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Evaluation of pentavalent rotavirus vaccination in neonatal intensive care units

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ABSTRACT

Background & objectives: Preterm infants are at highest risk for severe rotavirus gastroenteritis. While rotavirus vaccination is recommended for age-eligible, clinically stable preterm infants, controversy exists regarding vaccination of these infants during hospitalization. The objectives of this study were to examine tolerance of pentavalent rotavirus vaccination (RV5) among hospitalized infants and nosocomial rotavirus transmission in the neonatal intensive care units (NICU) at two urban hospitals.
Methods: A retrospective, medical chart review of patients receiving RV5 vaccine was conducted to examine clinical histories of vaccine recipients. Average risk differences of gastrointestinal complications were estimated between the three days prior and up to four weeks following RV5 vaccination. A generalized linear regression model was used to examine the association between days since RV5 administration and daily feeding totals, using fixed effects to account for individual-level clustering. Rates of nosocomial rotavirus from active surveillance were compared between pre- and post-NICU-based vaccination periods.
Results: From July 1, 2011 to March 30, 2013, RV5 vaccination was initiated for 102 NICU patients. No changes in the average risk of gastrointestinal complications or daily feeding among participants overall were detected following RV5 administration. Rates of nosocomial rotavirus were similar during the periods before and after NICU-based vaccination.
Conclusions: On average, RV5 appeared to be well tolerated among vaccine recipients, with no increase in nosocomial rotavirus transmission observed following NICU-based rotavirus vaccination. While the benefits of a RV5 NICU-based vaccination program for otherwise eligible preterm infants seem to outweigh the possible risk of vaccine virus transmission, further studies are needed.

1. Introduction

Rotavirus was the major cause of emergency department visits and hospitalizations for gastroenteritis among Canadian infants and young children during the pre-vaccine era [1–6]. Currently, two live attenuated, oral rotavirus vaccines are available for use in Canada: RotaTeq® (RV5; Merck & Co Inc), a pentavalent vaccine approved as a 3-dose regimen at 2, 4, and 6 months of age, and Rotarix® (RV1; GlaxoSmithKline), a monovalent vaccine approved as a 2-dose regimen at 2 and 4 months of age. Similar to guidelines in the United States (U.S.) [7,8], Canada's National Advisory Committee on Immunization recommends 104 days (14 weeks and 6 days) as the upper age limit for initiation of either vaccine series [9]; effective November 2014, the Province of Quebec updated their maximum recommended age limit to 139 days [10]. Since licensure, both vaccines have demonstrated high vaccine effectiveness, with >70% effectiveness to prevent rotavirus hospitalizations and emergency department visits in high income countries [11–17]. Furthermore, the Global Advisory Committee on Vaccine Safety has concluded that the benefits of either rotavirus vaccine outweigh any modest risk of intussusception, on the basis of post-licensure data [18].

Preterm infants are at highest risk for severe rotavirus gastroenteritis [8,19,20]. While national guidelines in Canada [21,22]

Abbreviations: AEFI, adverse event following immunization; NICU, neonatal intensive care unit; RV1, Rotarix vaccine®; RV5, RotaTeq® vaccine.

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and elsewhere [7,8,23,24] recommend rotavirus vaccination for preterm infants if their chronological age meets the requirements for vaccination and the infant is clinically stable, there remains significant debate regarding whether rotavirus vaccine should be administered to eligible preterm infants during hospitalization, and few data exist to evaluate these recommendations [25,26]. This issue is concerning, since preterm infants admitted to the neonatal intensive care unit (NICU) often require prolonged hospitalizations exceeding 104 days of chronological age, and thus, may be age-ineligible for rotavirus vaccination upon NICU discharge. In fact, a recent U.S. study estimated that 23% of preterm infants exceed the age limit for vaccination during their NICU admission [27].

Debate regarding administration of rotavirus vaccine during hospitalization stems from the theoretic risk of horizontal rotavirus transmission from live vaccine virus shed in stool of recipients to unvaccinated patients [28]. Viral shedding is highest following the first rotavirus vaccine dose, with approximately 50% of recipients shedding virus after initiation of RV1 compared with only 10% after RV5 [29–31]. Documented, vaccine-associated transmission of symptomatic gastroenteritis from either vaccine, however, remains rare [29,30,32].

In consideration of the risks and benefits of rotavirus vaccination among hospitalized preterm infants, national guidelines in Canada permit vaccination of premature infants in the NICU at the discretion of medical professionals [21]. Similarly, guidelines in Australia [23] and the United Kingdom [24] allow vaccination of hospitalized, medically stable infants, including preterm infants. U.S. guidelines, however, recommend rotavirus vaccination only for age-eligible, clinically stable, preterm infants that are no longer hospitalized [7,8].

In July 2011, our institution began a NICU-based vaccination program to administer RV5 to eligible preterm infants during hospitalization at two urban, university hospitals located in Quebec, Canada. The purpose of this study is to describe our program's experience and outcomes.

2. Materials and methods

2.1. Vaccination program & study setting

We initiated a NICU-based vaccination program to administer RV5 to eligible, hospitalized infants during admission at either the Montreal Children's or Royal Victoria Hospitals; both hospitals are affiliated with the McGill University Health Centre and located in Montreal, Quebec. The Montreal Children's Hospital NICU is a level III, 28-bed unit facility providing specialized care to nearly 400 outborn infants annually that reside throughout Quebec [33]. The Royal Victoria Hospital is a birthing center and has a level II-III NICU with 350 newborn patients annually.

The first dose of RV5 was administered concurrently with routine vaccinations to age-eligible infants (42–104 days) tolerating at least 2 mL orally per feed. Subsequent doses were administered at 4- to 10-week intervals with the third dose not given beyond 32 weeks of age. RV5 was selected for vaccination in place of RV1 due to its lower reported rates of rotavirus shedding [29–31]. Routine infection control procedures without any additional precautions were applied following vaccination.

2.2. Study design

We conducted a two-part cohort study to examine (i) RV5 tolerance among vaccine recipients, and (ii) nosocomial RV infections among the NICU population at each participating hospital. We explored RV5 tolerance among recipients via a retrospective, medical chart review of patients receiving RV5 vaccine since the inception of the NICU vaccination program in July 1, 2011, through March 30, 2013. We investigated nosocomial rotavirus transmission among the NICU population overall via analysis of the hospitals' prospective, active nosocomial rotavirus gastroenteritis surveillance data from infection control departments collected from April 1, 2009 to March 30, 2013. The study protocol was approved by the pediatric research ethics board of the McGill University Health Centre.

2.3. Data collection

2.3.1. Medical chart review

Patients that received at least one dose of RV5 vaccination during NICU hospitalization were identified using electronic pharmacy dispensing records and included as study participants. Participant medical charts were reviewed by trained medical personnel to confirm RV5 administration and obtain vaccination date(s). Patient demographics, NICU admission & discharge dates, underlying conditions, and clinical histories were systematically collected from participant medical records using information obtained from medical orders and nursing/progress notes. Clinical history of death, seizure, anaphylaxis, fever, diarrhea, hematochezia, increase in abdominal girth, intussusception, melena, volvulus, vomiting, hepatic failure, Kawasaki, sepsis, urinary tract infection, bronchiolitis, intubation/reintubation, nasal discharge, pneumonia, secretions, upper respiratory tract infection, angioedema, urticaria, antibiotics, and apneas and bradycardias were ascertained during inpatient hospitalization in the three days preceding RV5 administration through the first of either 28 days following RV5 administration, or patient discharge. Feeding histories and total parenteral nutrition status on the day of and in the seven days following RV5 vaccination were also collected during hospitalization.

2.3.2. Active surveillance

Reports of nosocomial rotavirus gastroenteritis cases for the study period were collected from hospital infection control surveillance databases designed to track healthcare-associated infections. As part of routine infection control procedures, stool of NICU patients was actively tested for rotavirus antigen when ordered by a neonatologist if a patient experienced symptoms of gastroenteritis, as explicitly defined by the Centers for Disease Control & Prevention/National Healthcare Safety Network (CDC/NHSN) [34], without other apparent cause. At the time of the study, rotavirus was the only enteric viral pathogen for which hospital laboratory testing was routinely available. Stool specimens were tested at the hospital laboratory via the commercially available Premier™ Rotaclone® (Meridian Bioscience, Inc.) enzyme immunoassay (EIA) kit, per manufacturer instructions.

Total person-time spent in the NICU, aggregated by 28-day periods, during the study period was obtained from administrative databases that track patient admissions, discharges, and transfers by unit.

2.4. Outcomes & definitions

RV5 tolerance was examined based upon several clinical and feeding outcomes. Clinical outcomes examined were: (i) comparison of the risk of gastrointestinal complications in the 3 days preceding and up to 28 days following RV5 vaccination, where gastrointestinal complications were defined as: diarrhea (at least 3 stools within a 24-h period, with duration of liquid stools (i.e., diarrhea) lasting at least 12 h), hematochezia, an increase of at least 10% in abdominal girth from baseline, intussusception, melena, volvulus, or vomiting (per medical chart, does not differentiate from reflux or regurgitation); and (ii) any significant clinical event occurring up to 28 days following RV5

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