The purpose of the present statement is to provide recommendations for the use of rotavirus vaccine for infants in Canada, and to summarize information on the disease, epidemiology, as well as the safety and efficacy of vaccines currently authorized for the prevention of rotavirus disease in Canada. Routine rotavirus vaccination is recommended for infants.

CLINICAL DISEASE

Rotavirus is transmitted via the fecal-oral route and through fomites, including toys (1). The incubation period of rotavirus infection is one to five days. Acute onset of vomiting and fever generally precede the diarrhea (2-4). In the first three months of life, disease is generally mild because of transplacental maternal antibodies. Between the ages of three months and five years, there is a spectrum of disease from mild watery diarrhea, to severe diarrhea with vomiting, to dehydration with shock. The gastrointestinal symptoms usually resolve in three to eight days.

After natural infection, children develop partial protection against subsequent severe disease. In a Mexican study (5), after a single natural infection, 40% of children were protected against any infection with rotavirus, 75% were protected against rotavirus diarrhea and 88% were protected against severe rotavirus diarrhea. Second, third and fourth infections progressively increase protection against disease (5).

EPIDEMIOLOGY OF ROTAVIRUS DISEASE

It is estimated that all children will experience at least one episode of rotavirus infection by five years of age. Because rotavirus gastroenteritis is not a nationally notifiable disease, the exact prevalence and associated disease burden are not known. These are estimated by several Canadian studies that examine acute rotavirus diarrhea in children seen in family physician offices, paediatric clinics, emergency departments and hospital admissions. It is estimated that one in 62 (6) to one in 312 (7) children younger than five years of age will experience at least one episode of rotavirus gastroenteritis in any given year.

Rotavirus infection occurs in the majority of healthy children before five years of age, and is the most common diarrheal illness associated with hospitalization. The majority of children present with symptoms of vomiting, diarrhea and fever. As a result, rotavirus gastroenteritis is responsible for greater morbidity than other common childhood diarrheal illnesses. The highest risk of severe disease is in children younger than two years of age. It is estimated that one in 20 children will require an emergency department visit. In addition to community-acquired infections, hospital-acquired infections are also significant. There are currently two licensed rotavirus vaccines in Canada. Both vaccines are administered orally and are highly effective against severe disease and hospitalization. Large pre- and postmarketing studies have shown no increased risk of intussusception with the current rotavirus vaccines. The present statement provides information concerning the clinical disease and rotavirus vaccines in Canada.

Key Words: Acute gastroenteritis; Children; Diarrhea; Oral vaccine; Rotavirus; Vaccine


M Salvadori, N Le Saux; Société canadienne de pédiatrie, comité des maladies infectieuses et d’immunisation. Des recommandations au sujet de l’usage des vaccins antirotavirus chez les nourrissons

L’infection à rotavirus touche la majorité des enfants en santé avant l’âge de cinq ans, et c’est la principale maladie diarrhéique associée à l’hospitalisation. La majorité des enfants ont des symptômes de vomissements, de diarrhée et de fièvre. Par conséquent, la gastroentérite à rotavirus est responsable d’une plus grande morbidité que d’autres maladies diarrhéiques courantes de l’enfance. Le plus fort taux de maladie grave s’observe chez des enfants de moins de deux ans. On estime qu’un enfant sur 20 devra consulter au département d’urgence. Outre les infections non nosocomiales, les infections nosocomiales sont également importantes. Deux vaccins antirotavirus sont actuellement homologués au Canada. Tous deux administrés par voie orale, ils sont hautement efficaces contre une maladie grave et une hospitalisation. De grandes études précommercialisation et postcommercialisation ne démontrent aucune augmentation du risque d’invagination par les vaccins antirotavirus actuels. Le présent document de principes fournit de l’information au sujet de la maladie clinique et des vaccins antirotavirus au Canada.

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five years of age will be hospitalized with rotavirus infection. More than one-half of rotavirus hospitalizations occur in the six- to 24-month age group (8).

Rotavirus gastroenteritis is typically a self-limited disease and very rarely results in long-term sequelae or death. However, it is associated with considerable health care resource use. In a study (9) of child care centres in Toronto, Ontario, over an eight-month period, 60% of children sought medical care for diarrhea, 17% went on to visit an emergency room, and 6% were hospitalized or received intravenous hydration in the emergency room for diarrheal illnesses. The Rotavirus Gastroenteritis Cohort Model (10) estimated the impact of rotavirus gastroenteritis in Canada for children younger than five years of age. The authors found that one in seven children will seek health care, one in 20 will visit an emergency department or be hospitalized, and one in 62 will be hospitalized (10).

A study of 1359 children hospitalized for community-acquired rotavirus infection between 2005 and 2007 in 12 Canadian paediatric hospitals indicated that more than 60% of children were younger than two years of age. Most (68%) had no underlying illnesses. The majority (69%) had all three symptoms of vomiting, diarrhea and fever. Children younger than two years of age, especially those younger than three months of age, were more likely to have a 'sepsis-like' clinical picture at presentation compared with children who were older. One-third of patients had more than one outpatient visit before hospital admission. The median duration of hospitalization was three days (11). Concurrent three-year surveillance also revealed that hospital-acquired rotavirus infections represented more than one-quarter of all rotavirus infections among hospitalized children during 36 months of surveillance at the same 12 paediatric hospitals in Canada. Most of the children with hospital-acquired rotavirus were younger than one year of age (N Le Saux, personal communication). A previous study in 1997/1998 in Canada at 10 paediatric hospitals indicated that of 1243 patients diagnosed with symptomatic rotavirus infections, two-thirds were treated as outpatients and one-third required admission to hospital (N Le Saux, personal communication).

Although there are many limitations to the available data on rotavirus morbidity, they suggest that rotavirus is a common viral illness in Canada resulting in a considerable burden of illness and health care resource use.

Mortality from rotavirus is extremely rare in Canada, with only two known attributable deaths in recent years. However, because routine testing is not recommended and diagnosis does not change management, nor is rotavirus a reportable disease, cases could go unrecognized or unreported. In the United States, there are 20 to 60 deaths attributed to rotavirus annually (12). Rotavirus infections are estimated to account for 4% to 5% of hospitalizations in children younger than five years of age in the United States (13).

It is estimated that in the developing world, more than 600,000 children die as a result of rotavirus-related disease per year, and rotavirus causes 5% of all deaths in children younger than five years of age. This is mostly attributable to the lack of clean water for oral rehydration and the lack of access to medical care.

There are few recognized risk factors for severe rotavirus disease. In a Canadian prospective study (8), socioeconomic factors, parental marital status, daycare attendance and ethnicity did not influence the rates of hospitalization due to rotavirus. Premature infants are at an increased risk of rotavirus infection, partly because they lack transplacental maternal antibodies. Although the impact of breastfeeding is not entirely clear, one study (14) has shown breastfeeding to be somewhat protective against symptomatic rotavirus infection. Immunocompromised children are known to be at an increased risk for severe, prolonged and even fatal rotavirus gastroenteritis (15,16). This includes those with congenital immune deficiencies, hematopoietic transplantation or solid organ transplantation.

Gastroenteritis caused by rotavirus varies seasonally, but generally peaks earlier (February to March) in western Canada than in eastern Canada, which generally has its peak one to two months later (2,3).

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 protease-cleaved protein (P protein). Most human infections to date have been caused mainly by four rotavirus serotypes: G1P[8], G2P[4], G3P[8] and G4P[8]; however, some regions have had more variability, with other serotypes (G9, G5, G6 and G8) presenting. The prevalence of rotavirus serotypes varies geographically and from year to year.

DIAGNOSIS

Because the clinical features of rotavirus infection are very nonspecific, diagnosis cannot definitively be made on clinical grounds (17). The most frequently used laboratory test to confirm diagnosis is antigen detection in stool by enzyme immunoassay.

ROTAVIRUS VACCINATION

In 1998, the previously licensed rotavirus vaccine, RotaShield (Wyeth Lederle Vaccines, USA) was recommended for routine vaccination for all infants in the United States. This vaccine was a tetravalent rhesus human reassortant rotavirus vaccine that was withdrawn from the market within one year because of an association with intussusception that was noted in postmarketing surveillance (18). It was due to this experience with RotaShield that new rotavirus vaccines required extremely large and carefully performed studies for the assessment of safety, particularly for the relatively rare event of intussusception.

Efficacy of current vaccines

There are currently two vaccines that are authorized for use in Canada for the prevention of rotavirus gastroenteritis in
infants six to 32 weeks of age. Comparisons of the two vaccines are presented in Table 1 (17,19).

The first, RotaTeq, manufactured by Merck Frosst Canada, was approved in 2006. This is a live, oral, pentavalent vaccine that contains five live reassortant rotaviruses from human and bovine sources. The vaccine contains antigens G1, G2, G3, G4 and P[8]. It is supplied in single prefilled 2 mL tubes given in three oral doses starting at six weeks of age, with a minimal interval between doses of four weeks. This vaccine can be given simultaneously with other regularly scheduled routine childhood immunizations.

The second, Rotarix, approved in 2008, is manufactured by GlaxoSmithKline Biologicals (Belgium). This is a live-attenuated monovalent G1[P8] human rotavirus vaccine derived from a human strain. A single strain is used because G1 types are the most common circulating strain worldwide, and most other circulating strains share P[8]. Also, it is believed that there is some cross-reactivity between the G1 in the vaccine and the other G types. It is given orally in two doses starting at six weeks of age, with a minimal interval of four weeks. This vaccine can also be given with other regularly scheduled routine childhood immunizations.

Both vaccines have been studied for efficacy and safety in large randomized controlled trials (20,21). Because these trials were performed in very different populations and with different outcome end points, they are not directly comparable. RotaTeq was studied in a trial involving 69,274 infants; efficacy against severe rotavirus gastroenteritis was 98.2% (95% CI 89.6% to 100%) and efficacy against rotavirus gastroenteritis of any severity was 73.8% (95% CI 67.2% to 79.3%) (20). Similarly, Rotarix was studied in a large randomized placebo controlled trial of 63,225 infants in Latin America and Finland (21). The efficacy against severe rotavirus gastroenteritis in the first year of life was 84.7% (95% CI 71.7% to 92.4%). A smaller European trial (22) demonstrated Rotarix efficacy against gastroenteritis of any severity to be 87.1% (95% CI 79.6% to 92.1%) in the first year of life and 71.9% (95% CI 61.2% to 79.8%) in the second year of life (23). Both vaccines have shown efficacy against rotavirus-related emergency room visits and hospitalizations (24).

The United States recently reported a greater than 50% decrease in rotavirus activity for the 2007/2008 season compared with the 1991 to 2006 seasons within a defined surveillance network. It is estimated that rotavirus vaccine coverage for infants three months of age was 49.1% (range 40.1% to 65.4%) (25).

**SAFETY**

The large trials for both vaccines were designed to monitor for vaccine-associated intussusception, and both showed no increase in intussusception compared with the placebo group (26). To date, postmarketing surveillance performed by the Centers for Disease Control and Prevention (USA) suggests no increased risk of intussusception following the widespread use of the RotaTeq vaccine (22,27,28). In postmarketing surveillance after distribution of 23 million doses of Rotarix, there has also been no increased risk of intussusception. It is important to note that with the previous vaccine, RotaShield, the risk of intussusception appeared to be age dependent and that the risk increased with the age at vaccination (particularly when the first dose was given after three months of age) (29,30). No deaths have been attributed to the two approved rotavirus vaccines.

In randomized controlled trials with RotaTeq, the incidence of serious adverse events, including sudden infant death syndrome, were similar in the vaccine and placebo recipients. In postmarketing surveillance in the United States, there has been no increased risk of hematochezia, meningitis, encephalitis, seizures, Kawasaki disease, myocarditis or Gram-negative sepsis.

Recipients of the RotaTeq vaccine experienced a small but statistically significant increase in vomiting (15% versus 14%), diarrhea (24% versus 21%), nasopharyngitis (7% versus 6%), otitis media (15% versus 13%) and bronchospasm (1.1% versus 0.7%) when compared with control infants. These differences were not, however, believed to be clinically significant.

Rotarix has also been evaluated for safety in 12 clinical trials involving 76,918 children. There has been no increased risk of serious adverse events. The incidence of fever, cough, diarrhea, vomiting and irritability did not differ between the vaccine and the placebo group.

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**TABLE 1**

Selected differences and characteristics of two licensed vaccines in Canada

<table>
<thead>
<tr>
<th></th>
<th>RotaTeq (Merck Frosst Canada)</th>
<th>Rotarix (GlaxoSmithKline, Belgium)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type and origin of vaccine virus</td>
<td>Human-bovine pentavalent G1-G4P[8]</td>
<td>Human monovalent G1P[8]</td>
</tr>
<tr>
<td>How vaccine is supplied and administered</td>
<td>Supplied as a liquid in a squeezable latex-free dosing tube. Given orally without reconstitution</td>
<td>Supplied as a prefilled syringe, given orally</td>
</tr>
<tr>
<td>Volume per dose</td>
<td>2 mL</td>
<td>1.5 mL</td>
</tr>
<tr>
<td>Number of doses required</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Minimum age at dose 1</td>
<td>6 weeks</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Maximum age at dose 1</td>
<td>14 weeks plus 6 days</td>
<td>14 weeks plus 6 days</td>
</tr>
<tr>
<td>Minimum interval between doses</td>
<td>4 weeks</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Maximum age for last dose</td>
<td>8 months plus 0 days</td>
<td>8 months plus 0 days</td>
</tr>
<tr>
<td>Storage</td>
<td>Should be stored in a refrigerator at 2°C to 8°C. After removal from refrigeration, use as soon as possible (&lt;4 h) and only if temperature has not exceeded 25°C</td>
<td>Should be stored in a refrigerator at 2°C to 8°C and protected from light</td>
</tr>
</tbody>
</table>

Adapted from references 17 and 19
There is a difference in fecal shedding of vaccine virus between the two vaccines. With RotaTeq, 12.7% had shedding of virus one to 15 days after the first dose, but no shedding was documented after the second or third dose. Following administration of Rotarix, viral antigen shedding could be detected in 80% of vaccine recipients. Data regarding the horizontal transmission of vaccine virus have not been published. The clinical significance of viral shedding and the potential for horizontal transmission are unknown.

CONTRAINDICATIONS AND PRECAUTIONS
Presently, the National Advisory Committee for Immunizations notes the following contraindications to vaccination with rotavirus vaccines:

- Hypersensitivity to the vaccine or any of its ingredients or components of the container.
- History of intussusception (based only on previous association with RotaShield, with the pathogenesis still being unclear – no association has been shown between the new vaccines and intussusception).
- Infants known or suspected to be immunocompromised, especially those with severe combined immunodeficiency.

Precautions include acute gastroenteritis and pre-existing chronic gastrointestinal conditions including congenital malabsorption syndrome, Hirschsprung’s disease or short gut syndrome. In these cases, the benefits likely outweigh the theoretical risks (31).

SPECIAL GROUPS
Infants with documented previous rotavirus infection can still receive the full course of rotavirus vaccines provided they are in the recommended age group for administration of this vaccine. The clinical trials showed that efficacy is similar in breastfed and non-breastfed infants. Rotavirus vaccine can be given to infants with transient mild illness, with or without fever. Premature infants are also candidates for the vaccine, and the vaccine should be administered between six and 32 weeks of chronological age (31).

RECOMMENDATIONS
The levels of evidence reported in the recommendations have been described using the evaluation of evidence criteria outlined by the Canadian Task Force on Preventive Health Care (32).

- Rotavirus vaccination is recommended for all infants because it significantly decreases the incidence and morbidity associated with rotavirus infection. Although these vaccines may not prevent all cases of rotavirus diarrhea, they do prevent severe disease and significantly decrease the risk of dehydration and hospitalization in vaccinated infants. Either vaccine is safe and efficacious. There are no interchangeability data, so whenever possible, the rotavirus vaccination series should be completed with the same product. (I-A)
- Vaccination must be started between six and 14 weeks plus six days of age, with the series completed by eight months of age. Adherence to recommendations regarding the time of administration should be ensured because the safety of rotavirus vaccine administration outside of these recommendations is unknown.
- Canadian physicians should advocate for universal funding and integration of this vaccine into provincial programs to ensure equitable access for all children.
- Advocating for the availability of rotavirus vaccination programs in the developing world should be a priority because the impact on global childhood mortality and morbidity due to rotavirus infections in this context is expected to be the greatest.

ADDITIONAL RESOURCE: A handout to print and share with parents and caregivers titled “Rotavirus vaccine” is available at <www.caringforkids.cps.ca>

REFERENCES


32. Canadian Task Force on Preventive Health Care. Infectious Diseases and Immunization Committee Members: Drs Robert Bortolussi, IWK Health Centre, Halifax, Nova Scotia (Chair); Jane Finlay, Richmond, British Columbia; Jane C McDonald, The Montreal Children’s Hospital, Montreal, Quebec; Heather Onyett, Kingston General Hospital, Kingston, Ontario; Joan L Robinson, Edmonton, Alberta; Elisabeth Rousseau-Harsany, Sainte-Justine UHC, Montreal, Quebec (Board Representative) Liaisons: Drs Upton D Allen, The Hospital for Sick Children, Toronto, Ontario (Canadian Pediatric AIDS Research Group); Charles PS Hui, Children’s Hospital of Eastern Ontario, Ottawa, Ontario (CPS Liaison to Health Canada, Committee to Advise on Tropical Medicine and Travel); Nicole Le Saux, Children’s Hospital of Eastern Ontario, Ottawa, Ontario (Immunization Program, AC/Te;); Larry Pickering, Elk Grove, Illinois, USA (American Academy of Pediatrics); Marina I Salvadori, Children’s Hospital of Western Ontario, London, Ontario (CPS Liaison to Health Canada, National Advisory Committee on Immunization) Consultants: Drs James Kelner, Calgary, Alberta; Noni E MacDonald, IWK Health Centre, Halifax, Nova Scotia; Dorothy L Moore, The Montreal Children’s Hospital, Montreal, Quebec Principal authors: Drs Marina I Salvadori, Children’s Hospital of Western Ontario, London, Ontario; Nicole Le Saux, Children’s Hospital of Eastern Ontario, Ottawa, Ontario

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