National guidelines recommend rotavirus vaccination to inpatient preterm infants

Lina Schollin Ask¹, Lisen Wingren², Jann Storsaeter¹

¹Public Health Agency, Sweden
²Sachsska Children and Youth Hospital, Stockholm, Sweden
Abstract:

Aim: The aim was to perform a literature search of the latest evidence of administration of dose 1 of rotavirus vaccine to children admitted in neonatal intensive care or special care unit settings.

Methods: The literature search focused on the outcome of serious adverse events of rotavirus vaccination in vaccinated children and on possible symptomatic infection in controls and in unvaccinated children via transmission of the vaccine virus in the same ward. Results and guidelines were discussed with a working group selected from the national advisory group of child health. Also, a survey to neonatal care units in Sweden were sent out due to the subject.

Results: Administration of rotavirus vaccine is safe for age-eligible preterm children and unvaccinated children in the same ward. A satisfactory immune response has been shown and basic hygiene routines is enough. Also, hospitalized age-eligible children with paediatric surgical conditions should be considered the rotavirus vaccine.

Conclusion: The Swedish Public Health Agency recommends that preterm infants as well as children who are admitted for other reasons in the neonatal ward be vaccinated with dose 1 against rotavirus infection when hospitalized and when age-eligible.
Key notes:

- Preterm children are at risk for severe rotavirus infections but often miss out the vaccine against these infections due to long hospital stays.

- The literature review showed that vaccination leads to a satisfactory response for rotavirus infection and is safe for both vaccinated and unvaccinated children in the same ward.

- This review resulted in national guidelines for rotavirus vaccine administered to age-eligible children in hospital, also preterm children.

Key words: rotavirus vaccine, neonatal intensive care unit, preterm children
Background

Preterm children are at risk for severe rotavirus infection, but these children often miss the rotavirus vaccine (1). In Sweden, this vaccine has been included in the Swedish national immunization programme since September 2019. The World Health Organization (WHO) recommends administration of the first dose of rotavirus vaccine to hospitalised age-eligible children (2), but many countries have not implemented this fully, including Sweden.

The reasons for missed rotavirus vaccinations have mostly been reported as long duration of hospitalisations in this group of children and concerns of symptomatic viral transmission of vaccine strains to unvaccinated children. The first dose has to be administered between the age of 6 to 12 weeks after birth, with no opportunity of delaying the vaccine series. Preterm infants are thereby often too old for the vaccine at the time of discharge.

A need for Swedish national guidelines on this issue has been expressed by the profession. Therefore, the Public Health Agency has performed a literature search of the latest evidence and has discussed guidelines together with a working group selected from the national advisory group of child health.

Methods

PICO

This review focused on the outcome of serious adverse events of rotavirus vaccination in vaccinated children and on possible symptomatic infection in controls and in unvaccinated children via transmission of the vaccine virus in the same ward.

P (Patient, Population): Children admitted in neonatal intensive care units (NICUs), mostly premature children and often with long hospital stays.

I (Intervention): Rotavirus vaccine administered in hospital.

C (Comparison): Non-vaccinated children in NICUs, historical controls.

O (Outcome):

a) Rotavirus infection with symptoms in other non-vaccinated children in NICUs.

b) Severe adverse events in vaccinated children.

c) Uncontrolled spread of vaccine virus in the hospital or outside of the hospital.
Procedure
A literature search was performed in February 2020 and repeated in September 2020. The search strategy was applied in Scopus, PubMed, Web of Science, DiVA, SveMed+ and Google Scholar. Search terms used were immunity, immunization, vaccination*, vaccine*, nicu, "neonatal intensive care unit*", rotavirus, RV. Publications between the years 2000-2020 were included in the search process. Articles from Google Scholar, Pubmed, Web of Science and Google Scholar were included in the review process. The selection process of relevant articles was further carried out by two persons independently of each other (LSA, JS). References from the reference lists of the chosen articles were also considered. Thereafter, consensus was reached through discussion according to the pre-defined PICO.

Reference group
The evidence and recommendations have been discussed repeatedly with a national reference group consisting of representatives from child health care, paediatric care, and neonatal care units from different regions in Sweden. The participants in the reference group were selected by the national advisory group on child health.

Survey of the neonatal wards
A questionnaire-based survey was sent by e-mail to 24 of all 36 Swedish neonatal special care units. We had contact information of only those 24. The questions focused on whether the unit was administering rotavirus vaccine already to hospitalised children, and if so, their experiences from this. There were also questions regarding concerns and barriers for administering rotavirus vaccine in the units. The questionnaire can be sent upon request to the authors.

Results

Literature review
The selection process from the literature search is presented in figure 1. In total, 70 articles were found at first due to the search terms, in the searched databases. Out of these, 24 articles were selected from titles and abstract review, resulting in altogether seven articles that corresponded with the defined PICO. Two of the seven articles were found via the reference lists from the first five selected articles (Figure 1). An additional two major studies (Table 2) and three articles (Table 3) related to paediatric surgery patients, not included in the PICO, are also presented in the results below due to their important findings.
A literature review with the same ambition was recently conducted by Canadian and American researchers, and for studies of rotavirus transmission from vaccinated children to unvaccinated children but without symptoms, see Sicard et al (3). The work by the Swedish Public Health Agency was based on this previous review plus some further studies, as described below.

Figure 1.

Summary of the included articles in the PICO
The seven articles included in the PICO presented evidence that administration of the rotavirus vaccine in the neonatal special care unit is safe for both vaccinated and unvaccinated children and results in a good immune response in vaccinated infants.

Studies not included in the PICO but important to present
Three articles about children with gastrointestinal conditions needing surgery presented results showing that these children tolerated the vaccine well. However, the responsible surgeon needed to be consulted in each case in this group of children.

Two larger studies, not included in the PICO, of administration of rotavirus vaccine to preterm children during hospitalisation also presented results of safe and immunogenic in-hospital vaccination.

Table 1.

Results from the survey
In November and December 2020, a questionnaire-based survey was sent by e-mail to all neonatal wards in Sweden regarding the current administration of rotavirus vaccine to hospitalised patients and concerns regarding in-hospital rotavirus vaccination. Twenty-two out of 24 contacted units answered the survey, and four of these units were already administering rotavirus vaccine to patients admitted to the neonatal ward. The most common practice was to administer the rotavirus vaccine concomitantly with the hexavalent vaccine (against diphtheria, tetanus, pertussis, polio, *Haemophilus influenzae* type b, and hepatitis B). The experiences so far regarding giving the first dose of rotavirus vaccine to admitted patients have been positive.
Concerns were raised primarily due to the theoretical risk of horizontal transmission of rotavirus to unvaccinated patients.

**Discussion**

The Swedish Public Health Agency recommends that preterm infants as well as children who are admitted for other reasons in the neonatal ward be vaccinated with dose 1 against rotavirus infection when hospitalised and when age-eligible.

The evidence shows that this leads to a good immune response to the vaccine and is safe both for those who are vaccinated and for unvaccinated children in the same ward.

In addition to the usual hygiene routines, no extra hygiene measures are needed regarding vaccination against rotavirus infection. An important issue in the context of rotavirus vaccination is the described increased risk of the rare but serious condition of intussusception with 1-6 cases per 100,000 vaccinated children, most often the first week after the first dose (16). It is important to both educate the staff in the neonatal wards and to inform the parents about this in the light of administration of the rotavirus vaccine in hospital.

The studies included based on the predefined PICO were relatively small studies and included different outcomes, presented in the result-part, table 1. In addition, we presented two larger studies, which were not included in the defined PICO but which served as a clear support for the overall conclusions. Also, three studies were presented as a supplement, focusing on infants with special paediatric surgical conditions because this is a group of children important to consider for rotavirus vaccination in hospital due to the increased risk of severe rotavirus infection. These recommendations need to be followed up in the near future by the Public Health Agency in order to assure that premature and other hospitalised infants have access to the complete national immunisation programme.
Acknowledgments: A big thank you to the national reference group consisting of representatives from child health care, paediatric care, and neonatal care units from different regions in Sweden.

List of abbreviations:
The World Health Organization          WHO
Neonatal intensive care units          NICU
Population Intervention Control Outcome PICO
Rotavirus vaccination                  RV

Statement: No conflict of interest. No funding.
References:

1. Newman RD, Grupp-Phelan J, Shay DK, Davis RL. Perinatal risk factors for infant hospitalization with viral gastroenteritis. Pediatrics. 1999;103(1):E3.

2. World Health Organization. Rotavirus. https://www.who.int/immunization/diseases/rotavirus/en/ Accessed May 2021.

3. Sicard M, Bryant K, Muller ML, Quach C. Rotavirus vaccination in the neonatal intensive care units: Where are we? A rapid review of recent evidence. Current opinion in pediatrics. 2020;32(1):167-91.

4. Briggs-Steinberg C, Aboudi D, Hodson G, Shah S. Clinical Tolerance of In-Neonatal Intensive Care Unit Administration of Rotavirus Vaccine. American journal of perinatology. 2019.

5. Jaques SC, Ogley L, Duffy D, Kennea N. Rotavirus immunisation in NICU: A 1-year experience in a uk tertiary neonatal surgical unit postvaccine introduction. Arch Dis Child Fetal Neonatal Ed. 2015;100(2):F186-F7.

6. Monk HM, Motsney AJ, Wade KC. Safety of rotavirus vaccine in the NICU. Pediatrics. 2014;133(6):e1555-e60.

7. Hiramatsu H, Suzuki R, Nagatani A, Boda H, Miyata M, Hattori F, et al. Rotavirus vaccination can be performed without viral dissemination in the neonatal intensive care unit. J Infect Dis. 2018;217(4):589-96.

8. Thrall S, Doll MK, Nhan C, Gonzales M, Perreault T, Lamer P, et al. Evaluation of pentavalent rotavirus vaccination in neonatal intensive care units. Vaccine. 2015;33(39):5095-102.

9. Kilich E, Sadarangani M. Use of rotavirus vaccines in preterm babies on the neonatal unit. Expert review of vaccines. 2016;15(12):1463-5.

10. Roue JM, Nowak E, Le Gal G, Lemaitre T, Oger E, Poulhazan E, et al. Impact of rotavirus vaccine on premature infants. Clinical and vaccine immunology : CVI. 2014;21(10):1404-9.

11. Fang AY, Tingay DG. Early observations in the use of oral rotavirus vaccination in infants with functional short gut syndrome. Journal of paediatrics and child health. 2012;48(6):512-6.
12. McGrath EJ, Thomas R, Duggan C, Asmar BI. Pentavalent rotavirus vaccine in infants with surgical gastrointestinal disease. Journal of pediatric gastroenterology and nutrition. 2014;59(1):44-8.

13. Javid PJ, Sanchez SE, Jacob S, McNeal MM, Horslen SP, Englund JA. The Safety and Immunogenicity of Rotavirus Vaccination in Infants With Intestinal Failure. Journal of the Pediatric Infectious Diseases Society. 2014;3(1):57-65.

14. Hofstetter AM, Lacombe K, Klein EJ, Jones C, Strelitz B, Jacobson E, et al. Risk of rotavirus nosocomial spread after inpatient pentavalent rotavirus vaccination. Pediatrics. 2018;141(1).

15. Omenaca F, Sarlangue J, Szenborn L, Nogueira M, Suryakiran PV, Smolenov IV, et al. Safety, reactogenicity and immunogenicity of the human rotavirus vaccine in preterm European Infants: a randomized phase IIIb study. The Pediatric infectious disease journal. 2012;31(5):487-93.

16. World Health Organization. Global Advisory Committee on Vaccine Safety, 6-7 December 2017. https://www.who.int/vaccine_safety/committee/reports/Dec_2017/en/ Accessed May 2021

Figures

Figure 1. Procedure of the literature review
Summary of the included articles

- **PICO**
- Literature search
  - Title and Abstract review
    - Full text review, 5 fulfilling PICO
      - 13 Additional relevant references from reference lists
        - 7 articles included in the rapid review

70 articles
→ 24 articles
→ 5 articles
→ + 2 articles

Accepted Article
### Table 1. Studies included in the literature review

| Author                | Journal, Year | Context | Population | Intervention | Comparison group | Outcome | Conclusion |
|-----------------------|---------------|---------|------------|---------------|------------------|---------|------------|
| Briggs-Steinberg, C.  | Am J Perinatol, 2019 (4) | USA, NY, 2015-2017 | Preterm children N=201 (from who 193 <GA (gestational age) week 32) | RV(rota-virus vaccine) administered in the NICU | Historical controls (N=189) | Serious adverse events, mainly apnea and bradycardia | 5-valent rotavirus vaccine was well tolerated in preterm infants, administered during admission. No increase in serious side effects related to the 5-valent rotavirus vaccine. |
| Jaques, S. C.         | Archives of Disease in Childhood | Children GA week 24-40) N=19 | RVadministered in the NICU | - | Serious adverse events | No serious adverse events. |
| Author            | Study Details                                                                 | Methods                                                                 | Results                                                                 |
|-------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------|------------------------------------------------------------------------|
| Monk, H. M.       | American Academy of Pediatrics, 2014 (6)                                       | Children in NICU (N=96) followed until 15 days after RV administered in the NICU | Gastrointestinal symptoms within 15 days after RV. In the unvaccinated group focus on symptoms followed until 15 days after RV of the “neighbour” |
|                   | USA, Philadelphia 2008-2010                                                   | Unvaccinated children in the same NICU, near the vaccinated children (N=801) followed until 15 days after RV | No symptomatic transmission of vaccine virus. |
| Hiramatsu H.      | J Infect Dis, 2018 (7)                                                        | Children in the NICU, median GA week 27. RV administered in the NICU | Rotavirus in faeces (PCR) Clinical symptoms \(N=19\) unvaccinated children per vaccinated child, in the same ward, the same “pod” (distance inbetween 0.6-1.5 m). | No transmission of rotavirus strains from vaccinated to unvaccinated children within the same neonatal ward. After dose 1 of the rotavirus vaccine, secretion of virus in faeces was noted in all 19 vaccinated children on day 1–8. After the second dose, |
The duration of excretion of rotavirus was shorter (up to 5 days). No excretion was seen in unvaccinated children from the same ward.

**Thrall, S.**

*Vaccine, 2015 (8)*  
Canada, Montreal, two hospitals  
2011-2013

| Children in the NICU, N=102 | RV administered in the NICU | Historical controls | -Gastro-intestinal symptoms, 3 days-4 weeks after RV | -Levels of nosocomial rotavirus infection. |
|-----------------------------|-----------------------------|---------------------|------------------------------------------------------|------------------------------------------|

It was notable that apnoea and bradycardia were reported in 18% of infants after rotavirus vaccination. In all of those cases however, the rotavirus vaccine was administered at the same time as other routine vaccinations.

**Kilich, E.**

*Arch Dis Child Fetal Neonatal Ed, 2015*(9)  
UK,  
N=5 preterm children GA < week 32

| RV administered in the NICU | Historical controls | Serious adverse events | No serious adverse events. |
|-----------------------------|---------------------|------------------------|--------------------------|

No spread of rotavirus to unvaccinated children.
II) Studies of specific risk groups needing rotavirus vaccination outside the PICO

| Fang, A. Y. | Infants with ileostomy, in hospital and fully enteral feeded, age-eligible for RV. | RV administered in the NICU | Historical controls | Feeding situation and fluid losses via the ileostomy. | Suspected/confirmed sepsis | Sodium in the urine | Faeces-culture | Data was collected daily 1 week before to 2 weeks after vaccination. | The rotavirus vaccine was tolerated in the included small study population. |
|-------------|----------------------------------------------------------------------------------|-----------------------------|---------------------|----------------------------------------------------|--------------------------|-------------------|---------------|---------------------------------------------------------------|---------------------------------------------------------------------|
| J Paediatr Child Health, 2012 (11) Australia, Melbourne | N=9 (7 of these were preterm born and have suffered from necrotisizing enterocolitis ) | | | | | | | | | One child developed serious losses of fluid after the rotavirus vaccination. |
| July 2007 - July 2009 | | | | | | | | | | The rotavirus vaccination did not affect weight development, body temperature, or sodium levels in the urine in the included children. |

Preterm children both admitted in the NICU and outside the NICU N=217

Preterm children tolerated the rotavirus vaccine well.

RV Full-grown children N= 6883 Subanalysis: Severe adverse events

Hospitalized gastroenteritis

Preterm children tolerated the rotavirus vaccine well.
| Study                          | Country | Subjects | Intervention | Outcomes                                                                 |
|-------------------------------|---------|----------|--------------|---------------------------------------------------------------------------|
| McGrath, E. J.                | USA     | N=5      | RV           | Controls are healthy infants matched for age and GA (36-40 gestational weeks). N=3 | Immune response The rotavirus vaccine was well tolerated with an adequate immune response in the vaccinated children. |
| Javid, P. J.                  | USA     | N=14     | RV           | Historical controls Virus-shedding in faces Bloodtest, vaccine derived antibodies Follow up 6 months after RV (N=12) | Excretion of rotavirus in faeces was seen in 47% of the vaccinated children, but only one child remained excreting after 2 weeks. Rotavirus vaccination is safe and results in an adequate immune response in preterm children. |

III) Studies outside the PICO but important for vaccination against rotavirus in hospital

| Hofstetter, A. M.             | USA     | N=127    | RV adminstered in hospital | N=258 Non vaccinated children, treated in hospital same period | Shedding Rotavirus strains i faeces Rotavirus vaccine strains were not detected in unvaccinated children. One |
USA, Georgia
Feb 2013 - April 2014
N stools= 1192 (976 unvaccinated and 216 vaccinated)

| Eligible for RV | As vaccinated children | Unvaccinated children had virus strains wild-type. |
|----------------|------------------------|--------------------------------------------------|

12 vaccinated children had virus-related strains in the faeces.

Omenaca, F.
Pediatr Infect Dis J, 2012 (15)
Spain, France, Poland and Portugal

N=1009
Early preterm GA week 27-30 and children GA week 31-38
RV, 2 doses administered at discharge
Placebo 2 doses
Adverse events and levels of IgA for rotavirus

No differences were seen in adverse events between vaccinated and unvaccinated preterm children.

* included through reference lists after the first literature search