

Safety of Rotavirus Vaccine in the NICU

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KEY WORDS

infant, preterm infant, rotavirus, vaccine/immunization

ABBREVIATIONS

ID₅₀—50% infectious dose
 PCR—polymerase chain reaction
 RV1—Rotarix
 RV5—RotaTeq
 VI—vaccinated infants
 UVI—unvaccinated infants

Dr Monk conceptualized and designed the study (including data collection instruments), completed all data collection, performed data analysis, and drafted the initial manuscript; Dr Motsney conceptualized and designed the study (including data collection instruments), completed all data collection, and performed data analysis; Dr Wade conceptualized and designed the study (including data collection instruments) and performed data analysis; and all authors critically reviewed the copy for intellectual content, and revised and approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Rotavirus vaccination is discouraged during hospitalization, given concerns regarding live-attenuated virus transmission; vaccination is recommended upon NICU discharge for eligible infants, however. Vaccination must be initiated before 104 days of age or infants become age-ineligible.



WHAT THIS STUDY ADDS: RotaTeq vaccine administered with routine 2-month vaccinations within the NICU was tolerated in recipients, with no suggestion of symptomatic nosocomial transmission to neighboring unvaccinated infants.

abstract

BACKGROUND AND OBJECTIVE: Rotavirus vaccination is discouraged during hospitalization given concerns regarding live attenuated virus transmission, although recommended upon discharge. Infants should have vaccination initiated by 104 days of age or they become age-ineligible. Our institution believed the known risk of severe disease in unvaccinated infants outweighed the theoretical risk of transmission. We routinely administer RotaTeq (RV5) to age-eligible hospitalized infants on enteral feeds. The objective of this study was to determine the safety of RV5 vaccination among vaccinated (VI) and unvaccinated infants (UVI) within the NICU.

METHODS: A retrospective review identified VI between 2008 and 2010, and UVI geographically located near VI within 15 days of vaccination. We screened for gastrointestinal symptoms among UVI by using an electronic medical record query (trigger tool) to identify infants with orders for bowel rest, abdominal imaging, and antibiotics. Trigger-positive infants had full chart review.

RESULTS: Most VI (76%) were either asymptomatic (25% [24 of 96]) or symptomatic but unchanged from baseline (51% [49 of 96]) postvaccination. Although 24% of VI had clinical status changes postvaccination, none were directly attributed to RV5. Among 801 neighboring UVI, 10 (1.2%) had clinical status changes, none directly attributed to RV5, but mostly bacterial sepsis or preexisting gastrointestinal pathology. Two UVI underwent stool analysis; both negative for rotavirus.

CONCLUSIONS: RV5 was well tolerated in hospitalized infants, with most postvaccination symptoms attributed to preexisting symptoms. UVI seemed to have a low risk of symptomatic transmission. Inpatient administration ensures that age-eligible infants are vaccinated regardless of hospital duration. Prospective evaluation of safety and transmissibility is needed. *Pediatrics* 2014;133:e1555–e1560

Rotavirus is the leading cause of severe diarrhea, dehydration, hospitalization, and death from acute gastroenteritis in young infants worldwide.¹ Two rotavirus vaccines are currently available in the United States. RotaTeq (RV5; Merck & Co Inc, Whitehouse Station, NJ) is a live, pentavalent, oral, attenuated rotavirus vaccine approved in 2006 as a 3-dose regimen at 2, 4, and 6 months of age.¹ Rotarix (RV1; GlaxoSmithKline, Research Triangle Park, NC) is a live, monovalent, oral, attenuated rotavirus vaccine approved in 2008 as a 2-dose regimen at 2 and 4 months of age. Rotavirus vaccination should be initiated before 104 days of age.

Many infants hospitalized in the NICU are very preterm infants or infants with significant congenital abnormalities who require hospitalization beyond 104 days of age; therefore, inpatient administration would be required if these infants were ever to receive rotavirus vaccine. Preterm infants are at an increased risk of hospitalization from rotavirus gastroenteritis during the first year of life.^{2–4} Very preterm infants have a lower level of maternal antibody against prevalent rotavirus serotypes, which increases the risk of severe gastroenteritis.³

In 2006 to 2007, the Advisory Committee on Immunization Practices and the American Academy of Pediatrics supported RV5 vaccination before 84 days of age and recommended the use of RV5 for “preterm infants who were at least 6 weeks old, discharged or being discharged from the hospital, and clinically well.”^{5,6} Standard precautions were advised if infants were admitted to the hospital after receiving RV5. In clinical trials, RV5 had a 74% prevention rate against any severity of rotavirus gastroenteritis and a 98% prevention rate against severe rotavirus gastroenteritis, after completion of the 3-dose regimen.⁷ RV5 has similar safety and efficacy in premature

infants born between 25 and 36 weeks’ gestation.

In 2007, RV5 was the only approved rotavirus vaccine. After comprehensive literature review, our Divisions of Neonatology and Infectious Disease recommended that RV5 be administered in the NICU with routine 2-month vaccinations to infants receiving some amount of enteral nutrition.^{5–9} The reported RV5 shedding rate at that time was 8.9% of infants.⁷ The risk of symptomatic transmission was thought to be low due to the poor replication of bovine–human vaccine in human intestines.⁹ The benefit of RV5, specifically the significant decrease in severe native rotavirus-associated gastroenteritis in the first year of life (particularly among preterm infants), was believed to outweigh the minimal risk of inpatient vaccination. This strategy was chosen to maximize the RV5 vaccination rate regardless of length of NICU hospitalization and to protect infants against native rotavirus infections after hospital discharge. Our institution used standard precautions but did not routinely recommend contact precautions after rotavirus vaccination of inpatients or infants admitted or readmitted to the hospital after rotavirus vaccination.

In 2009, the American Academy of Pediatrics and the Advisory Committee on Immunization Practices released updated rotavirus vaccine administration guidelines that extended the maximum age for vaccine initiation to 104 days (14 weeks, 6 days), continued to discourage the use of rotavirus vaccine in the inpatient hospital setting due to theoretical risk of transmission, and promoted contact precautions for any infant admitted to the NICU within 2 to 3 weeks of vaccination.^{4,10} Specifically, these guidelines stated “preterm infants who are age-eligible and clinically stable may be immunized at the time of discharge from the NICU or nursery.”¹⁰

We maintained our previously established practice of including RV5 with routine vaccinations to infants receiving some enteral nutrition and the use of standard precautions after vaccination.

There is significant debate regarding the risk/benefit ratio when considering the risk from shedding attenuated virus compared with the benefit of vaccination among high-risk infants who remain hospitalized. Although shedding of attenuated virus has been demonstrated, symptomatic disease transmission is rare.^{11,12} Transmission of RV5-derived attenuated virus leading to disease in immunocompetent patients is limited to 1 case report.¹³ Nearly one-quarter of all very low birth weight infants become ineligible to receive rotavirus vaccination if not administered as an inpatient vaccination because they remain hospitalized beyond 104 days of age.¹⁴

The purpose of the present study was to evaluate the safety of administering RV5 in the NICU concomitantly with routine 2-month vaccinations. This practice allows for vaccination of infants whose medical conditions require prolonged NICU hospitalization.

METHODS

An institutional review board–approved retrospective chart review was conducted at Children’s Hospital of Philadelphia to identify RV5 vaccination among vaccinated infants (VI) between September 1, 2008, and September 30, 2010, and unvaccinated infants (UVI) hospitalized in the same “pod” as VI within 15 days of vaccination. The 75-bed NICU was designed in a pod-like fashion, each pod containing 2 to 7 beds ~9 to 32 feet apart. Nursing staff shared patients within the same pod. We defined neighboring UVI as those infants who resided within the same pod as VI. If nosocomial transmission

were to occur, UVI in that same pod as VI would be at the highest risk.

VI were identified by using pharmacy dispensing records. Medication administration records were used to confirm administration of RV5 and to identify the pod location of VI. The NICU admission census, including bed location, was used to identify UVI in the same pod as VI during the 15 days' postvaccination. A report of all rotavirus-positive stool (polymerase chain reaction [PCR]) test results from the Division of Virology was used to identify any case of rotavirus disease in the NICU.

VI included infants in the NICU who received any scheduled dose of RV5. Chart reviews were performed for all VI to determine the frequency of fever $>38^{\circ}\text{C}$, diarrhea or increased stool frequency, vomiting, abdominal distention, hematochezia, feeding intolerance, or intussusception for 7 days after vaccination. This 7-day screening window was consistent with previous RV5 safety trials among preterm infants.⁷

UVI were identified as patients hospitalized in the same pod as VI within 15 days of vaccination. We used an electronic medical record order query that was referred to as a "trigger tool" to identify UVI who had orders for bowel rest, abdominal radiography, and intravenous antibiotics. Chart reviews were performed on all UVI if all 3 orders were placed within 24 hours of each other (positive trigger tool) to determine the presence or absence of fever $>38^{\circ}\text{C}$, diarrhea, vomiting, abdominal distention, hematochezia, feeding intolerance, or intussusception. The 15-day observation window was chosen to be consistent with previous Phase III clinical trials that documented a viral shedding duration of up to 15 days after RV5 vaccination.⁷ Demographic information was collected for all VI and UVI with positive trigger tool findings. Infants' medical

histories and diagnoses that contributed to gastrointestinal symptoms were documented for all symptomatic infants, including but not limited to, chronic feeding intolerance, culture-positive bacterial sepsis, necrotizing enterocolitis, Hirschsprung's disease, malrotation with volvulus, intestinal perforation or resection, and duodenal atresia. A clinical status change was defined as new or worsening symptoms compared with baseline. The frequency of stool analysis for rotavirus was evaluated. PCR-positive stool analyses confirmed rotavirus gastroenteritis; however, it is not standard practice in our NICU to send rotavirus stool specimens for analysis unless viral gastroenteritis is suspected.

RESULTS

During 2008 to 2010, ~2500 infants were admitted to the NICU. Nearly all (82%) infants were either transferred from another hospital or admitted from home. We identified 96 infants who received RV5 vaccine (VI) in the inpatient setting and 801 neighboring UVI who resided in the same pod. The electronic medical record query, referred to as a trigger tool, identified 51 UVI (6.3%) who were ordered for bowel rest, received intravenous antibiotics, and had abdominal imaging within 15 days of exposure to a neighboring VI. Most VI and UVI with positive trigger tool were preterm, and their demo-

graphic characteristics are presented in Table 1.

Infants were eligible to receive the first dose of RV5 if they were receiving scheduled 2-month vaccinations and tolerating at least some enteral feeds. Most VI received 1 dose of RV5 (89 of 96) whereas 5 of 96 VI received 2 doses, and 2 of 96 received 3 doses. RV5 was administered with other scheduled vaccinations in 83% of VI (80 of 96). If RV5 was administered separately, it was administered, on average, 9 days after scheduled vaccinations. Among VI, gastrointestinal symptoms were commonly noted in progress notes before and after RV5 vaccination: feeding intolerance (52% vs 56%), emesis (44% vs 49%), abdominal distention (25% vs 30%), and hematochezia (8% vs 13.5%). Episodes of diarrhea (35% vs 52%) or fever $>38.0^{\circ}\text{C}$ (0% vs 8.3%) were more common after vaccination ($P < .05$). Most VI (76%) were either asymptomatic (25% [24 of 96]) or symptomatic but unchanged from baseline (51% [49 of 96]) postvaccination.

Some VI (24% [23 of 96]) were symptomatic with clinical changes after vaccination from baseline. Among these infants with new symptoms postvaccination, the most frequent clinical changes were for diarrhea or increased stool frequency, feeding intolerance, or vomiting (Table 2). In the progress notes, none of the clinical changes were attributed to RV5 or viral gastroenteritis but rather to narcotic withdrawal

TABLE 1 Characteristics of VI at First Dose of RV5 and Neighboring UVI With a Positive Trigger Tool

Characteristic	VI (n = 96)	UVI (n = 51)
Gestational age, wk	32.6 \pm 5.0 (22 6/7–41)	34.8 \pm 5.0 (24–40 4/7)
Postnatal age, d	68.8 \pm 10.7 (44–99)	34.4 \pm 50.3 (1–264)
Birth weight, kg	1.97 \pm 1.0 (0.5–4.42)	2.34 \pm 1.0 (0.6–4.6)
Male infants	51 (53)	34 (67)
History of intestinal pathology ^a		
Total	31 (32)	24 (47)
Requiring surgery	21 (22)	20 (39)
Short bowel syndrome	7 (7)	9 (18)

Data are presented as mean \pm SD (range) or n (%).

^a Intestinal pathology defined as necrotizing enterocolitis, intestinal perforation, bowel atresia or malformation, or Hirschsprung's disease.

TABLE 2 Gastrointestinal Symptoms Among Infants With Clinical Status Change From Baseline After Either Vaccination or Potential Exposure to VI

Variable	VI	UVI
Total cohort	96	801
No. of infants with clinical changes	23	10
Diarrhea	18 (78)	1 (10)
Feeding intolerance	16 (70)	6 (60)
Vomiting	13 (56)	5 (50)
Abdominal distention	10 (43)	3 (30)
Fever >38°C	6 (26)	4 (40)
Hematochezia	6 (26)	1 (10)
No. of infants with rotavirus PCR stool testing	0 tested	2 tested; results were negative for both

Unless otherwise indicated, data are presented as *n* (percentage with symptom among infants with clinical status change from baseline).

(39%), feed fortification (17.4%), formula change (13%), nasogastric tube displacement (4.4%), enteral multivitamin (4.4%), or feed advance (4.4%). All VI with fever had concomitant administration of other vaccines. None of the VI had stool testing for viral gastroenteritis, and no VI developed intussusception. We identified 1 VI who was readmitted to the NICU within 15 days of RV5 vaccination with a diagnosis of gastrostomy tube site cellulitis and emesis after a trial of bolus gastric feeds. The infant eventually required Nissen fundoplication. The progress notes did not report concern for gastroenteritis.

Among 801 neighboring UVI, 51 (6.4%) had a positive trigger tool defined as orders placed for bowel rest, intravenous antibiotics, and abdominal radiography within a 15-day potential exposure window to VI. Further chart review revealed that the majority (78% [40 of 51]) had these orders placed on admission to the NICU; therefore, the gastrointestinal symptoms existed before their potential exposure to a VI in the same pod. Among the remaining 11 UVI, 1 had no gastrointestinal symptoms and 10 (1.2% of all UVI) had clinical status changes, including feeding intolerance, vomiting, fever >38°C, abdominal distention, hematochezia, and diarrhea (Table 2). All UVI with clinical status changes were found to have concomitant medical conditions likely

responsible for their new symptoms: culture-positive bacterial sepsis (3 of 10; organisms included coagulase-negative *Staphylococcus*, *Pseudomonas*, and polymicrobial sepsis after central line contamination), intolerance of feed advancement (2 of 10), necrotizing enterocolitis (2 of 10), postoperative symptoms secondary to gastrostomy tube placement and Nissen fundoplication (1 of 10), ileostomy malfunction (1 of 10), or Hirschsprung's disease (1 of 10). Two symptomatic UVI had stool test results that were negative for rotavirus according to PCR. One of these infants developed diarrhea and hematochezia and was diagnosed with necrotizing enterocolitis; the other infant developed vomiting and feed intolerance and was diagnosed with Hirschsprung's disease. No cases of intussusception were identified. A report obtained from the Division of Virology confirmed zero documented nosocomial rotavirus gastroenteritis cases in the NICU.

DISCUSSION

Premature infants are at high risk of severe symptoms and hospitalization if infected with rotavirus, and this risk is highest within the first year of life.²⁻⁴ However, 23% of very low birth weight infants are ineligible for rotavirus vaccination under the current guidelines that discourage in-hospital vaccination.¹⁴ We report our experience

with routine inpatient RV5 vaccination in a NICU that used standard precautions for infants who received RV5. RV5 was found to be well tolerated in at least 75% of VI, with the remaining 25% having gastrointestinal symptoms attributed to other clinical conditions. Only 1% of UVI who resided in the same pod as the VI had gastrointestinal symptoms that were associated with orders for antibiotics, bowel rest, and abdominal imaging, and all symptoms were attributed to other clinical conditions.

Viral shedding occurs after vaccination with live attenuated rotavirus vaccines. Viral shedding rates after the first dose of RV5 vary in the literature from 1% to 87%, particularly due to differences in frequency of stool sampling and stool testing methods (enzyme-linked immunosorbent assay, PCR, or culture).^{8,11,12,15,16} Shedding seems to be highest after the first dose and among preterm infants.^{7,12} This shedding with RV5 is rarely associated significant clinical disease in immunocompetent patients or transmission to household contacts.^{12,13}

Transmission to unvaccinated infants has been assessed according to seroconversion in unvaccinated individuals. After RV5 vaccination, seroconversion in at least 50% of infant recipients (ID₅₀) is associated with exposure to ~10⁶ to 10⁷ PFU/mL of attenuated vaccine-derived virus.⁸ Ingestion of at least 1 to 100 mL of stool would be necessary to meet the ID₅₀ for RV5, which is unlikely to occur.¹¹ Even at this amount of ingestion, it does not mean that infants would develop severe disease; it merely indicates the potential for development of antibodies. RV1 vaccine-derived virus has a lower ID₅₀ (~10⁵ PFU/mL or less) that may present a higher chance of viral transmission.¹⁷ Transmission of rotavirus vaccine strain RV1 to unvaccinated individuals has been assessed in many studies¹⁸⁻²⁵

but only documented as occurring in 3.^{18–20} In studies documenting RV1 transmission, seroconversion varied from 2% to 6% among placebo recipients. A recent study evaluated the potential for transmission of RV1 from a vaccine recipient to an unvaccinated twin sibling among 80 twin pairs.²⁰ Although the vaccine strain was detected in stool samples from 19% of placebo infants, only 26% of these infants developed anti-rotavirus immunoglobulin A, and none of these transmission cases were associated with gastroenteritis symptoms.

Rotavirus transmission among immunocompetent patients after RV5, although not as well studied, has been minimally described. Transmission might be less likely to occur because of the low rate of positive culture results and larger inoculums required to establish infection.¹¹ Despite high shedding rates of 53% to 87% according to either immunoassay or PCR, respectively, in 15 premature infants who received RV5 at NICU discharge, only 9.3% were positive according to cell culture results, and no household transmission was observed.¹² A single case report described outpatient transmission of rotavirus from an infant vaccinated with RV5 to an older, unvaccinated sibling; this transmission resulted in symptomatic gastroenteritis requiring emergency department care.¹³ The isolated virus obtained from the sibling was a new virus apparently derived from re-assortment

between known RV5 vaccine strains P7[5]G1 and native rotavirus strain P1A [8]G6 that potentially occurred during intestinal replication in either 1 of the subjects. This re-assortment of vaccine and native strains potentially explained an increase in virulence.

The rotavirus vaccine guidelines are based on theoretical risk of transmission due to shedding that could result in disease. However, without inpatient administration, approximately one-quarter of very low birth weight infants would not receive rotavirus vaccination because they remain hospitalized.¹⁴ One-third of all VI reviewed in this study remained hospitalized beyond 104 days of age and would not have been vaccinated under the present guidelines. Preterm infants are at an increased risk of hospitalization from native rotavirus gastroenteritis after NICU discharge during the first year of life. Current Australian guidelines allow rotavirus vaccination in medically stable hospitalized infants, including preterm infants, specifically citing that “vaccination should not be delayed, particularly if the delay would result in an infant being beyond the upper age limit for vaccination.”²⁶

The major limitation to the present study was the retrospective design and absence of routine rotavirus PCR stool analysis. We cannot specifically address the incidence of shedding or transmission. In addition, most infants had complicated medical histories,

leading to a high incidence of gastrointestinal symptoms. Without rotavirus stool analysis in all patients, we cannot exclude RV5-associated adverse events. Among UVI, our trigger tool only identified infants who had all 3 orders (bowel rest, intravenous antibiotics, and abdominal radiography) placed within a 24-hour time period; therefore, infants with mild symptoms may have been missed. The study was too small to identify adverse events occurring at a low frequency. Furthermore, gastrointestinal adverse events could have occurred beyond our observation periods. This study only addressed the safety of RV5, and the results should not be generalized to RV1.

CONCLUSIONS

Preterm infants are at high risk for severe rotavirus gastroenteritis after discharge from the NICU. Administration of RV5 with routine 2-month vaccinations in this single hospital seems to have been tolerated by both VI and neighboring UVI; however, we cannot exclude the possibility that RV5 contributed to clinical changes in these infants. A large number of infants are not being vaccinated due to the age restriction and prolonged NICU hospitalization. A prospective study with stool rotavirus PCR testing and monitoring for symptoms of gastroenteritis is necessary to assess shedding, transmissibility, and safety of rotavirus vaccination in the NICU.

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