

# Recommendations for the use of rotavirus vaccines in infants

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## Abstract

The present statement provides information concerning the clinical rotavirus disease and rotavirus vaccines in Canada. Since the implementation of publically funded rotavirus vaccine programs in Canada, increasing evidence has been accumulating globally as to the effectiveness of rotavirus vaccines in the prevention of acute gastroenteritis. Current data estimate vaccine effectiveness to be in the order of 85% for preventing severe disease, including hospitalizations and emergency department visits, when vaccine coverage is high. Also, substantial herd protection in older children has been documented. Post-marketing surveillance has detected a very small increased risk of intussusception (one to three per 100,000) in children, usually occurring within 1 week of vaccination. Infants who have an identified significant immune deficiency or are suspected of having such a condition should not receive rotavirus vaccine.

**Keywords:** Acute gastroenteritis, Diarrhea, Intussusception, Oral vaccine, Rotavirus, Vaccine

The purpose of the present statement is to provide recommendations for the use of rotavirus vaccine to protect infants in Canada. It summarizes information on clinical disease and epidemiology, as well as on the safety and efficacy of rotavirus vaccines currently licensed for the prevention of rotavirus disease in Canada. Routine rotavirus vaccination is recommended for infants and is publically funded in most provinces and territories. This statement replaces a previous rotavirus statement published in 2010 [1].

## THE VIRUS

Rotaviruses are double-stranded RNA viruses. The serotype is defined by two outer capsid proteins: VP7, the glycoprotein (G protein) and VP4, the P protein which defines the virus serotype. Most human infections to date have been caused by four rotavirus genotypes: G1P(8), G2P(4), G3P(8) and G4P(8), with the G1 strain being the most common in Canada [2]. Other regions of the world may have emerging serotypes, including G9, G5, G6 and G8 [3].

## CLINICAL DISEASE AND DIAGNOSIS

Rotavirus is transmitted via the fecal-oral route and by fomites and can remain viable for months on objects (including toys and inanimate objects in the environment) if they are not disinfected. The incubation period of rotavirus infection is short, usually less than 48 hours. Acute onset of vomiting and fever may precede diarrhea. Rotavirus gastroenteritis is generally considered to be more severe than gastrointestinal illness due to other causes because it is associated more often with vomiting and leads to significant diarrhea caused by injury to gut epithelium. The clinical disease may also be accompanied by viremia, which contributes to its often severe presentation, especially in young infants [4]-[6]. In the first 3 months of life, disease is generally mild due to the presence of maternal antibodies. Between the ages of 3 months and 5 years, there is a spectrum of disease from mild watery diarrhea to severe diarrhea, with or without vomiting. The gastrointestinal symptoms usually resolve in 3 to 7 days. When the illness is severe, it can lead to significant dehydration, shock and death if infection is not managed with adequate, appropriate fluids. The most severe manifestations usually occur with the first episode of infection, while subsequent infections are milder or subclinical. In one study done in Mexico, after a single natural infection, 40% of children were protect-

ed against any subsequent infection, 75% were protected against rotavirus diarrhea, and 88% were protected against severe rotavirus diarrhea [7].

There are few recognized risk factors for severe rotavirus disease. In one Canadian prospective study, socioeconomic factors, parental marital status, child care attendance and ethnicity did not influence the rates of hospitalization due to rotavirus [8]. Premature infants are at higher risk for severe rotavirus infection, possibly because they lack transplacental maternal antibodies. One study has shown breastfeeding to be somewhat protective against symptomatic rotavirus infection [9]. Immunocompromised children are known to be at higher risk for severe, prolonged and even fatal rotavirus gastroenteritis [10][11].

Because the clinical features of rotavirus infection are nonspecific, diagnosis cannot be made on clinical grounds alone. The laboratory test most frequently used to confirm diagnosis is antigen detection in stool by enzyme immunoassay, but molecularly-based testing is now also available in some laboratories.

## ROTAVIRUS VACCINES

In 1998, RotaShield (Wyeth-Lederle Vaccines, USA), a tetravalent rhesus human reassortant rotavirus vaccine, was withdrawn from the market within 1 year of release because of an increased association with intussusception occurring within 3 to 14 days of immunization [12]. The risk was greatest with the first dose and when given after 8 months of age. It was because of this experience with RotaShield that currently licensed rotavirus vaccines have required extremely large studies to ensure detection of a relatively rare event.

Two vaccines are currently licensed in Canada. The first, RotaTeq (RV5), manufactured by Merck Frosst Canada, was approved in 2006. This is a live, oral, pentavalent bovine human reassortant vaccine composed of five strains. Four reassortant strains express the outer capsid proteins G1, G2, G3 and G4 derived from human parent strains and the attachment protein P7 from the bovine RV parent strain. The fifth reassortant strain expresses the outer capsid protein G6 from the bovine rotavirus parent strain and the attachment protein P1(8) from a human parent strain. RotaTeq is supplied in single prefilled 2 mL tubes and given as three oral doses.

The second vaccine, Rotarix (RV1), approved in 2008, is manufactured by GlaxoSmithKline Biologicals (Belgium). This is a live-attenuated monovalent G1P1(8)

vaccine derived from a single human strain, RIX4414. G1 types are the most common circulating strains worldwide, including Canada, and many other circulating strains share the same P antigen. Also, there is some cross-reactivity between the G1 in the vaccine and other G types. Rotarix is given orally in two doses and is supplied in single prefilled 1.5 mL tubes.

Both vaccines can be started at 6 weeks of age or given at the same time as regularly scheduled routine childhood immunizations, with a minimal interval between doses of 4 weeks. The last dose must be given before 8 months, 0 days of age because of concern about intussusception when given later. The Public Health Agency of Canada's National Advisory Committee on Immunization (NACI) indicates that the first dose should be given before a child is 14 weeks, 6 days of age. However, if this first dose of RV1 was not administered before that point, a catch-up first dose can be administered up to 20 weeks of age [13]. Both vaccines are latex-free. Since both are live virus vaccines, they should be stored in a refrigerator at 2°C to 8°C, and they do not require reconstitution before administration.

Because rotavirus vaccines contain sucrose, which helps decrease pain experienced with injectable vaccines, it may be helpful to administer the oral rotavirus vaccine before injectable vaccines [14].

It is not known whether these vaccines are interchangeable, so the series should be completed using the same product as for the first dose, if practical. However, if any dose in the series was the RV5 vaccine, a total of three doses of vaccine should be administered [13].

## EPIDEMIOLOGY OF ROTAVIRUS DISEASE BEFORE AND AFTER ROTAVIRUS VACCINE PROGRAMS

Before the widespread use of vaccines, the vast majority of children experienced at least one episode of rotavirus infection by 5 years of age, regardless of socioeconomic status or geographic location. In the pre-vaccine era, gastroenteritis caused by rotavirus had predictable seasonality, with onset in November and December and peaking in February to March in Western Canada and a correspondingly later peak in incidence in March to April in Eastern Canada.

Because only a minority of children with rotavirus disease require hospitalization, most children who need medical attention are seen in family physician or paediatric

atricians' offices or clinics, or in emergency departments. In one study of child care centres in Toronto, Ontario, over an 8-month period, 60% of children received medical care for diarrhea: 17% went on to visit an emergency room, while 6% were hospitalized or received intravenous hydration in the emergency room for diarrheal illnesses [15]. In the pre-vaccine era, rotavirus infections accounted for 4% to 5% of hospitalizations for any indication in children younger than 5 years of age in the USA [16]. A study of 1359 children hospitalized between 2005 and 2007 for community-acquired rotavirus infection in 12 Canadian paediatric hospitals indicated that >60% of children were <2 years of age. Most (68%) had no underlying illnesses. The majority (69%) had all three symptoms of vomiting, diarrhea and fever. One-third of patients had more than one outpatient visit before hospital admission. The median duration of hospitalization was 3 days [17]. In Quebec, 58% of all hospitalizations took place in short-stay units and accounted for 50 to 74 per 10,000 hospitalizations in the pre-vaccine era [18]. Surveillance in paediatric hospitals in Canada also revealed that 27% of all hospitalized children with rotavirus had hospital-acquired infection [19].

Although mortality from rotavirus is extremely rare in Canada, morbidity associated with an acute rotavirus infection is not dissimilar to that for other common childhood illnesses, such as uncomplicated pneumonia or acute otitis media [20]. As such, without vaccination, the societal costs borne by parents are substantial. These costs, in addition to health care costs, were estimated at \$125 million over 5 years for each birth cohort [21]. Rotavirus vaccines were publicly funded in parts of Canada starting in late 2011 and to date are part of the routine immunization programs in most provinces and territories (<http://healthycanadians.gc.ca/healthy-living-vie-saine/immunization-immunisation/children-enfants/schedule-calendrier-table-1-eng.php>).

Since the introduction of rotavirus immunization programs, numerous studies have demonstrated a substantial decline in rotavirus disease. Efficacy in the group <2 years of age has been estimated at 85%, with sustained protection in the first 2 to 3 years of life [22]–[28]. The Canadian Immunization Monitoring Program, ACTive (IMPACT), a paediatric hospital surveillance system, has also noted a decrease in the incidence of rotavirus hospitalizations in jurisdictions with immunization programs [29]. Ontario, using RV1, specifically reported significant rate reductions for RV-specific gastroenteritis as well as acute unspecified gastroenteritis hospitalizations and emergency department

visits compared with the pre-program period. There was a 79% decrease in RV gastroenteritis hospitalizations among infants <1 year of age and a 73% decrease among babies 12 months to 23 months of age relative to the pre-program period [30]. With early and sustained uptake of rotavirus vaccine, the typical seasonal peaks of yearly activity have been shortened and in some areas even eliminated [31]. Herd protection extending to cohorts of nonvaccinated children—and adults—also demonstrates reductions in disease that are undoubtedly attributable to decreased transmission of wild-type rotavirus. The Ontario study, done only 20 months post-implementation of their public program, clearly demonstrated herd effects, with significant decreases in RV gastroenteritis hospitalizations for all age groups ≤19 years and significant decreases in acute gastroenteritis hospitalizations for all age groups, including those ≥65 years of age [30].

One American study using RV5 reported reductions in rotavirus disease and acute gastroenteritis for children and adults ≤24 years of age, as well as nonsignificant declines in older age groups [32]. In resource-deprived areas of the world, rotavirus vaccine immunization programs have led to significant decreases in death from diarrheal disease and morbidity associated with diarrheal illness [33][34].

There is also emerging evidence of the protective effect of rotavirus vaccination in decreasing seizure-related hospitalizations in childhood, most marked in children <2 years of age [35][36]. It is hypothesized that this effect may be occurring as a result of decreasing illness in children who have a predisposition to febrile seizures or by eliminating potential direct neurological effects of systemic rotavirus infection.

The duration of protection for rotavirus vaccine is not known with certainty, although its effectiveness in decreasing health care utilization for at least the first 3 years of life—the period when children are at highest risk for serious disease—has been clearly demonstrated. In the USA, this effect has led to substantial cost-savings in the first 3 years following implementation of rotavirus vaccine programs [37][38].

There is some evidence to suggest that the circulating wild-type genotypes of rotavirus may shift after universal vaccination. Both Brazil and Belgium have reported increasing G2 genotypes after using RV1, but vaccine efficacy has not changed substantially with shifts in wild-type genotypes [39][40].

## SAFETY

Two large pivotal trials of RV1 and RV5, involving about 130,000 infants, were designed to detect vaccine-associated intussusception. Neither found an increase in incidence in vaccinated versus placebo groups [25][41]. However, post-licensure surveillance of larger populations in several countries detected a small increased risk of intussusception among infants 1 to 7 days after receiving their first and second rotavirus vaccine doses. These risks were in the order of one to three excess cases for every 100,000 infants vaccinated [42][43]. A similar possible risk was determined in Australia using both the RV1 and the RV5 vaccines [44].

In the USA, the Vaccine Adverse Event Reporting System (VAERS), reported an attributable risk of 0.8 per 100,000 doses with RV5 and 1.6 per 100,000 doses with RV1 [45][46]. In other post-marketing surveillance, an attributable risk of 5.3 per 100,000 doses of RV1 was reported by the Centers for Disease Control and Prevention's Vaccine Safety Datalink, and of 1.1 to 1.7 per 100,000 doses by another multicentre study [47][48]. One meta-analysis determined the RR of intussusception post-dose one with RV1 was 5.4 (95% CI 3.4 to 7.4) and 5.5 with RV5 (95% CI 3.3 to 9.3) based on six published studies. The risk post-dose two was smaller: 1.7 to 1.8 for RV5 and RV1, respectively. Overall, the risk of intussusception was estimated at 1 to 3 per 100,000 children vaccinated with rotavirus vaccine [42][43][45][47]-[50]. In Canada, 19 case reports of intussusception following rotavirus vaccine were reported between 2011 and 2014. Fifteen of these cases occurred within 21 days of immunization, representing a rate of 0.74 cases per 100,000 doses distributed during that time period [51].

Based on the data, it is now generally accepted that there is a small increased temporal risk of intussusception with either RV1 or RV5. Parents and caregivers should be informed of the benefits of disease prevention, which are substantial, relative to the very small increased risk of intussusception [52][53]. The risk occurs particularly in the first week after receiving rotavirus vaccine. Health care providers should do follow-up for all infants who have persistent vomiting or appear to have severe abdominal pain, bloody stools and/or a high fever or who have a documented intussusception, and inquire specifically about recent rotavirus vaccination. Care providers should report all cases of intussusception occurring within 21 days of receiving rotavirus vaccine to local public health authorities, using the adverse event reporting system administered by

the Public Health Agency of Canada (<http://www.phac-aspc.gc.ca/im/aefi-essi-form-eng.php>).

No other serious adverse events were noted during initial trials or in the post-marketing surveillance studies of rotavirus vaccine. Canada has a robust vaccine safety monitoring system with pre- and post-marketing phases to detect serious or rare adverse events.

Only a few studies of specialized populations (such as in infants being cared for in neonatal intensive care units) have been conducted since the rotavirus vaccine has been licensed. In one such trial, RV5 was well tolerated, with about one-quarter of infants having gastrointestinal symptoms attributable to other conditions, not to rotavirus vaccine [54].

In 2010, components from the DNA of porcine circovirus-1 were detected in both RV1 and RV5. These findings were traced to batches of trypsin used in the manufacturing process. There is no known human disease or safety risk associated with finding this enzyme and manufacturers are committed to eliminating this component from rotavirus vaccines.

Fecal shedding of rotavirus vaccine virus is common (50% to 80%) in the first week following vaccination, but falls to <24% at 30 days. Shedding becomes less common with subsequent doses. The clinical significance of viral shedding and the potential for horizontal transmission are unknown, but to date there has been no reported adverse clinical effect on household members or contacts. Infants who live in households with an immunocompromised patient or a pregnant woman should be vaccinated as per the routine schedule because the indirect protection provided by preventing wild-type rotavirus infection outweighs the risk of transmitting vaccine virus. Good hygiene practices, including the cleaning of surfaces and hand hygiene after diapering, should be emphasized.

## CONTRAINDICATIONS AND PRECAUTIONS

At the present time, the NACI notes the following contraindications to administering rotavirus vaccines [13]:

- A history of intussusception or greater susceptibility to intussusception (e.g., uncorrected Meckel's diverticulum).

- Hypersensitivity to any of the ingredients in rotavirus vaccines (refer to product monographs for details).
- Known or suspected severe combined immunodeficiency (SCID) or other significant immunocompromising condition.

As with other vaccines, rotavirus vaccines can be given to infants with a mild illness, with or without fever. If there is a significant acute gastroenteritis or other acute illness, health care providers should assess whether delaying vaccination could preclude receipt of the first dose or completing the vaccine series. If an infant spits out a dose or regurgitates after receiving it, the dose should not be repeated. However, the remaining vaccines in the series should be continued, as appropriate.

## SPECIAL GROUPS

Infants with a previous documented rotavirus infection should still receive the full course of rotavirus vaccination, provided they are in the recommended age group for receiving this vaccine. Preterm infants are also candidates for rotavirus vaccine. The NACI recommends that infants born prematurely who are between 6 weeks and 8 months of age should receive rotavirus vaccine at or following discharge from the neonatal intensive care unit or other nursery<sup>[13]</sup>, and on the same schedule as for term infants. For infants who remain hospitalized, the risk of not receiving vaccine within a specified time period should be weighed against the potential risk for shedding vaccine virus in hospital. Infants who are HIV-exposed should receive vaccine according to chronological age.

## RECOMMENDATIONS

- Rotavirus vaccine prevents severe disease and significantly decreases the risk of dehydration and hospitalization associated with rotavirus. Rotavirus vaccination is recommended for all infants except those who are immunocompromised or have a history of or a known condition that predisposes them to intussusception.
- Both licensed rotavirus vaccines are efficacious, and there are no interchangeability data. Whenever practical, the rotavirus vaccination series should be completed using the same product. However, if any dose in the series was the RV5 vaccine, a total of three doses of vaccine should be administered.
- Rotavirus vaccines are given orally and can be started at 6 weeks of age. Doses are usually administered as part of the routine infant vaccine schedule at 2 and 4 months of age if using RV1, with a third dose at 6 months if using RV5. On the rare occasion that a first dose of RV1 (Rotarix) has been delayed beyond 15 weeks, NACI has indicated that a catch-up first dose of RV1 can be given up to 20 weeks chronological age. This extension regarding the timing of doses does not apply to RV5 at the present time.
- Parents and caregivers of infants should be informed of the slightly higher temporal risk for intussusception, especially in the week after receiving rotavirus vaccine. All cases of intussusception should be reported to local public health authorities: [www.phac-aspc.gc.ca/im/aeffi-essi-form-eng.php](http://www.phac-aspc.gc.ca/im/aeffi-essi-form-eng.php)
- Physicians should continue to advocate for the universal funding and integration of rotavirus vaccines into provincial/territorial programs in Canada—and into global immunization schedules—to ensure equitable access for all children. The impact of decreasing morbidity and mortality due to rotavirus diarrheal illness through universal rotavirus vaccination will be especially critical in resource-poor settings worldwide.

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