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An Advisory Committee Statement (ACS)
National Advisory Committee on Immunization (NACI)†
Literature Review on Rotavirus: Disease and Vaccine Characteristics

Preamble

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada with ongoing and timely medical, scientific and public health advice relating to immunization. The Public Health Agency of Canada 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 Public Health Agency of Canada's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

Introduction

On August 1, 2006, the rotavirus (RV) vaccine, Rotateq™, was approved for use in Canada. Rotateq™, produced by Merck Frosst Canada Ltd., is a live, oral, human-bovine reassortant vaccine. It was licensed in the United States in February 2006 by the Food and Drug Administration (FDA) and recommended for routine use in infants by the Advisory Committee on Immunization Practices (ACIP) in August 2006[1] and by the Committee on Infectious Diseases of the American Academy of Pediatrics.[2] The European Rotavirus Vaccination Advocacy Committee (ERVAC) has recently advocated introduction of rotavirus vaccine into childhood immunization programs, although the members agree that further studies on the burden of rotavirus gastroenteritis in Europe need to be done for a better evaluation of the cost and benefit of rotavirus vaccination programs.[3]

In 1998 an RV vaccine consisting of a Rhesus-human reassortant (Rotashield™, Wyeth) was licensed in the U.S., but was withdrawn in 1999 after only a few months of usage following reports in post-marketing surveillance of intussusception among vaccine recipients. The shadow cast by these safety concerns is highlighted, although the new RV vaccine has undergone extensive safety testing in approximately 35,000 recipients to estimate the risk of intussusception in vaccinees.

This review was prepared by E.L. Ford - Jones, and S. Calvin and approved by NACI.

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A need for a systematic literature review on the characteristics of the RV vaccine was identified. This review was commissioned by the Public Health Agency of Canada (PHAC).

The purpose of this document is to apply the Erickson, De Wals and Farand framework[4] on immunization programs to review the following:

- the disease burden attributed to RV; and
- the vaccine characteristics of Rotateq™.

Methods

This report is based on literature retrieved from peer-reviewed publications and the Rotateq™ product monograph. Sections 1 and 2 of the Erickson, De Wals and Farand framework were used to frame the components of this document, with the exception of section 1.8 "economic impact of the disease."[4] This report will be divided into two sections: the burden of disease caused by RV and a review of the RV vaccine, Rotateq™.

Literature search: Literature was identified using a variety of search strategies: systematic search of electronic medical databases (Medline and EMBASE), search of reference lists in relevant articles and pharmaceutical company data.[5]

Medline and EMBASE databases were searched for English-language articles from the time period January 1, 1966, to December 1, 2006. Specific MeSH subject headings used as search terms included "Rotavirus," "Rotavirus Infections," "Vaccines," "Vaccines, Attenuated," "Vaccination," "Gastroenteritis," "Intussusception," "Cost of Illness," "Cost Benefit Analysis," "Epidemiology," "Canada," "Children," "Pediatrics" and "Safety." Information regarding disease and vaccine use in the developing world has not been included.

Results

1. Burden of Disease Caused by RV

1.1 Nature and Characteristics of the Infective Agent

RV is a complex virus that belongs to the Reoviridae family. It is composed of a 70-nanometre (nm) viral nucleocapsid that has three concentric shells: an inner core, an internal capsid and an outer capsid. Within the virus, there are 11 segments of double-stranded RNA that encode a variety of proteins required for the viral lifecycle. Sixty spikes, 10–12 nm in length, protrude from the outer capsid. There are at least seven different antigenic groups (A to G), with Group A being the most common worldwide as a cause of human infections.

The outer capsid contains two structural viral proteins (VP):

- VP4, the protease-cleaved protein (P protein);
- VP7, the glycoprotein (G protein).[6],[7]

These two outer capsid proteins are the determinants of the viral serotype classification and elicit neutralizing antibodies believed to be important for protection.[6] There is considerable diversity of circulating strains among the known 15 G and 26 P genotypes, 10 G and 11 P serotypes. Since the two gene segments that encode these proteins can segregate independently,[6] a typing system consisting of both P and G types has been developed. Numbering of G genotypes match G serotypes (e.g., G1, G2, G3, etc.), but the P genotypes do not exactly match the P serotypes. For example, P genotype 8 is equivalent to P serotype 1A[8]. The P genotypes are therefore tentatively designated in brackets (e.g., P1A[8]).

In the U.S. and as described by limited Canadian data,[9],[10] viruses containing six distinct P and G combinations are most prevalent: G1 P1A[8], G2 P1B[4], G3 P1A[8], G4 P1A[8], G9 P1A[8] and G9 P2A[6] (Table 1).[11],[12] These strains are generally designated by their G serotype specificity (serotypes G1–4, G9). P1A is the predominate P serotype, with lesser presence of P1B, P2A and P3.[8] A number of reports suggest G9 P1A[8] is emerging and spreading.[13]–[19]

Table 1. Prevalent Strains of RV Among Children Aged <5 Years, United States, 1996–1999,[1] and Two Canadian Studies[109]

	Frequency of types (%)		
	U.S., 1996–1999	**Toronto, 1997–1998**	**Canada, 2005**
G1 P1A[8]	52.0	65.0	55.0
G2 P1B[4]	10.0	32.0	3.0
G3 P1A[8]	2.0	0.01	10.0
G4 P1A[8]	2.0	0.01	22.0
G9 P2A[6]	3.0	0.02	8.0
Other	10.0		
Total identified	79.0	97.0	98.0

Reservoirs: RV strains are mostly species-specific. Humans are the main reservoir of human RV strains; however, humans can occasionally be infected by rare or novel strains.[20]

Mode of transmission: The main mechanism of transmission is fecal-oral transmission. Since the virus is environmentally hardy, it can also be transmitted through both close person-to-person contact and fomites such as toys and hard surfaces.[21] The virus can survive on hands for at least four hours and remains viable on surfaces or fomites for days.[22]–[25] Other recognized transmission modes include fecally contaminated food and water, and respiratory droplets.[26] Transmission is facilitated by a very small infectious dose of <100 viral particles,[27] high viral concentration within the stool (10^{12} particles per gram of stool in infected children) and prolonged shedding of virus. Shedding can begin a few days prior to the onset of symptoms and can continue until 21 days after the onset of illness. Asymptomatic shedding has also been described.[22]

Both asymptomatic and symptomatic health care workers have been linked to the spread of the virus in some outbreaks. Since the virus can survive for long periods on hands, hand washing is an important preventive measure. Increased hand washing by hospital staff resulted in decreased nosocomial RV infections.[23],[24]

Pathogenic mechanisms: Following ingestion and passage through the stomach, viable virions attach to the epithelial surface of the small intestine; they enter the mature enterocytes near the tips of the villi and begin replication.[20] Once more copies of the virus are made and appropriately assembled, they bud and are released to infect new enterocytes. The enterocytes, particularly at the tips of the villi where absorption occurs, are damaged and sloughed. This leads to inadequate adsorption and impaired digestion. In the epithelial cells, the virus produces the potent enterotoxin non-structural protein 4 (NSP4). In mice, this enterotoxin causes diarrhea due to release of calcium from the endoplasmic reticulum and resultant villous cell secretion.[20],[28] Infection with RV leads to an imbalance in the function of the villi, associated with increased secretion with a relative impairment in adsorption and digestion. Limited human biopsy information and animal studies of proximal small intestine show shortening of the villi, mononuclear cell infiltration in the lamina propria, mitochondrial swelling, and sparse irregular microvilli with impaired D-xylose absorption, and sometimes depressed disaccharidases (maltase, sucrase, lactase).[6],[28],[30] Stimulation of the enteric nervous system by NSP4 and villous ischemia may also be responsible for diarrhea.[27],[30],[31]

The mechanism that causes vomiting, which characterizes the early illness, is poorly understood. It may be the result of early cytokine release acting centrally, or delayed gastric emptying.[32]

The relative importance of viremia and extraintestinal replication is not clear.[27],[33],[34] Acute RV gastroenteritis in children is commonly associated with antigenemia and viremia (e.g., antigen detected in 43%–64% by enzyme immunoassay (EIA) and confirmed by reverse transcription PCR in 67%–93% of children). Antigenemia is most common on the first day of illness. It peaks between day one and three days after symptom onset, with a minority being positive at one week. Persistent antigenemia (up to 11 weeks) has been seen in immunocompromised children.[35] Primary infections are associated with higher viral loads.[36],[37] Antigenemia was associated with G1 strains and lower levels of serum IgG.[33] Quantitative studies showed RV titers in the blood are substantially lower than in the stool, suggesting viremia is usually benign and silent with little risk of extraintestinal disease. It may be that RV is passively present in the blood as a result of transepithelial transport.[38] Severity, as measured by diarrhea and dehydration, has not been linked to viremia.[33]

Although long thought to be confined to the small intestine, RV has now been identified in other sites.[27] RV antigen and/or RNA has been found in the cerebrospinal fluid of children with seizures, as well as in the livers and kidneys of immunocompromised children.[27],[33] RV RNA has been detected in the

spleen, heart, lungs, kidney, bladder and pancreas of children who experience RV deaths.[33],[34] There is no proof of extraintestinal RV replication in immunocompetent children, and it has been shown only rarely in immunodeficient children,[39] but it is considered plausible.[33],[34]

Extra-intestinal replication does occur in animals, including: mesenteric lymph nodes, liver and lungs of mice[40] and multiple organs of rats, including macrophages.[41]

Diagnosis: Confirmation of the diagnosis requires laboratory testing of fecal specimens. There are several commercial EIA kits available that detect antigen in the stool, directed at an antigen common to all group A RVs.

Serologic methods that detect a rise in serum antibodies, primarily EIA for IgG and IgA, have been used to confirm recent infections.[42],[43] Additionally, stool examination by electron microscopy can provide a diagnosis, and further strain information is available using techniques such as real time polymerase chain reaction (RT-PCR).

1.2 Clinical Manifestations and Complications of Infection

RV infections can occur with a variety of presentations including asymptomatic infection, mild disease to severe infection leading to severe dehydration and death. After an incubation period of 18 to 36 hours, there is typically an acute onset of fever (53%–89%) and vomiting (89%–97%).[44]–[46] This is usually followed by diarrhea, which typically lasts for five to seven days. There are often fewer than 10 non-bloody, but mucusy bowel movements per day.[31]

There are few distinguishing singular features among those who have RV gastroenteritis versus those with other causes of gastroenteritis.[27] The presence of all three symptoms (fever, vomiting and diarrhea) is reported more commonly with RV than with other gastrointestinal viruses (61.8% versus 38.7%).[44]

In the first three months of life (in a term infant), illness is generally mild as a result of passive transplacental transfer of RV antibody. Between 3 months and 5 years of age, there is a spectrum of disease, although disease is often most severe in children aged 3 months to 24 months.

The duration of illness was less than a week in 80% of RV cases, with a mean of 5.8 to 6.1 days.[46] Of hospitalized children, <1% had persistence of fever, vomiting or diarrhea for more than two weeks.[45] At one-month follow-up, 88% of children had returned to their usual health status and the remainder had almost regained any weight lost.[45] Children can be sequentially infected, although subsequent courses of RV gastroenteritis are typically milder than initial infections.[42]

While extraintestinal disease has been reported and is biologically plausible, this is not the predominant clinical manifestation of RV.

1.3 Epidemiology of the Disease

Incidence: All children have been infected with RV by 5 years of age.[20] In the U.S., RV is responsible for 5% to 10% of all gastroenteritis episodes among children aged under 5 years old. In Toronto, RV caused 18% and 20% of laboratory-tested gastroenteritis cases in day care centres and pediatric practices, respectively (Table 2).[47] In a 2005 study, RV caused 55% of laboratory-tested gastroenteritis cases that were seen in physician offices and pediatric clinics across Canada.[44] In Toronto[47] and Quebec,[46] 37% (0–18 years old) and 72% (0–5 years old), respectively, of childhood gastroenteritis hospitalizations were due to RV. This compares with 39% of childhood gastroenteritis hospitalizations generally reported worldwide. [48]

Table 2. Overview of Canadian Studies of Children Received in Hospital Admissions, Emergency Departments (ER), Pediatric Practices and Day Care Centres with Diarrhea and RV-Associated Diarrhea

Study site	Hospital (n=7) Rivest, 2004[46]	Hospital (n=18) Ford-Jones, 2000[45]	ER (n=9) Ford-Jones, 2000[47]	Pediatric practices (n=4) Ford-Jones, 2000[47]	Day care centres (n=19) Ford-Jones, 2000[47]	Physician offices and pediatric clinics (n=59) Senecal[44]
Study timing	Dec. 1999–May 2000 (6 mos.)	Nov. 1997–June 1998 (8 mos.)	Nov. 1997–June 1998 (8 mos.)	Nov. 1997–June 1998 (8 mos.)	Nov. 1997–June 1998 (8 mos.)	Jan–June 2005 (6 mos.)
Region	Academic and regional centres in Quebec Province	Greater Toronto	Greater Toronto	Greater Toronto	Greater Toronto	Across Canada
Age	<5 yrs.	<18 yrs.	<18 yrs.	<18 yrs.	<6 yrs.	<3 yrs.
No. with diarrhea	944	1,638	449	226	211	395
No. (%) tested	565 (59.9%)	1,001 (61%)	64 (14%)	147 (65%)	186 (88%)	336 (85%)
No. RV positive (%)	405 (72%)	372 (37%)	29 (45%)	30 (20%)	33 (18%)	186 (55%)

In a comprehensive review of diarrhea-associated hospitalizations in Quebec in the 13-year period between 1985 and 1998, there were 63,827 hospitalizations of children under the age of 5 years.[49] The number of cases attributable to RV in Quebec is estimated to be 1,506 per year using the method of Jin,[50] and 1,817 per year using the 37% RV causality rate in the Toronto area study.[45]

Adenovirus, torovirus, norovirus, astrovirus and calicivirus also cause hospitalized gastroenteritis cases, though far less commonly (Table 3).[45],[51] In pediatric practices and day care settings, where there is both RV-associated diarrhea and diarrhea due to more benign agents, the proportion due to RV is generally lower.[45],[51]

Table 3. Frequency of RV and Other Viruses Causing Diarrhea in Children and Youth 0–18 Years Old in Various Greater Toronto Area Sites, 1997–1998[51]

	Total/ proportion	Hospital	ER-IV	ER-oral	Pediatric practice	Day care centre
No. of sites	49	17	8	1	4	19
No. with diarrhea	2,524	1,638	360	89	226	211
% Tested EIA	55%	60%	12%	21%	66%	88%
RV	33%	37%	44%	42%	20%	18%
EM tested	1,365	981	41	18	144	181
% RV	32%	36%	49%	50%	21%	15%
% adenovirus	4%	4%	0%	22%	8%	0.5%
% torovirus	3%	4%	10%	0%	0%	0.5%
% norovirus	2%	1%	2%	0%	2%	7%
% astrovirus	1%	1%	0%	5%	3%	2%
% calicivirus	0.5%	0.3%	0%	0%	1%	1%
% small round viruses	0.4%	0.1%	5%	0%	0%	1%

Seasonal and geographic variations: RV has annual winter-spring peaks in temperate climates, whereas in tropical climates disease occurs year-round and at a younger age.[20] Annual activity usually begins in the southwestern U.S. during November to December, spreading to the northeastern U.S. and central Canada in April to May.[52]–[54] Data reported to the National Enteric Surveillance Program suggest that peak RV activity occurs earlier in the western provinces than it does in the eastern provinces (personal communication, Lisa Landry, Centre for Foodborne, Environmental and Zoonotic Infectious Diseases (CFEZID), PHAC). There are no data to indicate whether there are or are not concurrent seasonality of respiratory and RV hospitalizations across Canada; generally, the late winter-spring RV infections follow respiratory syncytial and influenza disease in Canada, in contrast to concurrent occurrence in Europe and the resultant health care system overload.[3]

The proportion of gastroenteritis attributable to RV in hospitalized children aged 6 months to 3 years varied from a high of 60%–78% in April-May to 30%–50% in December-February.[45],[46] There was essentially an absence of disease in June and November, and presumably the time in between.[45]

A similar early spring increase was observed in the proportion of RV in emergency departments, pediatric practices and day care centres; it accounted for half to two-thirds of diarrhea in 6-month-old to 35-month-old children in April and May.[47] In 1997 and 1998, peak RV activity was observed by the Canadian Immunization Monitoring Program, Active (IMPACT) during March and April, with 41% and 34% of all cases occurring in these months respectively. In contrast, during July and October, only 6% and 10% of all cases were observed, respectively (personal communication, Lisa Landry, Centre for Foodborne, Environmental and Zoonotic Infectious Diseases (CFEZID), PHAC).

Little is known, especially in Canada, about strain changes over time or by geography. In many regions the prevailing types change every one to two years, with associated increases in morbidity and severity with the new type.[8], [55]–[57] This can occur as a result of gene reassortment, point mutations or introduction of other species-specific rotavirus into human hosts.[15] While non-G1 are generally low in individual regions in one or more years, the other G types can predominate and cause more than 50% of illness in a specific year.[8]

There is no evidence to suggest the risk for RV gastroenteritis and its outcomes varies by geographic region within Canada.

1.4 Specific Populations Affected and Risk Factors

Age: Over three-quarters of all children hospitalized for diarrhea were between 6 months and 35 months of age.[45] In all settings, the proportion of children with RV was highest in the youngest age groups: 6 to 11 months and 12 to 23 months of age (Table 4).[47] This is also true of the age distribution found by both IMPACT in 1997 and 1998, and the Measuring the Impact of Rotavirus Acute Gastroenteritis (MIRAGE) study in 2005.[44] In the survey of children in day care centres, the incidence of RV-associated diarrhea in children under 24 months of age was 1.1 episodes per 100 child-months. This can be compared to children 24 months to 35 months of age, with an incidence of 0.23 episodes per 100 child-months, and those 36 months and older with an incidence of 0 per 100 child-months.[47]

Sex: In a Canadian study, significantly more male than female children presented with diarrhea (57% versus 43%), although the proportion that was RV positive was similar.[47] This is also consistent with findings by IMPACT, where 60% of RV cases presenting to ER or hospital were male (personal communication, Lisa Landry, IMPACT/PHAC database), and MIRAGE, where 59% of the RV positive cases were male (Table 4).[44] In a U.S. study, male children were identified as having a greater risk of RV diarrhea compared with females.[58]

Table 4. Sex and Age-Specific Prevalence of RV-Associated Diarrhea in Various Settings in Canada

	Hospital admissions, Quebec[46]	Hospital admissions, Toronto[45]	Emergency settings, Toronto[47]	Pediatric practice, Toronto[47]	Day care centres, Toronto[47]	Hospitalizations <2 yrs. ER outpatients <1 yr., IMPACT 1997–1998 (Personal communication, Lisa Landry, IMPACT/ PHAC database)	Pediatric clinics and MD offices across Canada[44]
Sex							
Male	55% (223/405)	57% (207/372)	60% (15/25)	66% (19/29)	58% (19/33)	60% (748/1,243)	59%
Female	45% (182/405)	44% (165/372)	40% (10/25)	34% (10/29)	42% (14/33)	40% (495/1,243)	41%
Age-specific prevalence of RV							
0–5 mos.	<1 yr. 63% (n=115)	0–2 mos.: 7% (n=10) 3–5 mos.: 29% (n=23)	29% (2/7)	22% (5/23)	20% (2/5)	No data	28% (10/36)
6–11 mos.		6–8 mos.: 44% (n=27) 9–11 mos.: 49% (n=56)	53% (8/15)	19% (5/27)	20% (11/56)	No data	58% (52/89)
12–23 mos.	82%(n=142)	56% (n=153)	75% (12/16)	33% (14/43)	18% (15/82)	No data	60% (86/143)
24–35 mos.	77% (n=67)	50% (n=55)	29% (2/7)	16% (3/19)	14% (5/35)	No data	(24–36 mos.) 54% (38/70)
36-47 mos.	78% (n=57)	42% (n=42)	67% (2/3)	10% (1/10)	0% (0/2)		
48–59 mos.	62% (n=24)	40% (n=24)	0% (0/5)	0% (0/4)	0% (0/0)		
≥60 mos.	N/A	15% (n=52)	27% (3/11)	10% (2/21)	0% (0/1)		

	Hospital admissions, Quebec[46]	Hospital admissions, Toronto[45]	Emergency settings, Toronto[47]	Pediatric practice, Toronto[47]	Day care centres, Toronto[47]	Hospitalizations <2 yrs. ER outpatients <1 yr., IMPACT 1997–1998 (Personal communication, Lisa Landry, IMPACT/ PHAC database)	Pediatric clinics and MD offices across Canada[44]
Proportion of RV cases by age							
0–5 mos.	<1 yr. 27% (254/944)	0–2 mos.: 3% (n=10) 3–5 mos.: 6% (n=23) 9% (33/372)	7% (2/29)	17% (5/30)	0% (0/33)	29% (356/1,243)	5% (10/186)
6–11 mos.		6–8 mos.: 7% (n=27) 9–11 mos.: 15% (n=56) 22% (83/372)	28% (8/29)	17% (5/30)	33% (11/33)	35% (431/1,243)	28% (52/186)
12–23 mos.	31%(289/944)	36% (133/372)	41% (12/29)	47% (14/30)	45% (15/33)	36% 456/1,243	47% (88/186)
24–35 mos.	19%(178/944)	15% (55/372)	7% (2/29)	10% (3/30)	15% (5/33)		24–36 mos. 20% (38/186)
36–47 mos.	15%(140/944)	6% (22/372)	7% (2/29)	3% (1/30)	0% (0/33)		
48–59 mos.	9% (83/944)	6% (24/372)	0% (0/29)	0% (0/30)	0% (0/33)		
≥60 mos.	N/A	6% (22/372)	10% (3/29)	7% (2/30)	0% (0/33)		

*Note: the data on age distribution from IMPACT is less valuable for the comparison between categories as <1-year-old outpatients were included while outpatients 12–23 mos. were not.
N/A: not available

Household contacts: In a Toronto study, the rates of diarrhea in contacts of young RV cases were: 65% to 74% in contacts under 3 years of age, 38% to 43% in contacts aged 3 to 18 years and 29% to 35% in adult contacts.[45],[47] Others have reported lower rates of infection in household contacts of about 50% of exposed children and 15% to 30% of exposed adults, with some children and most adults being asymptomatic.[59] A cross-Canada study in 2005 demonstrated that 47% of RV cases had at least one other family member experiencing gastroenteritis within two weeks before or after symptom onset. There was an average of one other case per family. Among these household contacts experiencing diarrhea, 11% were under 2 years of age, 27% were 2 to 5 years of age, 5% were 6 to 17 years of age and 57% were adults.[44] In a prospective Canadian family study in the late 1970s, Wenman showed that infection occurred significantly more often in adults caring for RV-infected children than among adults whose children had no documented RV infection (35% versus 5%).[60]

The presence of another child in the house less than 24 months of age has recently been identified as a risk factor for RV hospitalization in a U.S. study (odds ratio (OR) 1.6, 95% CI: 1.1–2.3).[61] It has also been identified as a risk factor for development of RV diarrhea.[62] It is important to note that neither study assessed household crowding.

Socioeconomic: A large Toronto study failed to identify that socio-economic-cultural factors were associated with hospitalization.[45] Limited data suggest that U.S. children with lower socioeconomic status are at greater risk.[58] U.S. children less than 24 months of age covered by Medicaid or without insurance (OR 2.1, 95% CI: 1.4–3.2) and children having a mother without a high school education (OR 1.5, 95% CI: 1.0–2.3) are at higher risk of hospitalization due to RV.[61]

Prematurity: In a Toronto study, a history of prematurity was found in 13% of children admitted with RV in the first year of life, which was higher than the regional rate of prematurity of 7%, suggesting the possibility of more severe disease in this group.[45] A Washington State study found that premature infants have an increased risk for hospitalization from gastroenteritis, including viral gastroenteritis.[58]

Low birth weight: In Washington State, infants with low birthweight (<2,500 g) had increased risk for hospitalization with viral gastroenteritis, for up to 24 months of age (OR 2.8; 95% CI: 1.6–5.0).[58] This has also been identified as a risk factor for diarrheal mortality in the U.S.[63] Since parental recall of birthweight versus prematurity may be problematic,[61] there may be some overlap between these two risk factors.

Breast feeding: Breast feeding was protective against RV hospitalization in the first six months of life (OR 5.1; 95% CI: 1.2–13.2) according to a recent U.S. study.[61] Several studies have shown breast feeding was protective against symptomatic RV infection,[61] and in one Bangladesh study exclusive breast feeding was found to be protective against severe RV diarrhea during the first year of life, with a more pronounced effect for exclusive vs. partial breast feeding. However, there was no overall protection during the first two years of life, suggesting that breast feeding postpones infection to a later age.[64] In one Canadian study, a quarter of all children admitted under the age of 1 year were receiving breast milk, suggesting that breast feeding does not provide complete protection.[45] Cohort studies report the highest infection rate between 4 to 6 months of age, coinciding with weaning, declining maternal antibody or increased opportunity for exposure. The benefit of breast milk itself is supported by the greater protection and likelihood of asymptomatic infection afforded to infants whose mothers' breast milk had higher levels of glycoprotein lactadherin.[65]

Day care centre attendance: U.S. children in child care were more likely to be hospitalized for RV than those cared for at home, particularly those 24 months of age or older.[61] It is important to note that there are marked differences between U.S. and Canadian child care in levels of provider education, age at entry and child-staff ratios.

Maternal age less than 25 years: This has been identified as a risk for infant RV hospitalization in U.S. studies (OR 1.4; 95% CI: 1.0–2.0).[58],[61]

Immunocompromised persons and concurrent illness: Children and adults who are immunocompromised because of congenital immunodeficiency, hematopoetic transplantation or solid organ transplantation sometimes experience severe, prolonged and even fatal RV gastroenteritis.[66]-[69] The median duration of viral shedding is 17 days (four to 73 days).[70]

Children who were regularly seeing a physician or who were taking a medication represented 20% of hospitalized children and had a longer mean hospital stay (four versus three days).[45] Rather than the diseases of a medically fragile population, the concurrent medical conditions were generally wheezing, repeat ear infections, eczema, iron deficiency anemia and urinary tract infection.

Nosocomial RV: Children hospitalized with community-acquired RV infection have the potential to be sources for nosocomial cases of infection. IMPACT identified that 32% to 35% of the cases in hospitalized children across Canada were nosocomial (personal communication Dr. P. Sockett, IMPACT/PHAC database). A Canadian study in 1990 noted a nosocomial diarrhea (not exclusively RV) rate of 4.5 infected children per 100 admissions.[71]

First Nations and Inuit: During the 1970s in Canada, the First Nations and Inuit populations had high rates of gastroenteritis. A prospective study done in the early 1980s found that Inuit infants in remote northern communities had significantly higher rates of RV-associated diarrhea in the first six months of life

(0.73 to 1.07 infections per child per year) than First Nations infants (0.36 infections per child per year).[72]

Adults: Among adults in the U.S., RV infection causes gastroenteritis primarily in travellers returning from developing countries, parents and persons caring for children with RV gastroenteritis, immunocompromised persons and older adults.[73]

1.5 Current Disease Treatment and Preventability by Measures Other Than Immunization

Study of preventive methods has been directed to diarrhea control and prevention in general, rather than RV specifically. There is clearly a role for handwashing, environmental cleaning and breast feeding as preventive measures; they will reduce, but not eradicate, the risk of disease. Handwashing with an alcohol-based hand sanitizer has been found to be effective in significantly reducing diarrhea transmission in households where children attend day care centres, compared with control households.[74] A 50% decrease in diarrhea was sustained over 35 weeks in a study randomizing day care centres to intensive handwashing programs.[75] Reduction in diarrhea has also been observed with sustained staff education and surveillance for diarrhea in day care centres.[76],[77] Further, international evidence of handwashing effectiveness is seen in households in Pakistan, where a 53% decrease in diarrhea was seen.[78] The critical role of thorough environmental cleaning to reduce the available infecting dose has been demonstrated in porcine RV infection.[79] The potential merits of promotion of breast feeding to reduce RV have recently been reiterated.[61]

There is also some literature to support the use of zinc in prevention or decreasing morbidity of gastroenteritis.[80] Ultimately, zinc may prove to be a highly effective preventive strategy, at least against diarrheal mortality in the developing world; however, the role in Canada will need to be determined.

To prevent severe dehydration from gastroenteritis due to RV or other agents, it is critically important that every parent be educated on correct oral rehydration. Despite the widespread availability of oral rehydration solutions and recommendations by experts on their use, including the Canadian Paediatric Society, the American Academy of Pediatrics and the U.S. Centers for Disease Control and Prevention (CDC),[81],[82] the rate of hospitalizations for gastroenteritis in young children declined only 16% during 1979–1995.[52],[83]

Use of the anti-emetic ondansetron or the anti-viral nitazoxanide is not generally a recommended treatment. In a Cochrane review of the antiemetic ondansetron there is "weak and unreliable" evidence to favour its use to reduce the number of episodes of vomiting.[84] While it is too early to conclude that nitazoxanide has a role in reducing the duration of severe RV, as further safety and efficacy studies are necessary, the drug may reduce intracellular viral replication by an indirect effect on the host cell, due to the salicylic ring.[85]

1.6 Health Impact of the Disease in the Population

The relatively high rate of health care utilization among children with RV-associated diarrhea is in contrast to findings with other viral agents causing diarrhea, which are much less likely to be associated with the need for hospitalization.[45] Among the various pathogens causing gastroenteritis, RVs lead to the most severe disease and account for a higher proportion of severe episodes leading to clinic or hospital visits.[45],[86],[87] Of hospitalized children, the mean duration of hospitalization was two to three days.[46]

RV positive cases were more likely to visit the emergency room (27% versus 14%, p=0.0082), to be hospitalized (13% versus 4% p=0.0079) and to receive IV hydration (13% versus 3%, p=0.0027) than were RV negative gastroenteritis cases.[44],[46] While a pediatrician's visit(s) was adequate for the overwhelming majority of children in the Toronto-area study with RV diarrhea, 17% went on to an ER visit and 6% were either hospitalized or received IV hydration in the ER.[47] The MIRAGE cohort model used these data to estimate that the majority (57%) of RV positive cases sought health care resources, with 35% visiting a physician, 15% an ER and 7% requiring hospitalization.[88]

Similarly, children requiring more health care were more likely to have RV infection than diarrhea due to other viral agents. Only 10% of children in child care centres with diarrhea who did not see a physician had RV. In contrast, 27% making a health care visit and 75% of those hospitalized or who received IV hydration in the ER had RV. While 20% of children in pediatric practices had RV, 60% of those progressing to require hospitalization or IV hydration in the ER had RV.[45],[47] Among children with gastroenteritis recruited from physician offices and pediatric clinics across the country, 70% of ER visits, 80% of hospitalizations and 83% of IV hydration had RV.[44]

The MIRAGE cohort model estimated the burden of RV-associated gastroenteritis in young children as:[88]

- one child in seven will have sought health care (45,700 cases ÷ 340,000 children)
- one child in 20 will have visited an ER or been hospitalized (17,300 cases ÷ 340,000 children)
- one child in 62 will have been hospitalized (5,500 cases ÷ 340,000 children)
- No deaths

The resulting health care burden is described in Table 5.

Table 5. Annual Epidemiological Burden of RV in Children <5 Years in Canada[88]

	Average	95% Confidence interval
RV Gastroenteritis	80,000	[60,000; 103,000]
Physician consultations	41,000	[27,000; 56,000]
Emergency room visits	17,000	[9,000; 27,000]
Hospitalizations	5,500	[4,200; 7,000]

In Toronto, the overall diarrhea admission rate was 4.8 per 1,000 among children under 5 years of age, with a peak RV rate of 2.3/1,000 observed in the 12 to 23 months age group. From the data collected, it was estimated that 1/160 children will be hospitalized for RV-associated diarrhea by 5 years of age. This rate may be an underestimate because only 65% of admitted children were tested, and there was a significant bias for testing of those under 36 months of age or those remaining in hospital for more than one day. By extrapolation, and adjusting for age and sex, the hospitalization rate for RV diarrhea may be as high as 1/106 by 5 years of age.[45]

The Canadian estimate for hospitalizations of 1/62 by 5 years of age may be high, given that the latest U.S. estimates have fallen from 1/73 to 1/80. The low rate of 1/106 in Toronto may be due to IV and oral hydration being widely practised in the ER. However, the Canadian estimate does reflect the experience in Europe, where 1/63 is reported. In Finland, where ER hydration is not used, 1/3 is reported.[89]

Mortality due to RV is now low and deaths have not been reported in recent Canadian studies, in contrast to a case series in the 1970s.[90] While the number of deaths due to RV-associated diarrhea may be underestimated because of the failure to routinely test for RV etiology, the low mortality rate is comparable to the American experience of deaths being rare (20–60 deaths per year).[91] Internationally, mortality is very different, with an estimated 610,000 children dying per year, mostly in developing countries. This accounts for 5% of all deaths in children under the age of 5 years.

1.7 Social Impact of the Disease

Given essentially an absence of sequelae or death after RV infection and the lack of routine diagnostic testing, there is essentially no social impact beyond the acute illness. There is also no currently associated fear. There is a health system demand that is seasonal, especially for a couple of months per year. It generally follows peak respiratory disease health care demands. The social impact is low but broad, essentially impacting a month of a family's life, without sequelae. Studies have found that out-of-pocket costs (e.g., rehydration therapy, non-prescription drugs, diapers and transport) and time lost from work are considerable for the families of affected children, even for cases of low severity.[92]–[94]

2. RV Vaccine, Rotateq™

2.1 Nature and Characteristics of Immunizing Agent

The options for vaccine development include those that are:

I. Animal-based

a. Monovalent attenuated (bovine/lamb/rhesus)
- LLR – Lanzhou Institute, China, lamb strain (licensed elsewhere)

b. Multivalent animal-human reassortant
- Rotashield™, rhesus-human, tetravalent,
- Rotateq™, bovine(WC3)-human, pentavalent
- United Kingdom bovine-human, NIH (early development stage)

II. Human-based – Attenuated
- Rotarix™, monovalent (GSK vaccine candidate)
- Australia, neonatal strain, RV3 (early development stage)
- India, Bharat Biotech, neonatal strain, 116E and 1132 (early development stage)[95]

This review will focus on Rotateq™, a pentavalent bovine-human reassortant RV vaccine, as it is the only RV vaccine currently approved in Canada. The existence of multiple G antigenic types, and their apparent change in prevalence over time, is one of the reasons that a polyvalent RV vaccine is considered attractive.[8]

The Rotateq™ vaccine is a live, oral vaccine that contains five reassortant RVs developed from human and bovine parent strains.[96] The goal was to combine human strain antigenicity with the animal strain property of rapid growth. The former feature provides immune responses against the human surface antigens; the latter permits production of large quantities of vaccine virus in tissue culture. The parent bovine RV strain Wistar Calf 3 (WC3) was isolated from a calf with diarrhea in Chester County, Pa., in 1981.[97]

Vaccine composition of the five reassortant strains:

G1 (human) x P7[5] (bovine)
G2 (human) x P7[5] (bovine)
G3 (human) x P7[5] (bovine)
G4 (human) x P7[5] (bovine)
G6 (bovine) x P1[8] (human)

2.2 Characteristics of the Commercial Products

Medicinal Ingredients: Each 2 mL unit dose of Rotateq™ contains the five reassortants. The minimum dose levels of the reassortants at the end of shelf life are as follows:

G1, P7[5] = 2.2 X 10^6 infectious units
G2, P7[5] = 2.8 X 10^6 infectious units
G3, P7[5] = 2.2 X 10^6 infectious units
G4, P7[5] = 2.0 X 10^6 infectious units
G6, P1[8] = 2.3 X 10^6 infectious units

There is an average of 2.3 x 10^6 infectious units of each reassortant strain per dose. The reassortants are propagated in Vero cells using standard tissue culture techniques in the absence of antifungal agents. Residual cell DNA content per dose of vaccine is below the World Health Organization (WHO) recommended upper limits of 100 µg/dose for orally administered vaccines.

Non-medicinal ingredients: The reassortants are suspended in a buffered stabilizer solution. Each vaccine dose contains sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, cell culture media and trace amounts of fetal bovine serum. There are no preservatives or thimerosal present.

Storage: Rotateq™ has a shelf life of 24 months at +2°C to +8°C.[89] The vaccine should be protected from light.

Administration: Rotateq™ is administered orally, without mixing with any other vaccines or solutions. It requires no reconstitution or dilution, since it is suspended in buffered stabilizer solution. Each dose of Rotateq™ is supplied in a container consisting of a squeezable plastic, latex-free dosing tube with a twist-off cap, allowing for direct oral administration. The dosing tube is contained in a pouch. Administer the vaccine as soon as possible after removing it from refrigeration. Once out of refrigeration, the vaccine should not be exposed to freezing temperatures and should be stored at temperatures at or below 25°C. Under appropriate conditions, administration may be delayed for up to four hours. Unused vaccine should be disposed of in approved biological waste containers according to local regulations.

2.3 Vaccine Manufacturers, Production Capacity and Supply to Canada

Merck, based in the U.S., is the sole producer of Rotateq™, which is distributed in Canada by Merck-Frosst Canada.

2.4 Administration Schedule, Number of Doses, Association with Other Vaccines

Three doses of Rotateq™ are administered orally at 2, 4 and 6 months of age. Correct timing of administration is *absolutely critical*. This is due to concerns relating to background or associated intussusception. The first dose should be administered between the ages of 6 and 12 weeks. The first dose should not be given before 6 weeks of age, as this is outside the study limits, and it should not be given after 12 weeks of age because of insufficient data on safety. Subsequent doses should be administered at four-to-10-week intervals. All three doses of vaccine should be administered by 32 weeks of age. No dose should be given after this age because of insufficient data on safety and efficacy.

Incomplete doses: If a dose is regurgitated or spit up, *no additional dose* is given. The infant should continue to receive any remaining doses in the recommended series as per the schedule.

Pre-term infants: Rotateq™ may be given to pre-term infants according to their chronological age.

Delayed initiation: For infants to whom the first dose of Rotateq™ vaccine is inadvertently administered off label at age ≥13 weeks, the rest of the Rotateq™ vaccination series should be completed as per the schedule because timing of the first dose should not affect the safety and efficacy of the second and third dose. However, the vaccine should not be administered after 32 weeks of age.

Previous RV infection: Infants who have had RV gastroenteritis before receiving the full course of RV vaccinations should still initiate or complete the three-dose schedule, since the initial infection frequently provides only partial immunity.[2]

Breast feeding: Infants who are being breastfed can receive RV vaccine. The efficacy of RV vaccine is similar among breastfed and non-breastfed infants.[2] Breast feeding did not appear to diminish the efficacy of a three-dose series of Rotateq™. Among 1,566 exclusively breastfed infants, the efficacy of Rotateq™ against RV gastroenteritis of any severity (68%; 95% CI: 54–78) was comparable to the efficacy in 1,632 infants who were never breastfed (68%; 95% CI: 46–82).[98]

Intercurrent illness: Like other vaccines, RV vaccine can be administered to infants with transient mild illnesses, with or without low-grade fever.[2]

2.5 Nature and Characteristics of Immune Response

Immune response following natural infection: Studies of the natural history of RV infection from Australia, Mexico and India confirm a first infection generally leads to good immunity against subsequent symptomatic disease. After a single natural infection:

- 88% of children are protected against severe RV gastroenteritis;
- 75% are protected against RV gastroenteritis;
- 40% are protected against asymptomatic infection with RV.

Although children can be infected with RV several times during their lifetime, initial infection from age 3 to 35 months is most likely to cause severe gastroenteritis and dehydration.[99]–[101] Second, third and fourth infections confer progressively greater protection against severe disease.[101] The 13% of severe infections that are second severe infections are most likely due to different serotypes.[101]

There is some evidence of cross-protection between serotypes. Heterotypic immunity was initially observed in natural exposures in day care centres, when infection against one G serotype decreased the likelihood of a second symptomatic infection with a different serotype. However, it is not clear if this was due to a shared P serotype.[56],[102] In Mexican studies, where multiple serotypes co-circulate in the same season, only one severe infection occurred in most children, suggesting protection against exposure to other serotypes.[101]

The immune correlates of protection from RV infection and disease are not fully understood. Both serum and mucosal antibodies are probably associated with protection. Local gut immunity mediated by IgA has been considered critical, but the absence of severe disease in the first months of life suggest passive maternal serum antibody is also important, perhaps through transudation into the gut.[20] In some studies, serum antibodies against G protein and P protein have been correlated with protection; however, in other studies, including vaccine studies, correlation between serum antibody and protection has been poor.[103] The first infection with RV elicits a predominantly homotypic, serum neutralizing antibody (SNA) response to the virus; subsequent infections elicit a broader, heterotypic response.[104],[105] The influence of cell-mediated immunity is less clearly understood, but probably is related both to recovery from infection and to protection against subsequent disease.[106],[107]

Until the mechanisms of immunity are better delineated, field trials of vaccines are the only way to demonstrate efficacy.[20]

Immune response following vaccination: Rotateq™ has been tested in three Phase III clinical trials, conducted to examine the efficacy, safety and immunogenicity of its final formulation. They have involved 71,799 infants who were vaccinated with at least one dose of Rotateq™ or placebo.[108] In these trials, three doses of Rotateq™ were administered orally, beginning at age 6 to 12 weeks with a four-to-10-week interval between doses. The third dose was administered to infants up to 32 weeks of age. There was no restriction of breastfeeding or other licensed childhood vaccines, except oral poliovirus vaccine. The studies were the following:

- Protocol 006 – REST (RV efficacy and safety trial): This was a large-scale clinical trial of approximately 70,000 infants in 11 countries, with the U.S. and Finland accounting for approximately 80% of all enrolled persons.[1],[109] It was designed to evaluate the safety of Rotateq™ with respect to intussusception (IS), because of the previous finding of IS in 1/10,000 recipients of Rotashield™, and also to evaluate the reduction in health care-related outcomes. Many sub-studies were nested within this large-scale study. The detailed safety sub-study evaluated vaccine safety with regard to all adverse events. The clinical efficacy sub-study assessed the immunogenicity and efficacy against all RV gastroenteritis, as well as the effect on reducing office visits due to RV disease. It also evaluated antibody responses to routine childhood immunizations administered concomitantly with Rotateq™.
- Protocol 007 (dose-confirmation efficacy study): This study included 1,310 vaccinated subjects and was performed to confirm the efficacy of the expiry potency of Rotateq™ in the final formulation intended for licensure. The study evaluated the efficacy against RV disease caused by the G1, G2, G3 and G4 serotypes during the first RV season after vaccination. It examined efficacy at the end of the 24-month shelf life.[89], [108]
- Protocol 009 (consistency lots study): The purpose of this study, among 793 vaccinated subjects, was to clinically assess the consistency of the manufacturing process for Rotateq™. In the study, the immunologic responses elicited by three manufactured lots were evaluated. Serum anti-RV IgA titers and SNA titers against RV serotypes G1, G2, G3, G4 and P1[8] were measured.[5], [108]

In the REST trial, sera were collected before vaccination and approximately two weeks after the third dose, and seroconversion was defined as a three-fold or greater rise in antibody titer from baseline. Seroconversion rates for SNA to G1, G2, G3, G4 and P1[8] were significantly higher in vaccine recipients than placebo groups (approximately 23% to 76% vs. 0 to 8%, estimated from bar graph data); p values were not reported.[110] Seroconversion rates for IgA antibody to RV were 95% (95% CI: 91.2–97.8) among 189 vaccine recipients versus 14.3% (95% CI: 9.3–20.7) in 161 placebo recipients.[109]

In the Protocol 007 study, the seroconversion rate for SNA in vaccine recipients was 57% for G1, 40% for G4, 15% for G2 and 9% for G3. In 96% of recipients, a three-fold rise in serum anti-RV IgA was observed.[89]

2.6 Immunogenicity in Different Population Groups

No data were found on immunogenicity in different population groups.

2.7 Short- and Long-Term Vaccine Efficacy, Including Reduction of Disease and Death Risks

First season: There are excellent data to support one-year efficacy of 86% (95% CI: 74–93) against physician visits, 94% (95% CI: 89–97) against ER visits, and 96% (95% CI: 91–98) against hospital admissions for RV diarrhea (Table 6).[109] The combined reduction in hospitalizations and ER visits was 94.5% (95% CI: 91.2–96.6). Further, there was a 58.9% reduction (95% CI: 51.7–65.0) in all-cause diarrheal hospitalizations after one dose. Among the parents/guardians of the 68,038 infants studied, there was an 86.6% (95% CI: 78.0–91.9) reduction in work loss days absent.[109]

Table 6. Efficacy of Rotateq™ in Reducing Hospitalizations, ER Visits and Other Health Contacts Due to Laboratory-Confirmed Rotavirus Diarrhea

Type of health care contact	Rotateq™	Placebo	% Rate reduction (95% CI)
Combined endpoint (hospitalizations and ER visits)*	20	369	94.5 (91.2, 96.9)
Hospitalizations	6	144	95.8 (90.5, 98.2)
ER visits	14	255	93.7 (88.8, 96.5)
Non-urgent visits**	13	98	86.0 (73.9, 92.5)

*N=68,038 infants vaccinated (34,035 vaccine, 34,003 placebo)
**Derived from a sub-study, where N=5,673 infants vaccinated (2,834 vaccine recipients, 2,839 placebo recipients)

Rotateq™ protected against the RV serotypes in circulation. The reduction by G-type is shown in Table 7. The overwhelming majority of study strains were G1 and thus the confidence intervals for disease of any severity caused by strains G2–9 were very broad, especially for G2. In the smaller 007 study, two of three G3 infections occurred in vaccine recipients.

Table 7. Reduction in the Number of Hospitalizations and ER Visits in the Per-Protocol Population of the Large-Scale Study, According to G Serotype Identified in the Subject's Stool*[109]

Serotype	No. of cases of rotavirus gastroenteritis		Percent efficacy (95% CI)
	Vaccine group (N=34,035)	Placebo group (N=34,003)	
G1	16	328	95.1 (91.6–97.1)
G2	1	8	87.6 (<0–98.5)
G3	1	15	93.4 (49.4–99.1)
G4	2	18	89.1 (52.0–97.5)
G9	0	13	100.0 (67.4–100.0)
G12	0	1	100.0 (<0–100.0)

*The number of subjects in each group is the number that received at least one dose. Some subjects had more than one event.

In the clinical efficacy sub-study of 4,512 subjects (2,207 vaccine, 2,305 placebo), severe gastroenteritis was defined as a numerical score of >16 points on a 24-point Clark scale[111] evaluating the duration and intensity of fever, vomiting, diarrhea and behavioural changes. Vaccine efficacy against severe G1–G4 disease was 98.0% (95% CI: 88.3–100) and any severity 74.0% (95% CI: 66.8–79.9). Also, the mean severity score of disease in vaccine recipients was 9.1

(range 1 to 17) versus 12.9 (2 to 21) in placebo recipients. In the Protocol 007 study,[89] efficacy in 1,312 infants against severe and any RV disease was 100% (95% CI: 13–100) and 72.5% (95% CI: 50.6–85.6), respectively.

Table 8. Clinical Efficacy against Rotavirus Gastroenteritis of Any Severity in the Per-Protocol Population of the Clinical Efficacy Sub-Study, According to G Serotype Identified in the Subject's Stool*[109]

Serotype	No. of cases of rotavirus gastroenteritis		Percent efficacy (95% CI)
	Vaccine group (N=2,834)	Placebo group (N=2,839)	
G1	72	286	74.9 (67.3–80.9)
G2	6	17	63.4 (2.6–88.2)
G3	1	6	82.7 (<0–-99.6)
G4	3	6	48.1 (<0–91.6)
G9	1	3	65.4 (<0–99.3)

The efficacy of Rotateq™ was evaluated among a subset of 204 pre-term infants who were followed for gastroenteritis. Efficacy in the subset of 153 evaluable pre-term infants was generally similar to the efficacy in the overall population, at 70% (95% CI: 15–95), but the confidence interval includes zero due to the small sample size.[1],[5]

Second season: Efficacy after two years was somewhat lower: among a subset of 4,451 (2,173 vaccine, 2,278 placebo), efficacy against severe and any RV gastroenteritis was 88% (95% CI: 49.4–98.7) and 62.6% (95% CI: 44.3–75.4) respectively.[109] The efficacy of Rotateq™ in preventing cases occurring only during the second season was 62.6% (95% CI: 44.3–75.4).[5]

Third season: The Finnish Extension Study collected additional data on ~21,000 infants from the REST study, in order to expand efficacy data to the third season.[112] Rotateq™ significantly reduced hospitalizations and ER visits for up to three years, regardless of serotype. Unlike in the REST study alone (see Table 7), a statistically significant efficacy against G2 was achieved in the extension study.

Partial series efficacy: Rotateq™ has been approved for use as a three-dose series. Data on the efficacy of fewer than three doses are limited. In a very small study of fewer than 100 children, estimated efficacy in reducing RV hospitalization after one, two and three doses were 29% (<0–73.3), 80% (8.5–95.8) and 95% (91.5–96.5), respectively.[113] In the REST trial, the one-dose efficacy of 59% in reducing all-cause diarrhea hospitalizations may be explained by differences in study time and place.[109]

2.8 Effect of the Vaccine on the Transmission of the Specific and Related Organisms

There are no data on the effect of Rotateq™ on the circulation of RV, nor on the possibility of new reassortants. There is a possibility of variants escaping vaccine-induced immunity,[8],[55] as well as the emergence of reassortant strains with unique virulence properties following concurrent RV infections, especially in regions of the world with high burdens of exposure.[8],[13] Reversion of vaccine virus to a virulent strain has not been shown, and should it occur, extra-intestinal disease is not considered likely at this time.[56]

There are some data to indicate fecal shedding of vaccine virus in infants after dose one, but no transmission studies were done and no household symptoms ascertained, so the potential impact of this is unknown. Fecal shedding was evaluated in the substudy of 134 infants within REST, using viral culture with a plaque assay and RNA electropherotyping on a single stool sample during days four to six following each vaccination. Shedding occurred in 12.7% after the first dose was administered, with none documented after dose two or dose three.[109] In the smaller 007 study, only one sample was positive for vaccine strain after dose one.[89] Further data from the manufacturer indicate that from all children who submitted an RV antigen positive stool specimen at any time during studies, vaccine virus was shed in 8.9% (95% CI: 6.2%–12.3%) after dose one, none (95% CI: 0%–1.5%) after dose two and 0.3% (95% CI: <0.1%–1.4%) after dose three.[8] Shedding occurred from one to 15 days after a dose.

2.9 Short- and Long-Term Population Effectiveness

More information is needed on the effect of infant vaccination with Rotateq™ on the incidence of rotavirus in the rest of the population. The impact of Rotateq™ on household transmission of rotavirus was not obtained directly in the REST trial, and the role of herd immunity is unknown. Given that milder disease is not eliminated, some circulation and disease caused by serotypes contained in the vaccine may continue.

Evidence of herd immunity was observed at a large national reference laboratory in the U.S. after licensure of Rotateq™ vaccine.[114]

2.10 Safety: Rates and Severity of Adverse Events, Contraindications, Precautions

Given the relatively low morbidity and unlikely mortality with natural RV infection in Canada, and past experience with the withdrawal of an animal-human reassortant RV vaccine due to a risk of IS, enormous attention has been given to the safety of Rotateq™. A new RV vaccine needs to be categorically safer than natural infection, as is the case with existing vaccines and the diseases they protect against.

As indicated previously, the large REST study was designed primarily to assess safety with respect to IS. Nested sub-studies included a detailing of adverse events. To meet the primary safety hypothesis that there be no increase in IS within 42 days of dose administration, a minimum of 60,000 patients were required. Ultimately 70,301 were enrolled and data for 69,274 were available in the clinical database. A total of 68,038 (98.2%) received at least one dose, of whom 67,756 (99.6%) were followed for 42 days. Of the 69,274 subjects, 56,310 (81.3%) were followed for one year after the first dose.[109]

Intussusception:

Extensive discussion of the experience of IS with the rapidly withdrawn quadrivalent rhesus-human reassortant vaccine Rotashield™ has been published elsewhere.[115] Developers of this next generation of vaccines were advised to limit administration of first dose of vaccine to less than 90 days of age and to conduct very large safety trials to ensure greater safety than with Rotashield™.[20] In short, in 1998, a rhesus-based tetravalent RV vaccine, Rotashield™ (Wyeth-Lederle Vaccines),[105] was recommended for routine vaccination of U.S. infants with three doses at ages 2, 4 and 6 months.[116] In the first nine months after licensure and immunization of more than 600,000 children with one to three doses, 15 children developed IS in the two-week period immediately following vaccine administration.[20] Rotashield™ was withdrawn from the U.S. market within one year of its introduction because of its association with IS.[117] At the time of its withdrawal, Rotashield™ had not yet been introduced in any other national vaccination program globally, and the vaccine was not further tested or used in any country.

The risk for IS was most elevated (>20-fold increase) within three to 14 days, and most marked in the three-to-seven-day period after receipt of the first dose of Rotashield™,[118] with a smaller (approximately five-fold) increase in risk within three to 14 days after the second dose.[1] Overall, the risk associated with the first dose of Rotashield™ was estimated to be approximately one case per 10,000 children immunized.[115] A higher incidence of IS in black and Hispanic infants following immunization with Rotashield™ was linked to socioeconomic status. Also, formula feeding and recent introduction of solids were identified as risk factors for the development of IS following Rotashield™.[118] Studies of the safety of animal-human reassortant RV vaccines in populations with various baseline rates of IS, including Vietnamese populations, a group with high rates, have been suggested as necessary to confirm safety.[119]

The search for a pathogenic mechanism continues.[120] Recent studies have ruled out natural RV as a cause of IS, and suggested a possible role of non-enteric adenovirus C in at least some IS cases.[119] Certain researchers have reassessed the data on Rotashield™ and have suggested that the risk for IS was age-dependent. They suggest that the absolute number of IS events, and possibly the relative risk for IS associated with the first dose of Rotashield™, increased with increasing age at vaccination, including receipt of the the first dose after 3 months of age.[121,122] However, the WHO Global Advisory Committee on Vaccine Safety (GACVS), after reviewing all the available data, concluded that the risk for Rotashield™ -associated IS was high in infants vaccinated after 60 days of age and that insufficient evidence was available to conclude that the use of Rotashield™ among infants <60 days of age was associated with a lower risk.[123] GACVS noted that the possibility of an age-dependent risk for IS should be taken into account in assessing future RV vaccines.

Post-licensure surveillance suggested that, besides IS, Rotashield™ was associated with a spectrum of other gastro-intestinal symptoms, including gastroenteritis and bloody stools.[124]

Several characteristic differences between the source of the G6P7 from the WC3 bovine parent strain of Rotateq™ and the Rotashield™ G3P5B rhesus strain have been defined.[8]

Specifically:

1. In a mouse model, simian RV augmented the occurrence of IS, but not bovine RV (abstract only)[115]
2. The finding of replication in Peyer's patches of simian, but not bovine, RV suggests a biologic difference at the suspected endpoint in IS[125]
3. Simian, but not bovine, RV spreads to the liver in inoculated mice [126]

Also, as stated below, the reactogenicity profile of Rotateq™ is lower than the rhesus-based Rotashield™.

The risk for IS was evaluated in 71,725 persons enrolled in Phase III efficacy trials of Rotateq™. In the REST trial, parents/legal guardians of all persons were contacted by telephone or home visit on approximately day seven, 14 and 42 after each vaccination, and every six weeks thereafter for up to one year after the first dose.[109] Parents were asked about all serious adverse experiences, including IS, among enrolled children. Each investigator-identified IS case was forwarded to a blinded adjudication committee and then to an unblinded safety committee to determine if the REST trial should continue.[8] Potential IS cases were adjudicated according to a prespecified case definition (not Brighton) that included radiographic, surgical and autopsy criteria. For the prespecified 42-day

postvaccination endpoint, six cases of IS were observed in the Rotateq™ group versus five cases of IS in the placebo group (multiplicity adjusted relative risk = 1.6; 95% CI: 0.4–6.4) (Table 9).[5] This provides a risk of IS of 1:4,934 in vaccine recipients versus 1:5,971 in placebo recipients.[56] For the six IS cases that occurred in the vaccine group, no cases occurred within 42 days of dose one, one case occurred within seven days of dose two and three cases occurred within 15 to 42 days of dose two. The final two cases occurred within 15 to 42 days of dose three. For the five IS cases that occurred in the placebo group, one case occurred within 15 to 42 days of dose one, one case occurred within 15 to 42 days of dose two, one case occurred within eight to 14 days of dose three and the final two cases occurred within 15 to 42 days of dose three.

For the one-year follow-up period after administration of the first dose, 13 cases of IS were observed in the Rotateq™ group versus 15 cases in the placebo group (multiplicity adjust-relative risk: 0.9; 95% CI: 0.4–1.9). Following the one-year safety follow-up period, four cases of IS were reported in children who had received placebo during the study.

Table 9. Confirmed Cases of Intussusception in Recipients of Rotateq™ as Compared with Placebo Recipients During the REST Study

	Rotateq™ (N=34,837)	Placebo (N=34,788)	Relative risk (95% CI)
Confirmed IS cases within 42 days after each dose	6	5	1.6 (0.4–6.4)
Confirmed IS cases within 365 days after dose 1	13	15	0.9 (0.4–1.9)

Hematochezia:

In REST, hematochezia was reported as an adverse event in 0.6% of both vaccine and placebo recipients, and as a serious adverse event in <0.1% of both groups.[5] Among negatively adjudicated cases of intussusception, there was no significant difference between 10 cases of hematochezia in vaccinees and three cases in the placebo group.[109]

Seizures:

All seizures reported in the Phase III trials of Rotateq™ (by vaccination group and interval after dose) are shown in Table 10 (Product Monograph).[5] These data come from the entire safety database across the three Phase III studies; thus, the denominator is 71,686 (number of subjects with safety follow-up). Adverse experiences of "seizure" are reported by day range in relation to any dose in the Phase III trials of Rotateq™, and include the MedDRA (Medical Dictionary for Regulatory Activities) adverse event terms of convulsion, febrile convulsion, partial seizure, epilepsy and infantile spasms. This table incorporates serious (in this case, hospitalizations) and non-serious adverse events of seizures (personal communication, teleconference, Jan. 25, 2007, Michelle Goveia, Medical Director, Vaccines, Merck).

Table 10. Seizures Reported by Day Range in Relation to Any Dose in the Phase III Trials of Rotateq™

Day Range	1–7	1–14	1–42
Rotateq™	10	15	33
Placebo	5	8	24

There were 27 and 18 serious seizures reported in the vaccine and placebo group, respectively. Therefore, seizures reported as serious adverse events occurred in <0.1% (27/36,150) of vaccine and <0.1% (18/35,536) of placebo recipients (not significantly different). The breakdown of these cases by adverse event term was: convulsion (16 V; 8 P); epilepsy (4V; 2 P); febrile convulsion (5 V; 5 P); infantile spasms (1 V; 3 P); partial seizure (1 V; 0 P) (personal communication, teleconference, Jan. 25, 2007, Michelle Goveia, Medical Director, Vaccines, Merck).

Serious Adverse Events:

Serious adverse events (SAE) were evaluated in 71,725 infants enrolled in Phase III trials. Among Rotateq™ and placebo recipients, the incidence of SAEs was 2.4% and 2.6%, respectively, which was not significantly different. SAEs most frequently associated with discontinuation of immunization in Phase III trials are reported in Table 11. Again, there were no statistically significant differences between the vaccine and placebo groups (personal communication, teleconference, Jan. 25, 2007, Michelle Goveia, Medical Director, Vaccines, Merck).

Table 11. Most Frequent SAEs that Led to Discontinuation in Phase III Trials

	Rotateq™ (N=36,356)	Placebo (N=35,750)
Gastroenteritis	4	9
SIDS	7	7
Inguinal hernia	6	7
Bronchiolitis	5	7
Convulsion	6	2
Vomiting	3	0
Pyrexia	2	2

Death:

Among the 71,725 infants enrolled in Phase III trials, there were no significant differences in death rates between the vaccine and placebo groups. There were 25 deaths in the Rotateq™ group (<0.1%) and 27 (<0.1%) in the placebo group. No deaths were attributed to vaccination by blinded investigators.[5],[109]

One death from post-operative sepsis following IS surgery occurred in a vaccine recipient, with the IS occurring at 98 days after the third dose and thus unrelated. This serves as a reminder of the potential severity of IS.[109]

The most common cause of death (accounting for 17 of the 52 deaths) was sudden infant death syndrome (SIDS), and deaths from SIDS were equally distributed among Rotateq™ and placebo recipients (n=8 and 9, respectively).[1]

Other adverse events:

In a subset of 11,722 infants, other potential adverse events were assessed (e.g., fever, diarrhea and vomiting). Parents/guardians of these infants were asked to report the presence of other events on the Vaccination Report Card for 42 days after each dose. Overall, 47.0% of infants given Rotateq™ experienced a vaccine-related adverse event, compared with 45.8% of infants given placebo. Vaccinees had a small but significantly greater rate of certain symptoms compared with placebo recipients, including 1% excess of vomiting (15% versus 14%, respectively) and 3% excess of diarrhea (24% versus 21%, respectively).[1],[8] None of these cases were severe.[8] Among Rotateq™ and placebo recipients, the incidence of reported episodes of fever was similar (43% versus 43%),[1] and thus Rotateq™ is considered to have low reactogenicity in comparison to Rotashield™. Unsolicited adverse events significantly more frequent among vaccinees included: 1% excess of nasopharyngitis (7% versus 6%), 2% excess of otitis media (15% versus 13%) and 0.4% excess of bronchospasm (1.1% versus 0.7%).[1],[8] None of the bronchospasm events was clinically severe.[8]

In the seven-day postvaccination period, vaccinees had a small but significantly greater rate of diarrhea, with an excess of 1% after dose one (10% versus 9%, respectively), 3% after dose two (9% versus 6%, respectively), and 3% after any dose (18% versus 15%, respectively). Similarly, vaccinees had a small but significantly greater rate of vomiting, with an excess of 2% after dose one (7% versus 5%, respectively) and 2% after any dose (12% and 10%, respectively). However, the incidence of fever and irritability during the seven-day period after any vaccine dose was similar among Rotateq™ and placebo recipients.[1] Only one study (007) has shown a greater rate of fever within seven days of immunization in vaccine recipients (13.4%) versus placebo recipients (8.8%); the numbers enrolled in this study are much smaller than the REST trial.[89] Fevers on day four coincide with the time of peak viral replication and may be of biologic interest because viral replication may in rare cases be associated with low-grade fever.[89] Dermatitis has been reported as more common among vaccine recipients, with a risk increase of atopic dermatitis in the 007 study of 1.5% (95% CI: 0.4–3.0).[109]

Safety in Pre-Term Infants:

Rotateq™ or placebo was administered to 2,070 pre-term infants (25 to 36 weeks gestational age, median 34 weeks) according to their chronological age in the REST trial. All pre-term infants were followed for serious adverse events; a subset of 308 infants was monitored for all adverse events. There were four deaths throughout the study: two among vaccine recipients (one SIDS and one motor vehicle accident) and two among placebo recipients (one SIDS and one unknown cause). No cases of IS were reported. Serious adverse events occurred in 5.5% of vaccine and 5.8% of placebo recipients. The most common serious adverse event was bronchiolitis, which occurred in 1.4% of vaccine and 2.0% of placebo recipients. Parents/guardians were asked to record the child's temperature and any episodes of vomiting and diarrhea daily for the first week following vaccination. The frequencies of these adverse events and irritability within one week after each of the three doses are summarized in Table 12.[5]

Table 12. Solicited Adverse Events within the First Week after Doses 1, 2 and 3 among Pre-Term Infants

Adverse event	Dose 1		Dose 2		Dose 3	
	Rotateq™	Placebo	Rotateq™	Placebo	Rotateq™	Placebo
Elevated temperature*	n=127	n=133	n=124	n=121	n=115	n=108
	18.1%	17.3%	25.0%	28.1%	14.8%	20.4%
	n=154	n=154	n=137	n=137	n=135	n=129
Vomiting	5.8%	7.8%	2.9%	2.2%	4.4%	4.7%
Diarrhea	6.5%	5.8%	7.3%	7.3%	3.7%	3.9%
Irritability	3.9%	5.2%	2.9%	4.4%	8.1%	5.4%

*Temperature ≥100.5ºF (38.1ºC) rectal equivalent obtained by adding 1 degree F to otic and oral temperatures and 2 degrees F to axillary temperatures.

2.11 Potential Interaction with Other Vaccines

Rotateq™ was well tolerated and efficacious when administered concomitantly with other licensed childhood vaccines. The efficacy of Rotateq™ was evaluated among a subset of infants in the U.S. who received *Haemophilus influenzae* type b and hepatitis B vaccine (Hib/Hb) (COMVAX, Merck), diphtheria, tetanus toxoids and acellular pertussis vaccine (DTaP) (INFANRIX, GlaxoSmithKline), inactivated poliovirus vaccine (IPV) (IPOL, Sanofi Pasteur), and pneumococcal conjugate vaccine (PN) (PREVNAR, Wyeth). The immune responses to the specified vaccines were largely unaffected by Rotateq™. Of the 17 antigens studied, the antibody responses were similar among vaccine and placebo recipients, except for a slightly diminished response to one of the three antigens tested for pertussis (pertactin). This diminished response was not confirmed in a recent study of concurrent administration of Rotateq™ and DPT-IPV-Hib.[127]

Rotateq™ can therefore be administered at 2, 4 and 6 months with existing pentavalent (DPT-IPV-Hib), hepatitis B and Prevnar™ products; no data have been provided to indicate that it can be administered with conjugated meningococcal C vaccine. Rotateq™ cannot be administered with oral poliovirus vaccine (OPV), as concomitant administration of Rotateq™ and OPV has not been studied; however, this is irrelevant in Canada where IPV is used exclusively.

2.12 Potential Impact of Immunization Program on Resistance to Antibiotics and Antivirals

Not applicable unless antibiotic use turns out to be common in the new pre-implementation IMPACT study.

Discussion

RV is a complex virus with considerable diversity among circulating strains.[9] It is extremely easily transmitted with a small infecting dose and environmental hardiness.[23],[128] The clinical manifestation usually includes enteric symptoms, such as fever, vomiting and diarrhea, with varying severity.[44] Extraintestinal disease, particularly of the CNS, is rarely reported. Recent publications suggest it is possible that the spectrum of natural disease may be under-recognized.[33],[128]

RV is a common infection among children. It is not a nationally notifiable disease in Canada and there are limited Canadian data. Estimates of RV infection and associated disease burden are based on available Canadian studies in select populations, such as children seen in physician offices, pediatric clinics, emergency departments and those admitted to hospital.[44]–[47] RV peaks seasonally in late winter/early spring.[20] Over half of hospitalizations occur in the 6-to-24-month age group, with nearly all hospital admissions in this young age group during the peak season being due to RV.[45]

Recent work suggests that there are factors that may, at least in U.S. studies, characterize children to be prioritized for intervention, such as: being in child care, having low socio-economic status (i.e., on Medicaid, or without insurance), or having another child in the household less than 24 months of age.[61] However, these factors are shared by large proportions of the population eligible for RV vaccine, making a targeted approach to immunization impractical. Further, some factors, like low birthweight, represent only very small groups, limiting the impact of a targeted approach. Therefore, in the U.S. a universal program was considered as the appropriate direction.[1] It is important to note that at least two of these three factors (day care and health coverage) are considerably different in Canada compared with the U.S. In a Canadian prospective study, socioeconomic factors, parental marital status, child care arrangement (including day care centre attendance) and ethnicity did not appear to influence RV hospitalization.[45]

Studies have shown that RV places a high burden on the health care system. According to a Canadian study, one child in 62 will have been hospitalized due to RV by age 5.[88] The severest cases of gastroenteritis among children, in terms of health care need/utilization, are most often caused by RV.

As with natural infection, which provides good protection against symptomatic disease, one-year efficacy of Rotateq™ was 98% against severe disease and 74% against disease of any severity. The combined reduction in hospital and ER visits after vaccination was 94.5%. There was also an 87% reduction in work loss days for parents/guardians.[109] Some data on efficacy can only be determined in post-licensure studies. These include:

- The efficacy of vaccine for fewer than three doses, especially given the strict age of approval
- The impact on the time of dosing in relation to season (REST Rotateq™ before season)[56]
- Impact of the vaccine on second-year disease and beyond
- The role of the vaccine in preventing disease caused by non G1 serotypes (especially G2 and G3) and non P1A infection
- Determination of protective efficacy through serotyping of circulating strains and relative importance of heterotypic and homotypic immune responses and protection.[129]

Lessons regarding vaccine safety that can be learned from experience with the previous RV vaccine, Rotashield™, include:[56]

- The importance of conducting post-marketing surveillance to identify very rare adverse events (i.e., less common than 1/10,000)
- The rarity of Rotashield™-associated IS events suggests a pathogenic mechanism that combines a susceptible host and intestinal stimulation provided by the simian virus. This fits with the fact that there was less IS in the year after vaccine, and with the high reactogenicity profile of Rotashield™
- The need for baseline IS rates, estimated in the two-week post-immunization window at 4.59–4.76 per 100,000 doses.[130]

In the results of the Phase III clinical trials for Rotateq™, it is important to note that there was no clustering of IS cases among vaccine recipients at any time after any dose, and that there were no confirmed cases of IS during the 42-day period after dose one. The published risk of IS provided to pediatricians, while not statistically significant, is stated as one in 4,934 Rotateq™ recipients compared to 1 in 5,971 placebo recipients.[56] The occurrence of hematochezia in vaccine recipients was higher than in the placebo group, but this was not statistically significant.[109] The occurrence of serious seizures (i.e., those that would qualify as serious adverse events) was not significantly different in vaccine and placebo recipients (personal communication, Merck). Rotateq™ had minimal reactogenicity: diarrhea and vomiting were very minimal but significantly higher in vaccine recipients than in controls,[1] but only one of three studies showed any difference in fever within seven days of immunization.[89]

Rationale for RV Immunization

- The rates of RV illness among children in industrialized and less developed countries are similar, indicating that clean water supplies and good hygiene have little effect on virus transmission; therefore, further improvements in water or hygiene are unlikely to have a substantial impact on disease prevention[87],[101],[131-133]
- In Canadian studies, hospitalization caused by RV occurs across the socioeconomic-cultural spectrum[45]
- In the United States,[52],[83] high levels of RV morbidity continue to occur despite available therapies. For example, the rate of hospitalizations for gastroenteritis in young children declined only 16% during 1979–1995, despite the widespread availability of oral rehydration solutions and recommendations by experts for their use in the treatment of dehydrating gastroenteritis.[81],[82] There is some evidence that this may also be the case in Canada, at least in 1997–1998 in the Toronto area even despite prior pediatric office visits,[45],[47] and in Quebec studies,[46] as well as more recent outpatient study across Canada.[44] Further Canadian data are needed.
- Studies of natural RV infection indicate that initial infection protects against subsequent severe gastroenteritis, although subsequent asymptomatic infections and mild disease might still occur.[101],[134],[135] Immunization early in life, which mimics a child's first natural infection, will not be expected to prevent all subsequent disease, but should prevent most cases of severe RV disease and their complications (e.g., dehydration, physician visits, hospitalizations and deaths).

In conclusion, Rotateq™ is an effective vaccine, especially against severe rotavirus gastroenteritis. More data are needed on efficacy of partial series vaccination, given the narrow age-window for administration of the three doses. Phase III clinical trials have shown Rotateq™ to be safe and minimally reactogenic, with no association with intussusception. Rotavirus is a frequent infection of Canadian infants, and although infection often results in mild disease, severe rotavirus gastroenteritis places a significant burden on the health care system on a seasonal basis.

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Appendix I: Summary of an Analytic Framework for Rotateq™

Domains	Components	Issues for Consideration
Disease Characteristics and Burden	• Disease (infectious agent, mode of transmission etc.) • Epidemiology (in Canada, risk groups)	• NACI • IMPACT retro/prospective studies • Nonfatal, no long-term morbidity, only acute illness • *By 5 years of age, 1 in 62 to 1 in 106 children will have been hospitalized due to RV diarrhea* • Little information about strains or strain changes over time in Canada
Vaccine Characteristics	• Efficacy, effectiveness (short and long-term) • Safety: short-term, long-term	• NACI • IMPACT retro/prospective studies • Proxy evaluation of efficacy through seasonal diarrhea hospitalization rates • Reservations about safety including slight increase in IS and first dose hematochezia in pre-licensure trials, afebrile seizures/any associated morbidity and mortality; biologic plausibility given derivation from animal strain Further safety: comment: • generally well tolerated • small increased risk of IS, hematochezia in 34,837 vaccinees in clinical trials; see CNS issue above • no increased risk of other serious adverse events • incidence of fever, vomiting and diarrhea ≥1% higher in vaccinees than in controls after each dose • no increased risk of adverse events when administered concurrently with DTaP, IPV, Hib, hepatitis B vaccine, and pneumococcal conjugate vaccine • Concurrent administration with other vaccines did not reduce immunogenicity for any antigen other than reduced response to pertactin. The significance of this reduction is not known and emerging data reassuring • Relatively few non G1 strains studied pre-licensure • Adjudication of safety with contemporaneous vaccine administration • Pertactin interaction and effect on pertussis
Alternative Immunization Strategies	• Schedules • Age group / Risk group • Modes of delivery (physician, public health, school-based)	• Need for strict timing of administration due to age of approval • Age group to be vaccinated: infants 2-6 months of age • Vaccine can be incorporated into the 2-month, 4-month, 6-month visits for other vaccines

Domains	Components	Issues for Consideration
Social and Economic Costs and Benefits	• Vaccine-related • Disease-related • Perspective (societal /individual)	***Cost-effectiveness*** *Disease costs per year in Canada are estimated to be $46.4 million.* *Only if total vaccine cost is <$110 will routine vaccination be cost-neutral to society.* • The costs of parent and physician education for introduction of rotavirus vaccine may be higher than expected because of: • 1. concerns over withdrawal of Rotashield vaccine; and • 2. rotavirus vaccine may reduce incidence of infant diarrhea by 20% because of other diarrheal pathogens unaffected by vaccine. • Cost of hematochezia, potential AEFI investigation
Feasibility and Acceptability	• Public • Professionals • Political	• Public: parents may not perceive importance of disease • Professionals: may have difficulty incorporating yet another vaccine into the already crowded infant immunization schedule • Political: will need education on the significance of rotavirus diarrhea as a health problem requiring preventive measures such as immunization
Ability to Evaluate Programs	• Vaccine effectiveness • Adverse events • Vaccine coverage • Disease	• Post-marketing surveillance will be required to assess true incidence of serious adverse events, including IS, CNS. IMPACT will be best system for such surveillance • Vaccine efficacy will require special studies to assess effect of vaccine on distribution of rotavirus serotypes causing disease • Vaccine coverage will require implementation of computer-based vaccine records throughout Canada • Impact of vaccine on disease incidence will require follow-up studies in areas of Canada where rotavirus epidemiology has already been studied • Need to add capacity to identify by PCR any vaccine strain that might occur in related CNS disease, IS, significant viremia or mortality
Research Questions	• Fundamental • Intervention • Program Delivery	• Adjudication of safety with contemporaneous vaccine administration • Pertactin interaction and effect on pertussis incidence • Mutant reversion/serotype replacement/performance • Level of vaccine coverage required to have an effect on disease and prevent transmission and to evaluate the effect herd immunity might have at a population level
Other Considerations	• Equity • Ethical • Legal • Political	• "Vaccine trust" and high stakes of introduction of vaccine previously associated with IS, for disease which is nonfatal, has no long-term morbidity, only acute illness • Negative impact on vaccine programs with effect on only 20% of diarrhea
Overall Recommendation	• Who should receive vaccine? • Should this vaccine be publicly funded?	• Reservations about safety, especially given the general lack of any long-term morbidity and mortality of natural disease • Insufficient current data re. burden of illness, strains and vaccine performance in non-G1 related disease

Appendix II: Potential Challenges to an RV Vaccine Program

- Burden of illness
  - Death is rare in Canada
  - 1/62 to 1/106 children by 5 years of age have short hospitalization for RV diarrhea
  - High secondary attack rate in household contacts but probably finished in household in a month without sequelae
  - Vaccine efficacy limited to a couple of months/year when RV outbreaks occur
  - Effect on only 20% of diarrhea seen in MD offices
  - Effect on only 20% of diarrhea seen in day care centres
  - Little information about Canadian strains, current burden of illness
- Vaccine dosing
  - Timing (6 wks. to 32 wks.) is tight (and relaxing administration to include after 32 wks. if started late and interval constant as per ACIP is unstudied)
- Vaccine interactions
  - Pertactin interactions and effect on pertussis are not completely evaluated
  - Post-introduction need to monitor rates of pertussis
- Potential safety concerns
  - Intussusception
  - Hematochezia
  - Afebrile seizures and possibility of related morbidity and mortality in the absence of data
  - Biologic plausibility of same given derivation from animal strain
- Safety monitoring
  - Need for active surveillance for IS, hematochezia, afebrile seizures, each of which is very hard and almost impossible to attribute on a case-by-case basis; even marginal increases would be unacceptable given natural disease; further questionable sensitivity to detect given available data on background rates
  - Need for capacity to detect vaccine-derived rotavirus by PCR in blood, CNS, tissue to adjudicate possible vaccine-related morbidity and mortality
  - In some regions of Canada, including Ontario, IMPACT surveillance cannot be counted on because IMPACT is based at 12 of the 16 tertiary care pediatric centres in Canada and does not cover the many community hospitals to which children are admitted
  - Even without another vaccine, infrastructure for management of adverse events following immunization (AEFI) (MD-feds) is taxing
  - AEFI adjudication with several vaccines administered contemporaneously can be difficult
- Safety teaching for each parent will be time-consuming
  - Parents need to be told about intussusception
  - Problem with old vaccine; is actively being followed

Appendix III: Strength of Recommendations and Quality of Evidence

Recommendations

Routine vaccination at ages 2, 4, and 6 months **I A**

Administer to breastfed infants **I A**

Co-administer with DTaP, Hib vaccine, IPV, hepatitis B vaccine and pneumococcal conjugate vaccine **I A**

Administer to infants with mild illness **I B**

Contraindications

Serious allergy to a vaccine component or a previous vaccine dose **III B**

Precautions

Altered immunocompetence **III I**

Moderate-to-severe illness, including acute gastroenteritis **III I**

Chronic gastrointestinal disease **III I**

History of intussusception **III I**

Special situations

Premature infants (aged <37 weeks) **I B**

Infants living in households with immunocompromised persons **III I**

Infants living in households with pregnant women **III I**

Regurgitation of vaccine **III I**

Children hospitalized after vaccination **III I**

Level of evidence

I Evidence obtained from at least one properly randomized, controlled trial

II-1 Evidence obtained from well-designed, controlled trials without randomization

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group (including immunogenicity studies)

II-3 Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category

III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Strength of recommendations

A There is good evidence to recommend the clinical preventive action

B There is fair evidence to recommend the clinical preventive action

C The existing evidence is conflicting and does not allow to make a recommendation for or against the clinical preventive action; however, other factors may influence decision-making

D There is fair evidence to recommend against the clinical preventive action

E There is good evidence to recommend against the clinical preventive action

I There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making.

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