WHAT’S KNOWN ON THIS SUBJECT: Preterm and low birth weight infants are at increased risk of hospitalization due to rotavirus gastroenteritis, and rotavirus vaccine is immunogenic and well tolerated among these infants when provided at or after discharge from the NICU.

WHAT THIS STUDY ADDS: Many preterm infants with a birth weight of ≤1500 g are not eligible to receive rotavirus vaccination because they remain in the NICU beyond the upper age limit recommended for immunization. New strategies are needed.

abstract

OBJECTIVE: Preterm infants are at increased risk of severe rotavirus gastroenteritis. Although immunization with rotavirus vaccine is safe and effective, age restrictions limit the number of infants eligible for vaccination at discharge from the NICU. The objectives of this study were to assess the implementation of the rotavirus vaccine program in our NICU, recognize missed opportunities for vaccination, and document how often very low birth weight (VLBW; birth weight ≤1500 g) and extremely low birth weight (ELBW; birth weight <1000 g) infants were eligible to receive rotavirus vaccine at the time of NICU discharge.

METHODS: This study reports on a prospective, observational cohort of all VLBW infants who were discharged from the NICU at Parkland Memorial Hospital from May 2008 to April 2010. Medical records were reviewed and data collected regarding the number of infants who were eligible for and received rotavirus vaccination at discharge.

RESULTS: A total of 63% (135 of 213) of VLBW infants did not receive rotavirus vaccine. The reasons for not providing vaccine included the following: <42 days of age at discharge (56 of 213; 26%), >84 or 104 days of age at discharge (48 of 213; 23%), or missed (35 of 213; 16%). The majority (75%) who were too old for vaccination at the time of discharge were ELBW.

CONCLUSIONS: The current age restrictions for rotavirus immunization resulted in more than half of ELBW infants being ineligible for vaccination at the time of discharge from the NICU. Alternative strategies for rotavirus immunization in this population are needed. Pediatrics 2013;132:e662–e665

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KEY WORDS: rotavirus, immunization, preterm infant, neonatal ICU

ABBREVIATIONS
AAP—American Academy of Pediatrics
ELBW—extremely low birth weight
PMH—Parkland Memorial Hospital
RV5—RotaTeq
VLBW—very low birth weight

Dr Stumpf drafted the initial manuscript and contributed to the study design, data acquisition, analysis, and interpretation; Ms Thompson contributed to the study design, data acquisition, initial analyses, and the revision of the manuscript; Dr Sánchez contributed to the conception and study design, analysis and interpretation of data, and critical review and revision of the manuscript; and all authors approved the final manuscript as submitted.

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Rotavirus is the most common cause of severe diarrhea in infants worldwide. 1,2 Immunization of infants with 1 of 2 licensed rotavirus vaccines, a live oral human-bovine reassortant rotavirus vaccine (RotaTeq [RV5], Merck & Co., Inc., West Point, PA) or a live, oral, human-attenuated rotavirus vaccine (Rotarix [RV1], GlaxoSmithKline, London, UK), has decreased hospitalizations due to rotavirus significantly in the United States and abroad.3,4 The American Academy of Pediatrics (AAP) and the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP) recommend that the first dose of rotavirus vaccine be administered as early as 24 weeks of age and no later than 20 weeks of age.2 The recommended age limit at the time of discharge was later revised to no later than 42 days of age and initially no later than 84 days, although this recommendation was later revised to no later than 14 weeks and 6 days (104 days).2

Preterm or low birth weight infants are at increased risk of rotavirus gastroenteritis and subsequent complications and hospitalizations in the first year of age.5,6 The AAP and Advisory Committee on Immunization Practices recommend that preterm infants who are age-eligible and clinically stable may be immunized at the time of discharge from the NICU. However, the risk from shedding of rotavirus vaccine virus and potential transmission to other high-risk infants in the NICU outweighs the benefit of immunizing infants who would remain in the NICU after vaccination.7

In May 2008, the NICU at Parkland Memorial Hospital (PMH) implemented routine vaccination with rotavirus vaccine at the time of NICU discharge if infants were within the recommended age parameters. The objectives of this prospective study were to assess the implementation of the rotavirus vaccine program in our NICU, recognize missed opportunities for vaccination, and document how often very low birth weight (VLBW; birth weight ≤1500 g) infants were eligible to receive rotavirus vaccine at the time of NICU discharge.

**METHODS**

This was a prospective observational cohort study in all VLBW infants who were discharged from the NICU at PMH, a large, urban county hospital in Dallas, Texas, from May 1, 2008, to April 22, 2010, when rotavirus vaccination with RV5 was provided at discharge to all age-eligible infants. The study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center.

The medical records of the infants were reviewed, and pertinent demographic, clinical, and laboratory data were recorded. The number of infants who received the rotavirus vaccine, the number of missed opportunities for vaccination, and the number of infants falling outside the recommended age limit for vaccination were recorded and analyzed. Data were assessed separately for VLBW and extremely low birth weight (ELBW; birth weight ≤1000 g) infants. During the study period, the upper age limit for vaccination changed from 84 days to 104 days, so the data collection and analysis also reflected the change in age limit requirements.

Descriptive analyses were performed by using frequency distributions and rates. Medians and means were used to summarize patient demographic and characteristics, and t test and χ² analysis were performed as appropriate.

**RESULTS**

A total of 213 VLBW infants were discharged from the PMH NICU from May 1, 2008, to April 22, 2010, 65 (31%) of these infants had a birth weight ≤1000 g. Their clinical characteristics are provided in Table 1. Only 78 (37%) infants received the RV5 vaccine at the time of discharge; 24 (37%) were ELBW infants and 54 (36%) had a birth weight from 1001 to 1500 g (Table 2). The total number of infants eligible for vaccination at discharge was 111 (52%), and among these 29 were ELBW infants and 82 had birth weights of 1001 to 1500 g. A total of 33 infants (33%; 7 ELBW and 28 with birth weights of 1001–1500 g) were eligible but not vaccinated at the time of discharge and therefore classified as missed opportunities.

Among the 135 infants who did not receive rotavirus vaccine at discharge, 56 (26% of the total number of infants) were <42 days old and therefore too young, whereas 48 (23% of all infants) were over the recommended age limit of 84 or 104 days and therefore too old at the time of discharge (Table 2). Of these latter 48 infants, 36 (75%) were ELBW. In addition, these 36 infants accounted for 58% of all ELBW infants discharged from the NICU during the study period. Extending the age limit of vaccination to 104 days resulted in an additional 6 ELBW infants receiving the RV5 vaccine.

There also were 4 infants (2 ELBW; 2 with birth weights of 1001–1500 g) who were vaccinated despite being older than the recommended age limit at the time of discharge (Table 2). There were no complications noted on follow-up in the Low Birth Weight Clinic at Children’s Medical Center Dallas. Nine additional infants had a previous diagnosis of necrotizing enterocolitis and were vaccinated at the time of discharge; 2 of these infants had required surgical intervention. All tolerated the vaccine without ill effects, and none had intussusception reported on follow-up. One eligible infant choked on the vaccine solution; this infant was counted as having received the vaccination and was not revaccinated.

**DISCUSSION**

Gastroenteritis due to rotavirus results in >2 million hospitalizations and half a million deaths per year worldwide.1 In the United States, its annual cost in the prevaccine era was ~$1 billion, with 500,000 clinic visits and 50,000
TABLE 1 Characteristics of the 213 Infants With a Birth Weight \(\leq1500\) g Who Were Discharged From the NICU During the Study Period

<table>
<thead>
<tr>
<th>Total</th>
<th>Rotavirus Vaccination</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Number of infants, n (%)</td>
<td>213</td>
<td>135 (63)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>109 (51)</td>
<td>68 (50)</td>
</tr>
<tr>
<td>Multiple gestation, n (%)</td>
<td>4 (2)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Twin</td>
<td>37 (17)</td>
<td>24 (18)</td>
</tr>
<tr>
<td>Triplet</td>
<td>4 (2)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Birth weight, mean ± SD (range), g</td>
<td>1129 ± 240 (570–1494)</td>
<td>1096 ± 191 (650–1490)</td>
</tr>
<tr>
<td>Gestational age, mean ± SD (range), wk</td>
<td>28 ± 3 (23–36)</td>
<td>28 ± 2 (25–36)</td>
</tr>
<tr>
<td>Age at discharge, mean ± SD (range), d</td>
<td>71 ± 38 (22–192)</td>
<td>72 ± 24 (52–120)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td>120 (56)</td>
<td>67 (50)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>49 (23)</td>
<td>34 (25)</td>
</tr>
<tr>
<td>Black</td>
<td>40 (19)</td>
<td>34 (25)</td>
</tr>
<tr>
<td>White</td>
<td>4 (2)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Gastrointestinal pathology, n (%)</td>
<td>17 (8)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>NEC</td>
<td>1 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Surgical NEC</td>
<td>3 (18)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrochisis</td>
<td>1 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Omphalocoele</td>
<td>1 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Ileal perforation</td>
<td>1 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Jejunal atresia</td>
<td>1 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Upper gastrointestinal hemorrhage</td>
<td>1 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrosomy tube</td>
<td>1 (0.5)</td>
<td>0</td>
</tr>
</tbody>
</table>

NEC, necrotizing enterocolitis.

a Refers to NEC only.

TABLE 2 Rotavirus Vaccination Among the Study Population of 213 Infants

<table>
<thead>
<tr>
<th>Birth Weight ≤1000 g</th>
<th>1001–1500 g</th>
<th>1001–1500 g</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period 1</td>
<td>Period 2</td>
<td>Period 1</td>
<td>Period 2</td>
</tr>
<tr>
<td>Chronological age at discharge, d</td>
<td>42–84</td>
<td>42–104</td>
<td>42–84</td>
</tr>
<tr>
<td>Number of infants</td>
<td>19</td>
<td>9</td>
<td>46</td>
</tr>
<tr>
<td>Eligible for vaccination, n (%)</td>
<td>7 (37)</td>
<td>22 (48)</td>
<td>12 (22)</td>
</tr>
<tr>
<td>Received vaccine, n (%)</td>
<td>2 (11)</td>
<td>22 (48)</td>
<td>12 (22)</td>
</tr>
<tr>
<td>Reason not vaccinated, n (%)</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>&lt;42 days (too young)</td>
<td>0</td>
<td>0</td>
<td>20 (37)</td>
</tr>
<tr>
<td>&gt;84 days</td>
<td>12 (63)</td>
<td>0</td>
<td>5 (9)</td>
</tr>
<tr>
<td>&gt;104 days</td>
<td>n/a</td>
<td>24 (52)</td>
<td>n/a</td>
</tr>
<tr>
<td>Missed opportunity, n (%)</td>
<td>5 (26)</td>
<td>2 (4)</td>
<td>17 (31)</td>
</tr>
<tr>
<td>Infants not vaccinated, n (%)</td>
<td>17</td>
<td>24</td>
<td>42</td>
</tr>
</tbody>
</table>

Period 1, initial age recommendations for rotavirus vaccination at discharge; Period 2, revised age recommendations for rotavirus vaccination at discharge; n/a, not applicable.
a Two infants were vaccinated at 109 and 112 d of age, respectively.
b Two infants were vaccinated at 105 and 110 d of age, respectively.

globulin G antibodies and are at increased risk of complications and death from rotavirus infection. Rotavirus vaccine is known to be immunogenic and well tolerated in preterm infants. Therefore, rotavirus vaccination is recommended for use in preterm infants at the time of discharge from the NICU as long as they are clinically stable and have an age range of 42 to 104 days. Our study highlights the limitations of the currently recommended schedule for rotavirus vaccination, because 22% of all VLBW infants were too old at discharge to receive the vaccine. In addition, 52% of all ELBW infants discharged from the NICU were older than 104 days and also were not vaccinated. Of the 3,953,593 live births in the United States in 2011, 56,931 were VLBW infants, and of these, 12,525 would not have been vaccinated. A relaxed age restriction could lead to increased vaccination rates and protection. In developing countries, Patel et al showed that increasing the age allowed for initiation of the rotavirus vaccine series to 1 year of age would result in a potential 28% decrease in rotavirus-associated deaths. Whether such a model is applicable to the United States remains unclear. In addition, vaccination of older infants may be associated with an increase in the absolute number of intussusception and possibly the relative risk for intussusception, and therefore the risks and benefits of such a practice require further study. Nonetheless, in our population, 4 infants received the vaccine beyond 104 days of age without any ill effects.

An alternative strategy could be vaccinating infants in the NICU if their likely discharge will not be before 104 days of age. The AAP does not recommend such an approach because up to 9% of infants shed the vaccine virus in stool from day 1 to day 15 postvaccination, thus posing a theoretical risk of disease transmission among high-risk infants in the NICU. The AAP states that, in usual hospitalizations as well as 40 to 50 deaths per year, mainly among infants with immune system compromise or preexisting illnesses such as preterm maturity. Unlike full-term neonates, preterm infants do not receive immunologic protection by transplacentally acquired maternal rotavirus immuno-
circumstances, the risk from shedding outweighs the benefit of immunizing infants who are age-eligible for vaccine but who will remain in the NICU or nursery after immunization. Moreover, if an infant immunized with a rotavirus vaccine requires readmission to the NICU within 2 weeks after receipt of vaccine, contact precautions should be instituted for the readmitted infant and should be maintained for 2 to 3 weeks after vaccine administration. However, these recommendations are not evidence-based, and safety studies of vaccinating infants in the NICU with documentation of any spread of vaccine virus are urgently needed.

Rivera et al15 showed that infants who received the human rotavirus vaccine transmitted the vaccine strain to their unvaccinated twin sibling ~19% of the time, but there was no increased risk of gastroenteritis in this group. This model of transmission may not apply to a NICU setting because the infants in this study were healthy twins, ≥32 weeks’ gestation, and already discharged from the hospital. Smith et al16 found that although preterm infants vaccinated with rotavirus vaccine shed rotavirus antigen for up to 2 weeks after vaccination, no household contacts developed symptomatic disease. These preterm infants also were vaccinated at the time of discharge and followed thereafter; and the applicability of these findings to the NICU population is questionable. In addition, a small series showed that infants with short gut who received rotavirus immunization tolerated it well.17

Limitations of this study include the lack of follow-up information on the occurrence of rotavirus infection as well as knowledge of breast milk feedings that may have protected unimmunized infants. Nonetheless, this study calls for further investigation on ways to increase rotavirus immunization of high-risk preterm infants. Such studies could incorporate assessment of postmenstrual rather than chronological age for administration of rotavirus vaccine, thus extending the eligibility time that these high-risk infants could receive the vaccine. In the meantime, all NICUs must implement strict guidelines for adherence to rotavirus vaccination recommendations at discharge so that no missed opportunities occur.

CONCLUSIONS

Alternative strategies for rotavirus vaccination of VLBW infants in the NICU are urgently needed to achieve optimal immunization rates and protection from rotavirus disease. The safety and efficacy of rotavirus vaccination provided to infants in the NICU, including those with gastrointestinal pathology, as well as vaccination of older age groups should be assessed.

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