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Malnutrition

A Risk Factor for Severe Respiratory Syncytial Virus Infection and Hospitalization

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Background: Longitudinal information examining the effect of poor infant growth on respiratory syncytial virus (RSV) severity is limited. Children hospitalized with RSV lower respiratory infection represent those at the severe end of the disease spectrum.

Methods: We followed up a cohort of 12,191 infants enrolled in a previous pneumococcal vaccine trial in Bohol, Philippines. Exposure measures were weight for age z-score at the first vaccination visit (median age 1.8 months) as well as the growth (the difference in weight for age z-score) between the first and third vaccination visits. The outcome was hospitalization with RSV lower respiratory infection.

Results: Children with a weight for age z-score ≤ −2 at their first vaccination visit had the highest rate of hospitalization with RSV lower respiratory infection, but this association was only evident in children whose mothers had >10 years of education (hazard ratio: 3.38; 95% confidence interval: 1.63–6.98). Children who had lower than median growth between their first and third vaccinations had a higher rate of RSV-associated hospitalization than those with growth above the median (hazard ratio: 1.34; 95% confidence interval: 1.02–1.76).

Conclusions: Poor infant growth increases the risk for severe RSV infection leading to hospitalization.

Key Words: epidemiology, nutrition, cohort study

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Respiratory syncytial virus (RSV) is responsible for approximately 1 in 15 deaths in infants globally. RSV is a ubiquitous infection: almost all children will have been infected by the time they are 2–3 years old. Thus, the burden of disease due to RSV is driven by the severity of infection and determining the factors that increase the risk of severe RSV infection is vital for reducing this burden. There is growing awareness that malnutrition increases the risk of infectious diseases. This is particularly the case in childhood, where poor nutrition leaves children underweight, weakened and vulnerable to infections. Poor nutritional status has been consistently shown to be a risk factor for developing acute lower respiratory tract infection (ALRI) in children. There is considerably less evidence available to determine whether poor nutritional status increases the risk of developing severe RSV disease. This lack of evidence has limited recent literature reviews on the topic. To address the lack of evidence, we have investigated the association between growth in young infants and the rate of subsequent hospitalization due to RSV ALRI, in a longitudinal analysis of data from Philippines.

MATERIALS AND METHODS

We investigated the association between infant growth and hospitalization due to RSV ALRI in children from Bohol province, Philippines. The data used in this study were collected during a randomized controlled trial to investigate the efficacy of pneumococcal conjugate vaccine (PCV) between July 2000 and December 2004. The PCV trial was approved and monitored by the Ethical and Institutional Review Board of the Research Institute of Tropical Medicine, Philippines. Informed consent was obtained from parents/guardians before enrolling infants into the trial. This retrospective analysis used deidentified data collected during the trial. Ethical approval for the analysis in this article was granted without the need to seek additional consent, by the University of Queensland School of Population Health Research Ethics Committee in June 2011 (Ethics approval SP070711).

Infants enrolled in the trial received 3 doses of either PCV or placebo vaccination and were weighed at each vaccination visit. We have used weight for age data from the first and third vaccination visits (median ages 1.8 and 3.9 months, respectively) to assess infant growth. Children were followed up until their second birthday or until the end of the study (December 31, 2004). In our first analysis, we examined the rate of RSV admission according to categories of weight for age z-score at the first vaccination visit. In our second analysis, we examined the rate of RSV admission according to growth between the first and third vaccination visits. All weight for age z-scores were calculated using World Health Organization child growth standards. During the PCV trial, trained study personnel were permanently assigned to hospitals involved with case ascertainment, where patients <2 years of age were screened for community-acquired pneumonia. For both analyses, the outcome was the child’s first hospital admission due to microbiologically
confirmed RSV ALRI. RSV infection was confirmed by either polymerase chain reaction or viral culture. All trial participants who had confirmed RSV ALRI during the PCV trial were included in this study.

**RSV Admission According to Weight for Age at First Vaccination**

Weight for age data were available at first vaccination for all 12,191 infants in the PCV trial. We divided infants into 4 categories according to weight for age z-scores at first vaccination (>0, 0 to −0.99, −1 to −1.99 and ≤−2).

**RSV Admission According to Growth Between First and Third Vaccination**

Of the 12,191 infants in the PCV trial, only 10,965 (89.9%) were weighed at the third visit. The remaining 1226 infants were excluded from this analysis. Demographic characteristics were similar in the included and excluded infants, except excluded infants had significantly smaller weight for age z-scores at the first vaccination visit (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/B713). Of the 10,965 infants who were weighed at third vaccination, a further 52 were excluded from this analysis as they were admitted to hospital with RSV ALRI before the third vaccination visit. The remaining 10,913 children were included in this analysis. Infant growth was defined as the difference in weight for age z-scores between first and third vaccination (z-score at third vaccination − z-score at first vaccination).

**Confounding Factors**

Household crowding, maternal education and sex are all known risk factors for RSV admission. The number of other children in the household was divided into 2 categories: 0–2 and 3 or more. We divided maternal education into 2 categories: elementary and secondary school level (0–10 years education) and beyond (11 or more years of education). As weight for age z-scores decrease with age in the study population, we also controlled for age at third vaccination. As the incidence of RSV ALRI admission varies with age, there is potential for those children who were not followed up until their second birthday to have biased rate estimates. For this reason, we also controlled for the time at risk by age, using 6-month age bands. Hazard ratios were calculated using Cox proportional hazards regression. Potential confounders [maternal education, number of children in the household, sex, age at third vaccination, age at risk and vaccination status (PCV or placebo)] were included as main effects.

**RESULTS**

**RSV Admission According to Weight for Age at First Vaccination**

Of the 12,191 children in this analysis, 312 were admitted to hospital with RSV ALRI during follow up from the date of their first vaccination. Of the 12,191 children, 8802 children (72.2%) were followed up until their second birthday and 2379 (19.5%) were followed up to the end of the trial, while 1010 (8.3%) were lost to follow up (many of these migrated out of the study municipalities). Of children lost to follow up, the median follow-up time was 284 days, compared with 670 days in the children followed up either to their second birthday or to the end of the study.

We found a statistically significant interaction between z-score at first vaccination and maternal education (P = 0.020). For this reason, we have presented the results separately according to level of maternal education. In those children whose mother had up to 10 years education, there was no association between weight for age z-score at first vaccination and the rate of RSV hospital admission (Table 1). In those children whose mother had more than 10 years education, those with a weight for age z-score <−2 (ie, moderately to severely underweight) had a significantly higher rate of RSV hospitalization than children in each of the 3 other weight for age categories (Table 2). The rate of RSV hospitalization was higher in those children whose mother had up to 10 years education than in those whose mother had >10 years education [hazard ratio: 2.08; 95% confidence interval (CI): 1.62–2.67]. Higher numbers of children in the household and male sex were both associated with an increased rate of RSV hospitalization (Tables 1 and 2). PCV vaccination status was not associated with RSV hospitalization (hazard ratio: 1.01; 95% CI: 0.81–1.26) and including vaccination status in the regression model did not alter the results of either the primary or secondary analyses; hence this term was dropped. Figure 1 shows the survival time to RSV admission curve, according to weight for age z-score at first vaccination.

**RSV Admission According to Growth Between First and Third Vaccination**

Of the 10,913 children in this analysis, 224 were admitted to hospital with RSV ALRI during follow up from the date of their third vaccination. Of the 10,913 children, 8059 children (73.8%) were followed up until their second birthday and 2060 (18.9%) were followed up to the end of the trial, while 794 (7.3%) were lost to follow up. Of children lost to follow up, the median follow-up time was 255 days, compared with 606 days in the children followed up either to their second birthday or to the end of the study.

**TABLE 1.** Rate (Per 1000 Child Years) of Hospitalization With RSV ALRI, According to Weight for Age z-score at First Vaccination, in Those Children Whose Mother Had up to 10 Years of Education; Bohol, Philippines, 2000–2004

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Category</th>
<th>RSV ALRI Admissions</th>
<th>n</th>
<th>Rate</th>
<th>RR</th>
<th>95% CI</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight for age z-score</td>
<td>&gt; 0</td>
<td>77</td>
<td>2366</td>
<td>19.7</td>
<td>1.00</td>
<td>—</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>0 to −0.99</td>
<td>97</td>
<td>2763</td>
<td>21.2</td>
<td>1.08</td>
<td>0.80–1.46</td>
<td>1.07</td>
<td>0.80–1.45</td>
</tr>
<tr>
<td></td>
<td>−1 to −1.99</td>
<td>36</td>
<td>1486</td>
<td>15.4</td>
<td>0.78</td>
<td>0.52–1.15</td>
<td>0.77</td>
<td>0.52–1.15</td>
</tr>
<tr>
<td></td>
<td>≤−2</td>
<td>21</td>
<td>513</td>
<td>25.2</td>
<td>1.28</td>
<td>0.79−2.08</td>
<td>1.26</td>
<td>0.78–2.05</td>
</tr>
<tr>
<td>Children in household</td>
<td>0–2</td>
<td>134</td>
<td>4610</td>
<td>17.8</td>
<td>1.00</td>
<td>—</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>3+</td>
<td>97</td>
<td>2468</td>
<td>23.6</td>
<td>1.34</td>
<td>1.04–1.75</td>
<td>1.36</td>
<td>1.05–1.77</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>87</td>
<td>3417</td>
<td>15.3</td>
<td>1.00</td>
<td>—</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>144</td>
<td>3661</td>
<td>24.1</td>
<td>1.57</td>
<td>1.20–2.05</td>
<td>1.57</td>
<td>1.20–2.05</td>
</tr>
</tbody>
</table>

*Adjusted for age at third vaccination and age at risk.

RR, rate ratio.

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Children with growth between first and third vaccination equal to or less than the median had an increased rate of hospital admission with RSV ALRI compared with those with growth above the median (Table 3). Higher numbers of children in the household, lower number of years of maternal education and male sex were all associated with an increased rate of RSV hospitalization (Table 3). Vaccination status was not associated with RSV admission (hazard ratio: 1.02; 95% CI: 0.78–1.32) and including vaccination status in the regression model did not alter the results of either the primary or secondary analyses; hence, this term was dropped. Figure 2 shows the survival time to RSV admission curve, according to growth between first and third vaccination.

**DISCUSSION**

This is the only published longitudinal analysis of RSV hospitalization according to infant growth. We have shown that infants with poor growth have an increased rate of RSV ALRI hospitalization in our study setting in Bohol, Philippines. This result is consistent with the available evidence examining the association between poor growth and more severe RSV infection. A large longitudinal study in Kenya using active surveillance to identify RSV cases found increased RSV ALRI incidence in children with stunting (height for age z-score $\leq -2$; rate ratio: 1.73; 95% CI: 1.08–2.76). Also consistent with our results is a population-based retrospective study from Spain: local infants admitted to hospital with community-acquired RSV infection were found to have a lower birth weight than the general infant population in the region (odds ratio: 2.18; 95% CI: 1.39–3.14), after controlling for gestational age. A retrospective cohort study from the United States found that low birth weight was a risk factor for RSV-associated mortality after controlling for gestational age: in infants with a gestational age of 37 weeks or greater, those with a birth weight $< 2500$ g had an RSV-associated mortality rate of 20.3 per 100,000 compared with those with a birth weight $\geq 2500$ g who had a rate of 4.9 per 100,000.

A number of hospital based cross-sectional studies have found that malnutrition is less common in children admitted with RSV ALRI than in children admitted with RSV-negative ALRI.

It is incorrect to interpret the data from these studies as indicating that malnutrition is protective against RSV ALRI, as has been suggested in the past. The key limitation of such an interpretation is that it uses RSV-negative cases of ALRI as the ‘baseline’ comparison group, which introduces selection bias. An analogy is the relationship between smoking, lung cancer and coronary artery disease: although smoking is less common in individuals with coronary artery disease than in individuals with lung cancer, it is clear that smoking does not protect against coronary artery disease. In a similar way, although malnutrition is less common in children with RSV...
We have used weight for age as our nutritional index as we had no height measurements for our study subjects. Without height measurements or other factors associated with lower socioeconomic status. Other factors for ALRI such as indoor smoke or micronutrient deficiencies may include known risk factors for RSV hospitalization and should probably be considered as an independent group for future RSV treatment and prophylaxis trials. Our findings add weight to the need to ensure adequate nutrition in all infants, not only to ensure that they grow and thrive, but also to reduce their risk of severe infection.

**ACKNOWLEDGMENTS**

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**REFERENCES**


CURRENT ABSTRACTS

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Listeria monocytogenes infection (listeriosis), recognized as a foodborne illness in the 1980s, leads to invasive disease during vulnerable stages of life. Older adults and persons with immunocompromising conditions are at higher risk for Listeria bacteremia and meningitis, which can be fatal. Listeriosis usually is a mild illness in pregnant women, but it can cause severe outcomes for the fetus or newborn infant, including fetal loss, preterm labor, and neonatal sepsis, meningitis and death. Listeriosis is rare. This report provides an overview of recent surveillance data on listeriosis, highlighting actions needed to protect vulnerable populations.

Data from 3 surveillance systems for the period 2009–2011 were analyzed to provide demographic and clinical characteristics of patients with listeriosis, estimates of incidence overall and in demographic subgroups and descriptions of foods associated with outbreaks. A case was considered pregnancy associated when it occurred in a pregnant woman, a fetus or an infant ≤31 days old; mother-infant pairs were counted as a single case. A listeriosis outbreak was defined as 2 or more cases linked to a food vehicle. Cheese was implicated in 6 outbreaks (50% of outbreaks) with 51 cases (23% of outbreak-associated cases). Soft cheeses labeled as made from pasteurized milk were implicated in 5 outbreaks: 4 implicated chicken salad) and whole cantaloupe, were implicated as listeriosis outbreak vehicles.

Comment: Many outbreaks have been linked to soft cheese made with unpasteurized milk. However, investigations described in this report and elsewhere also have implicated cheeses made from pasteurized milk. Pasteurization eliminates *Listeria*, but contamination can occur after pasteurization. *Listeria* grows in moist environments, even at refrigeration temperatures, so it can thrive when soft cheeses that support its growth are contaminated.

Consumers at higher risk for listeriosis and those who prepare their food can reduce their risk. Basic food safety measures (eg, clean, separate, cook and chill) reduce the risk for listeriosis and other potentially serious infections. Persons at higher risk should follow the guidance for the general population not to consume unpasteurized milk or dairy products made from unpasteurized milk (eg, soft cheese). They also should be aware that some Mexican-style soft cheeses made from pasteurized milk, like queso fresco, have been identified as a source of listeriosis. In addition, health care providers are uniquely positioned to provide credible information about listeriosis prevention to patients at higher risk (http://www.cdc.gov/listeria).