An Advisory Committee Statement (ACS) Update National Advisory Committee on Immunization (NACI)

Statement on Rotavirus Vaccines and Intussusception

PROTECTING CANADIANS FROM ILLNESS

Public Health Agency of Canada
Agence de la santé publique du Canada

Canada

TO PROMOTE AND PROTECT THE HEALTH OF CANADIANS THROUGH LEADERSHIP, PARTNERSHIP, INNOVATION AND ACTION IN PUBLIC HEALTH.

—Public Health Agency of Canada

Également disponible en français sous le titre :
Déclaration sur les vaccins antirotavirus et l'intussusception

This publication can be made available in alternative formats upon request.

Publication date: April 2016

Cat.: HP40-153/2016E-PDF
ISBN: 978-0-660-05017-1
Pub.: 150284

PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (hereafter referred to as the Agency) with ongoing and timely medical, scientific, and public health advice relating to immunization. The Agency acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian manufacturer(s) of the vaccine(s). Manufacturer(s) have sought approval of the vaccine(s) and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of the Agency's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

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SUMMARY OF INFORMATION CONTAINED IN THIS NACI STATEMENT

The following summary highlights key information for immunization providers. Please refer to the remainder of the Statement for details.

1. What

Intussusception occurs at a background rate of about 34 per 100,000 per year in the first year of life. The current rotavirus (RV) vaccines, Rotarix™ (GlaxoSmithKline [GSK] Inc.) and RotaTeq® (Merck & Co, Inc.), have demonstrated a small increased risk of intussusception, of between 1 and 7 cases per 100,000 doses.

2. Who

Infants receiving either their first or second dose of RV vaccine.

3. How

Although there is no evidence that children who have a history of intussusception are at a higher risk of another intussusception after receiving RV vaccine, as a precaution, infants with a history of intussusception should not be given RV vaccine.

4. Why

Parents should be informed of the benefit of RV vaccination in preventing or mitigating severe diarrheal disease in infants. Parents should be informed of the low risk of intussusception following RV vaccine, particularly during the 7 days following the first dose. Parent education should include the signs and symptoms of intussusception and the importance of seeking medical care, should symptoms develop.

I. INTRODUCTION

Intussusception in the first year of life occurs at a background rate of about 34 per 100,000 per year; however, the rate varies with age in the first year of life and peaks between 5 and 10 months[1].

In 1998, a RV vaccine (RotaShield®, Wyeth-Ayerst) was recommended for routine vaccination of infants in the United States of America (USA), but was withdrawn from the market after initial postmarketing surveillance and epidemiologic investigations confirmed an increased incidence of intussusception following vaccination.

As a result, when the next generation of RV vaccines was developed, very large safety trials were conducted and more attention was paid to the epidemiology of both RV illness and intussusception. Administration of the first dose of vaccine was limited to infants less than 90 days of age, before the period when intussusception is most common. The risk of intussusception was evaluated for Rotarix™ (Rot-1) and RotaTeq® (Rot-5) vaccines, and no evidence of clustering of cases of intussusception was observed within a 7-day or 14-day window after vaccination for any dose. Of 71,725 infants enrolled in Rot-5 vaccine trials, six cases of intussusception were observed in the Rot-5 vaccine group versus five cases in the placebo group within 42 days of any vaccine dose. Of 63,225 infants enrolled in Rot-1 vaccine trials, six cases of intussusception occurred within 31 days of either dose of vaccine in the Rot-1 vaccine group and 7 cases in the placebo group. Across all clinical trials, the reported frequency of intussusception was 0.047% for Rot-1 vaccine recipients and 0.05% for placebo recipients. None of these differences was statistically significant.

Subsequent to those trials, a signal emerged in early adopting countries, suggesting a small increased risk of intussusception. This Statement reviews the post marketing safety studies and the risk as it relates to the current RV vaccines available in Canada.

The burden of illness from RV disease in Canada before vaccine availability is documented in studies by the Canadian Immunization Monitoring Program, Active (IMPACT)[2]. Following the start of publicly funded immunisation programs in 3 provinces and one study jurisdiction - representing 7 of the 12 IMPACT hospitals - the overall rate of hospital admissions was documented before and after implementation[3]. From a total of 1592 hospitalizations for RV infection (1261 community and 331 hospital-acquired), admissions at sites with publicly funded programs have significantly decreased between 2011 and 2013, while the rates at sites without programs have not.

In Ontario, when comparing RV specific gastroenteritis hospitalization in the post-vaccine period (Aug 2011 to Mar 2013) to the pre-vaccine period (Jan 2003 to July 2006), the relative risk of hospitalization adjusted for age and seasonality was 0.25 (95% confidence interval [CI] of 0.20 to 0.32).

II. ROTAVIRUS VACCINE AND INTUSSUSCEPTION

Following the introduction of routine infant RV immunization programs in Mexico, Brazil and Australia, evidence from post-marketing surveillance for intussusception suggested a small increased risk. This increase appeared mainly in the period of 1-7 days following the first dose of RV vaccine. In Mexico, receipt of Rot-1 was associated with a small excess risk of intussusception in the 7 days following dose 1 of approximately 1.96 cases per 100,000 doses

in vaccinated infants[4]. A small but less consistent increased risk was observed following dose 2. In Brazil[4], where OPV is co-administered with Rot-1, there was no increased risk of intussusception in the 7 days following the first dose of ROT-1 when co-administered with oral polio vaccine (OPV) during routine surveillance, but OPV virus replication is greatest in this time period and has been shown to interfere with RV vaccine replication. However, there was a small excess risk of intussusception in the 7 days following dose 2 in 1.47 per 100,000 vaccinated infants. In Australia, post-marketing surveillance demonstrated a small excess risk of intussusception following the first dose of either Rot-1 or Rot-5 of 2 per 100,000 vaccinated infants.

Following those early signals, additional information regarding the risk of intussusception with the current RV vaccines became available from Australia[5] and the United States of America[6-8]. In Australia, both Rot-1 and Rot-5 vaccines continued to be used in their publicly funded program[5]. A total of 320 cases of intussusception were identified from national hospitalization databases and active surveillance between 2007 and 2010. These cases were used in a self-controlled case series analysis (n=306) and a case-control study (n=291). The vaccine attributable risk for intussusception in the 1–21 days after dose 1 and the 1–7 days after dose 2 was estimated to be 4.3 (95% CI, 0.8–23.3) cases per 100,000 infants vaccinated for Rot-1 and 7.0 (95% CI, 1.5–33.1) cases per 100,000 for Rot-5. Given the substantial overlap in the CI, the attributable risk was considered to be the same for both vaccines and the authors proposed a mid-range estimate of 5.6 additional cases of intussusception per 100,000 vaccinated infants.

In the USA, data were available from the Vaccine Adverse Event Reporting System (VAERS)[6], the Vaccine Safety Datalink (VSD) and the Post-licensure Rapid Immunization Safety Monitoring system (PRISM)[7, 8]. VSD is a network of linked databases involving nine health maintenance organizations and PRISM is a sentinel-like system using claims data from national health insurance companies. VAERS data for Rot-5 showed reported cases clustered between day 3 and 6 after doses 1 and 2, with 584 confirmed cases of intussusception reported for 47 million doses distributed. However the reporting ratio was not elevated after dose 2 indicating that that risk did not appear elevated for that dose. For Rot-1 (implemented some 2 years later), 66 confirmed intussusception cases were reported for 7.4 million doses distributed. The VSD analyses identified a small cluster of cases following Rot-1, with 3 cases of intussusception for 100,000 doses administered. In contrast, no such cluster was found with Rot-5, with 8 intussusception cases identified (4 each after dose 1 and dose 3) for 1.3 million doses administered. In the PRISM data, Rot-5 was associated with clusters of intussusception cases with an attributable risk of approximately 1 case per 100,000 doses. The number of cases was too small to allow a calculation for Rot-1.

In Canada, from 2011 to the end of 2014, over 2 million doses of RV vaccine were distributed. During that time period, a total of 556 Adverse Events Following Immunization (AEFI) reports were received, with 19 case reports of intussusception[9]. This represented a reporting rate of 0.9 cases per 100,000 doses distributed, similar to what has been observed from postmarketing studies in other countries. However, only fifteen of the cases occurred within 21 days of immunization and the remaining four had onset from 42 to 155 days, and thus were unlikely related to RV vaccination.

The Global Advisory Committee on Vaccine Safety (GACVS) of the World Health Organization reviewed the new findings from Australia and the United States of America, confirming a risk of intussusception following administration of both vaccines[10]. The Committee noted that attributable risk estimates vary across studies, likely reflecting differences in background rates of intussusception (for example, the rate is estimated to be double in Australia compared to the

USA) but also reflecting sampling uncertainty, differences in case definitions and limitations in surveillance systems. However, GACVS also noted that the findings remain reassuring that the risk of intussusception following current RV vaccines remains small compared to the benefits of preventing the impact of severe diarrhea.

III. RECOMMENDATIONS

Recommendation #1

RV vaccines continue to be recommended for infants starting at 6 weeks to less than 15 weeks of age. **(*NACI recommendation – Grade A)***

As post-licensure studies of Rotarix™ and RotaTeq® suggest a low but excess risk of intussusception, parents should be informed of this low risk of intussusception following RV vaccine, particularly during the 7 days following the first dose. Parents should also be counselled regarding the signs and symptoms of intussusception and the importance of seeking medical care, should symptoms develop. They should also be informed that the risk of intussusception remains small compared to the benefit of RV vaccination in preventing disease, and of the potential for severe diarrhea with Rotavirus. As to the magnitude, the differences between the vaccines are marginal, and overall amount to between 1 to 7 cases per 100,000 doses for the current vaccines.

Recommendation #2

NACI concludes based on expert opinion to recommend against immunization of children with a history of intussusception, as a precaution, based on the theoretical risk of recurrence following rotavirus vaccine. **(*NACI recommendation – Grade D)***

There is no evidence that children who have a history of intussusception are at a higher risk of another intussusception after receiving RV vaccine. The recommendation to avoid RV vaccination in children who have previously had intussusception is based on expert opinion, considering that about 4% of infants with intussusception will have another episode in the following year; there is an incomplete understanding of the pathogenic mechanisms underlying that increased risk, and as children with a history of intussusception were excluded from immunogenicity and efficacy trials, there are no data on use of the vaccine in infants who have had intussusception. Nevertheless, as a precaution, infants with a history of intussusception should not be given RV vaccines.

Finally, vaccine providers are asked to report intussusception in the first 21 days following any dose of RV vaccine, through local public health officials.

TABLE

Table 1. NACI Recommendation for Immunization -- Grades

A	NACI concludes that there is **good** evidence to recommend immunization.
B	NACI concludes that there is **fair** evidence to recommend immunization.
C	NACI concludes that the existing evidence is **conflicting** and does not allow making a recommendation for or against immunization; however other factors may influence decision-making.
D	NACI concludes that there is **fair** evidence to recommend against immunization.
E	NACI concludes that there is **good** evidence to recommend against immunization.
I	NACI concludes that there is **insufficient** evidence (in either quantity and/or quality) to make a recommendation, however other factors may influence decision-making.

LIST OF ABBREVIATIONS

Abbreviation	***Term***
AEFI	Adverse Events Following Immunization
CI	Confidence Interval
GACVS	Global Advisory Committee on Vaccine Safety
GSK	GlaxoSmithKline
IMPACT	Canadian Immunization Monitoring Program, Active
NACI	National Advisory Committee on Immunization
OPV	Oral polio vaccine
PRISM	Post-licensure Rapid Immunization Safety Monitoring system
Rot-1	Rotarix™
Rot 5	RotaTeq®
RV	Rotavirus
VAERS	Vaccine Adverse Event Reporting System
VSD	Vaccine Safety Datalink

ACKNOWLEDGMENTS

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