October 1993 and 30 September 1996. Information regarding age, underlying conditions, disease severity, and discharge diagnoses were collected by use of the same standardized form. Since NPAs from children admitted to JHH with ARI between 1 October and 1 May are routinely tested for RSV by direct fluorescent antibody assay (DFA) (Imagen; Dako Diagnostics, Ely, UK) and culture, it was unlikely that RSV infection was underdiagnosed. Charts were available for 83% of the children hospitalized with RSV at JHH during this period.

At both institutions, we defined as high risk those children who were premature (<36 weeks gestation), had chronic lung disease (bronchopulmonary dysplasia, congenital anomaly, or cystic fibrosis), heart disease, immunodeficiency, or other chronic systemic conditions (e.g., neurologic impairment with gastrostomy feeding) that predispose to respiratory compromise.

Laboratory methods. Each NPA obtained in Alaska was tested for RSV by rapid antigen EIA test pack (Abbott, Oak Park, IL) or by DFA (Bartels, Issaquah, WA). The rest of each sample was snap frozen and transported on dry ice to a virology laboratory (R.A.K.), where it was inoculated onto HEp-2, Vero, and Rhesus monkey kidney cells for culture. Virus isolates (RSV, parainfluenza viruses 1, 2, and 3, influenza A and B, and adenovirus) were identified by an indirect immunofluorescence assay (Bartels). RSV culture-negative specimens were retested by rapid EIA test (Abbott testpack or Kallestad Laboratories, Austin, TX). On the basis of virus culture and antigen testing results, RSV cases were classified as definite (culture-proven or test-positive by 2 different rapid antigen assays), probable (test-positive by the same rapid antigen assay twice in different laboratories), or possible (test-positive by 1 antigen test). RSV isolates were typed as group A or B by plaque assay [14] using monoclonal antibodies 92-11C and 102-10B (provided by Larry Anderson, CDC, Atlanta). Cord sera were tested for RSV neutralizing antibody by microneutralization assay as previously described [15].

Cost analysis. Economic costs associated with hospitalization for RSV disease during the 1994–1995 season were estimated on the basis of hospital bed costs and transport costs from Bethel to Anchorage for children requiring hospitalization in Anchorage. Hospital charges were based on the 1997 Medicaid reimbursement rate of $963 per day for children admitted to ANMC, CARH, and YKDRH and $2500 per day for children admitted to the PAMC Pediatric Intensive Care Unit. For children transported from Bethel to Anchorage by air ambulance, cost estimates were calculated from the average fee-for-service charged to the Indian Health Service according to the child’s age. For children transported by commercial air carriers, we estimated a cost of $1000 per child for transport of the child, one parent, and a health care provider, using average costs based on published air fares.

To approximate costs incurred for RSV hospitalization in the YK Delta region and throughout the United States, we used the most recent available RSV hospitalization cost data (from 1984 [6]). To estimate costs per child <3 years of age, we divided this total cost by the population <3 years of age in 1984 [6, 16]. Since hospitalization cost data for children <5 years of age were attributed only to children <3 years of age, the cost per child may be slightly overestimated.

Statistical analysis. We used the x² test to compare proportions and the Mann-Whitney U test to compare severity indices. Multiple logistic regression analysis was used to examine the effect of neutralizing antibody level on severity of disease while controlling for other potentially confounding factors. We categorized infants as having severe RSV disease (score ≥3) or less severe disease (score <3) [12, 13]. We also dichotomized age at diagnosis (≥2 vs. <2 months), microneutralizing antibody level in cord serum (≥1200 vs. <1200 meganunits/mL), and high-risk versus non-high-risk status. Odds ratios (ORs) reported are those resulting from simultaneous fitting of these factors. The microneutralizing antibody level of 1200 was chosen as the round number closest to the median value (1156) for our specimens; this is also near the level associated with protection against RSV lower respiratory tract infection in cotton rats [15]. We restricted our analysis to infants ≥6 months of age, because maternally derived antibody would be unlikely to afford significant protection to older infants. We did not include readmissions in our analysis.

Multiple logistic regression analysis was also used to assess the relative importance of age at initial admission, severity of disease during initial admission, and receipt of ribavirin during initial admission in predicting which Alaska Native infants were readmitted with RSV after their initial RSV admission during the study period. Steroid use was not included in this model because there was no significant difference in its use in readmitted and nonreadmitted children. Severity of disease was examined both on the original scale (0–7) and dichotomized as <3 versus ≥3. Age at admission was examined both by category (grouped as 0–2, 3–5, 6–11, 12–23, and 24–35 months and assigned scores of 1–5) and also dichotomized into the youngest children (<1 month at initial episode) versus all other infants (2–35 months at initial episode).

Results

Seasonality of RSV in the YK Delta. During the 3-year study, RSV epidemics occurred yearly during the winter months, with peak hospitalizations for RSV disease occurring between November and February. However, sporadic cases were detected in every month of the year, and a bimodal distribution occurred during two seasons. Although each YK Delta–wide RSV epidemic lasted 3–5 months (see figure 2A for 1994–1995), epidemics within subregions were brief, and most hospitalizations for RSV infection occurred during a single month (figure 2B). In the 1994–1995 season, the epidemic began in October in villages on the lower Kuskokwim River (subregion E [figures 1, 2B]), spread west to lower coastal villages and to Bethel in November (subregions I and Z [subregion Z, figure 2B]), and peaked in the southernmost villages and upper coastal villages in December (subregions G, A, and B; subregion B [figure 2B]). Few hospitalizations for RSV disease oc-
Figure 2. Hospitalizations of Yukon-Kuskokwim Delta children with respiratory syncytial virus (RSV) disease during 1994–1995 RSV season. A, Cases throughout region. B, Cases in 3 subregions (locations shown in figure 1).


Incidence of RSV hospitalization, characteristics of hospitalized population, and disease severity: Between 1 October 1993 and 30 September 1996, 431 YK Delta children <3 years of age were hospitalized for RSV illness (table 1). These represented 31% of all hospitalizations (1386) and 46% of ARI hospitalizations (940) for this population of children. In all, 140 (33%) of the YK Delta children admitted for RSV infection were transported to Anchorage hospitals: 47 (44%) because of patient condition and 93 (56%) because of lack of bed space at YKDRH. Of the 431 RSV hospitalizations, 74% were definite, 5% were probable, and 21% were possible as previously defined.

The majority of children from the YK Delta region hospitalized with RSV were <1 year of age. The rate of hospitalization for RSV infections for infants <1 year of age ranged from 53/1000 in the 1993–1994 season to 249/1000 during the 1994–1995 season (table 1; data do not include readmissions). During this study, RSV infection was the single most frequent cause of hospitalization for infants in the YK Delta.

In the YK Delta region and at JHH, neonates accounted for a substantial proportion of those hospitalized with RSV, and 9% and 8% of those hospitalized at YKDRH and JHH, re-

Table 1. Hospitalizations for respiratory syncytial virus (RSV) infection in the Yukon-Kuskokwim (YK) Delta, 1993–1996.

<table>
<thead>
<tr>
<th>Category</th>
<th>10/93–9/94</th>
<th>10/94–9/95</th>
<th>10/95–9/96</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>All admissions</td>
<td>364</td>
<td>563</td>
<td>459</td>
<td>1386</td>
</tr>
<tr>
<td>Acute respiratory illness admissions</td>
<td>226</td>
<td>413</td>
<td>301</td>
<td>940</td>
</tr>
<tr>
<td>RSV admissions</td>
<td>41</td>
<td>246</td>
<td>144</td>
<td>431</td>
</tr>
<tr>
<td>RSV admissions, infants &lt;1 year*</td>
<td>32</td>
<td>152</td>
<td>95</td>
<td>279</td>
</tr>
<tr>
<td>Births in YK Delta</td>
<td>609</td>
<td>611</td>
<td>581</td>
<td>1801</td>
</tr>
<tr>
<td>RSV admissions/1000 infants &lt;1 year*</td>
<td>53</td>
<td>249</td>
<td>164</td>
<td>—</td>
</tr>
</tbody>
</table>

* Data do not include readmissions.
Figure 3. Respiratory syncytial virus (RSV) cases by age at Yukon-Kuskokwim Delta Regional Hospital (YKDRH), Alaska (A, C), and Johns Hopkins Hospital (JHH), Maryland (B, D), during 1994–1995 RSV season. A and B. Darkest areas of bars indicate cases in children without risk factors for severe RSV disease; gray areas indicate cases in children with underlying cardiac, respiratory, or systemic illnesses. C and D. Gray areas of bars indicate children with less severe disease (severity index [SI], <3); white areas indicate children with more severe disease (SI, ≥3). For ease of presentation, cases are grouped by age in months to 12 months and in 3-month intervals for ages 13–24 months. Data from children 3–24 months old are grouped as a single category.

respectively, were <1 month old. The majority of these neonates had no risk factors for severe RSV disease (figure 3A, 3B). Of 38 non–high-risk neonates hospitalized with RSV infection at YKDRH, 6 (16%) were apneic, 3 (8%) required mechanical ventilation, and 9 (24%) had severity scores ≥3. Of these infants, 13 (34%) had bronchiolitis and 14 (38%) had pneumonia listed as a primary or secondary discharge diagnosis. At JHH, 31 non–high-risk neonates were hospitalized with RSV infection: 9 (29%) were apneic, 6 (19%) required mechanical ventilation, and 10 (32%) had severity scores ≥3; 20 (64%) had bronchiolitis and 5 (16%) had pneumonia listed as a primary or secondary discharge diagnosis. At YKDRH, hospitalization of infants 3–7 months old also occurred frequently (figure 3A), accounting for 34% of all RSV admissions.

Of 127 RSV culture-positive specimens that were typeable, 109 were group A and 18 were group B isolates (data not shown). All the B isolates were obtained during the 1995–1996 RSV season from each of 10 villages in 7 subregions (data not shown). Other respiratory viruses isolated from children hospitalized with ARI during the study included influenza A or B viruses (17 isolates), adenoviruses (9 isolates), parainfluenza type 1 (12 isolates), and parainfluenza type 3 (13 isolates).

Readmission for RSV infection occurred frequently among YK Delta children. During the study, 65 (19%) of all children admitted with RSV infection were readmitted with RSV infection at least once. Fifteen of these children were readmitted within the same month, which probably represents exacerbation of the existing illness rather than reinfection, and 5 additional children were also infected with other respiratory viruses (influenza A, parainfluenza type 1, parainfluenza type 3, or adenovirus). Of the remaining 45 children (12% of all those admitted with RSV infection), 37 were admitted twice, and 8 were admitted three times. In these 45 children readmitted with RSV infection, illnesses were more severe during the first admission
than during subsequent admissions ($P = .01$). Only 1 of the 8 children with more than 2 admissions for RSV had an underlying high-risk condition. Thirty-one of these children were readmitted during the same RSV season, and 16 were readmitted during different seasons (2 children with multiple admissions were readmitted during both). NPAs from 16 of these 45 children were repeatedly RSV culture-positive, 11 within the same RSV season. All typeable specimens were RSV type A; unfortunately, we were unable to type sequential specimens from individual children.

Severity of disease, both on a linear and on a dichotomous scale, age at illness (grouped scale), and receipt of ribavirin were all significantly associated ($P < .05$) with readmission with a subsequent RSV infection. Both the original severity scores (OR = 1.31 for each point increase in severity, $P = .001$) and the dichotomized version (OR = 3.37, $P = .001$) showed generally similar results and were associated with the highest overall $\chi^2$ value. No significant improvement was observed when ribavirin use or age was included in the model. Thus, severity of disease during the initial RSV admission appeared to be the most important predictor of readmission for RSV disease among YK Delta children.

To determine the relative severity of RSV disease in children hospitalized at YKDRH, we compared their illnesses with those experienced by children hospitalized with RSV at JHH during the same 3-year period. Because many more children hospitalized at JHH had underlying conditions that predisposed them to severe RSV disease than did children at YKDRH (56% vs. 32%; figure 3A, 3B), we chose to compare only children without risk factors for severe RSV disease. No significant differences in median severity index, median low $O_2$, or percentages of children with $S_{O_2} < 87$, $P_{CO_2} > 45$, pH $< 7.35$, or severe RSV disease (index $\geq 3$) were observed between the two groups (table 2). Children hospitalized with RSV infection at YKDRH had pneumonia diagnosed more often and had longer hospital stays than children at JHH (both, $P < .0001$) but were less often apneic and required mechanical ventilation less frequently than children at JHH ($P = .001$ and .003, respectively). A single death attributable to RSV infection occurred in a YK Delta infant with tetralogy of Fallot. Ventilatory support for RSV was needed for 0.8% of the total YK Delta infant population $\leq$1 year of age during the 3 years of the study and for 1.8% of the total YK Delta infant population during the peak epidemic season (1994–1995).

**Table 2.** Disease severity in non-high-risk children admitted to Johns Hopkins Hospital (JHH) or Yukon-Kuskokwim Delta Regional Hospital (YKDRH) with respiratory syncytial virus (RSV) infection.

<table>
<thead>
<tr>
<th></th>
<th>JHH (No. [%])</th>
<th>YKDRH (No. [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td>All admissions</td>
<td>198</td>
<td>294</td>
</tr>
<tr>
<td>Pneumonia diagnosed</td>
<td>32 (16)$^b$</td>
<td>132 (45)$^b$</td>
</tr>
<tr>
<td>Median severity index</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Median low $O_2$</td>
<td>91</td>
<td>92</td>
</tr>
<tr>
<td>$S_{O_2} &lt; 87$</td>
<td>26 (13)</td>
<td>44 (15)</td>
</tr>
<tr>
<td>$P_{CO_2} &gt; 45$</td>
<td>28 (14)</td>
<td>37 (13)</td>
</tr>
<tr>
<td>pH $&lt; 7.35$</td>
<td>19 (10)</td>
<td>27 (9)</td>
</tr>
<tr>
<td>Apnea</td>
<td>19 (10)$^b$</td>
<td>8 (3)$^b$</td>
</tr>
<tr>
<td>Ventilated</td>
<td>16 (8)$^c$</td>
<td>8 (3)$^c$</td>
</tr>
<tr>
<td>Age &lt;2 months</td>
<td>67 (34)</td>
<td>76 (26)</td>
</tr>
<tr>
<td>Severity index $\geq$3</td>
<td>26 (13)</td>
<td>29 (10)</td>
</tr>
<tr>
<td>Length of stay $&gt;5$ days</td>
<td>55 (28)$^d$</td>
<td>142 (48)$^d$</td>
</tr>
</tbody>
</table>

NOTE. Severity of disease was compared in children without high-risk conditions (as described in Methods) admitted to JHH or YKDRH with documented RSV infection. Only first admissions for RSV infection were included in this analysis. $^a P < .0001$, $\chi^2$ test. $^b P = .001$, $\chi^2$ test. $^c P = .007$, $\chi^2$ test. $^d P < .0001$, $\chi^2$ test.

### Discussion

In this study, we found that Alaska Native infants in the YK Delta region are hospitalized for RSV infection at rates of 53–249 per 1000, excluding readmissions. To our knowledge, these are the highest rates of hospitalization for RSV disease ever reported. Although children with RSV disease might be...
managed at home more effectively in Baltimore than in remote Alaskan bush villages, a comparison between non–high-risk children hospitalized with RSV infection at YKDRH and JHH showed little difference in overall disease severity. Thus, hospitalization for relatively mild disease does not appear to account for the increased hospitalization of YK Delta infants. Indeed, during this 3-year period, ~1/125 infants born in the YK Delta required ventilatory support for RSV disease. Comparable data regarding rates of ventilatory support for RSV in developed countries are not available but might range from ~1/550 to ~1/11,000 infants (assuming annual hospitalizations of 1–20,000 infants [3–5] and 9% of children hospitalized with RSV receiving mechanical ventilation [9, 13]). RSV infection was the single most frequent cause of hospitalization of YK Delta infants and imposed a substantial economic burden on YK Delta communities.

Some features of the RSV epidemics in the YK Delta may be unique to this region. For example, the brief epidemics within subregions are reminiscent of early descriptions of RSV epidemics in closed institutions in which outbreaks began and ended within a single month [17, 18]. Epidemics in YK Delta subregions may be brief because there is limited traffic between villages in the winter months. Analysis of the subtypes [19–22] of RSV isolates obtained during this study may allow a more detailed description of the spread of the epidemic through these remote communities.

The high frequency of readmission for repeated RSV infection may also be unique to the YK Delta region. Nineteen percent of all children hospitalized with RSV were readmitted with what appeared to be new RSV infections, and 10% were readmitted within a single RSV season. It is unlikely that these latter readmissions represent other respiratory infections with residual RSV carriage, since we were unable to isolate other respiratory viruses during these readmissions (adenovirus, influenza, and parainfluenza viruses were readily isolated from several children admitted with ARI during this study). Although reinfection with RSV during a single season has been achieved experimentally in adults [23] and has been observed in pediatric outpatients [24], it is unusual for children to be hospitalized with repeated RSV infections in a single season. Acute and convalescent sera were not obtained during this study, so it is not possible to determine whether the immune responses to primary RSV infections differed between readmitted and nonreadmitted children. However, infants whose first RSV admission was at <2 months of age were more likely to be readmitted than infants whose first RSV admission occurred later in the first year of life, and previous studies have shown that young infants may have suboptimal immune responses to primary RSV infections [25, 26]. Future studies that allow collection of convalescent sera in this population of children may help address this issue.

This study may also be useful in the continued analysis of the impact of RSV in developing countries. RSV is the leading cause of viral ARI in many developing countries [27–31], but lack of access to RSV diagnostic reagents and hospital facilities has made it difficult to quantify the effect of RSV in these countries. In contrast, children living in isolated bush villages in the YK Delta have access to primary and tertiary care facilities within the US health care system, so RSV infection can be readily diagnosed and hospitalization rates and disease severity can be determined. RSV infection is the leading cause of hospitalization of YK Delta infants. In addition, the relatively high frequency of RSV pneumonia in healthy YK Delta children (45% of YK Delta children vs. 16% of children hospitalized at JHH) is noteworthy. Since not all the diagnoses of pneumonia in the YK Delta or at JHH were made radiographically, future prospective studies that include radiographic evaluation and interpretation by 1 blinded observer would be of interest.

In YK Delta infants <6 months of age, levels of RSV neutralizing antibody measured in cord blood correlated inversely with RSV disease severity, even when controlling for high-risk status. Although several studies have shown that high titers of maternally derived RSV antibody are inversely proportional to the incidence of RSV infection in the first 6 months of life [3, 32–34], only two studies have assessed the impact of passively acquired antibody on RSV disease severity [3, 35]. In both studies, assessments of severity were partially based on physical findings or clinical diagnoses, which may have been subject to observer bias. The severity index used in the current study is not observer-dependent [12, 13]. Our results therefore provide evidence that maternally derived antibody is protective even in settings where severe RSV disease occurs frequently. Further studies are needed to determine whether group-specific antibody influences the rate or severity of infection with viruses belonging to RSV group A or B.

One unexpected finding from this study was the occurrence of severe RSV disease in neonates at YKDRH in Alaska and at JHH in Maryland. Previous studies have indicated that se-
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