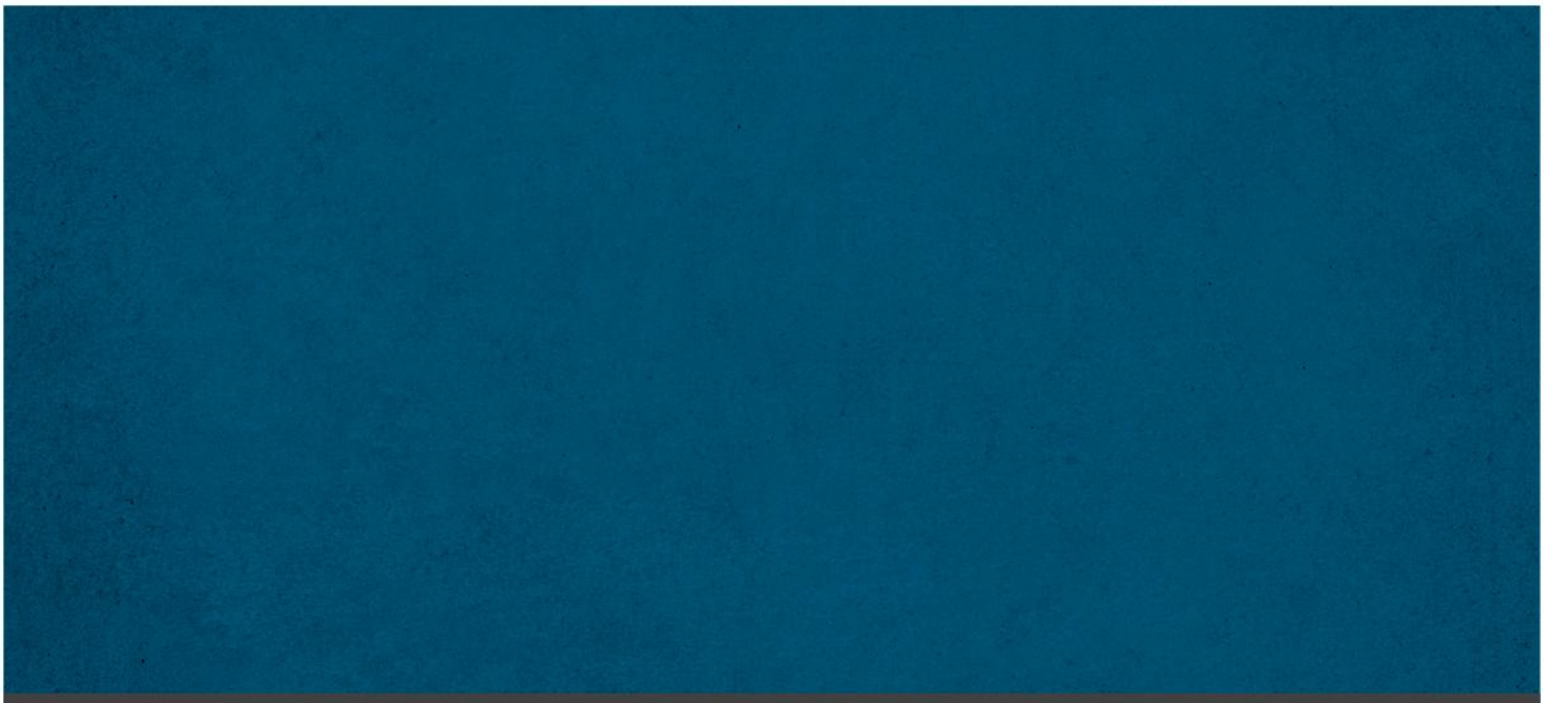
RECOMMENDATIONS FOR ROTAVIRUS IMMUNIZATION PROGRAMS

CANADIAN IMMUNIZATION COMMITTEE



PROTECTING CANADIANS FROM ILLNESS

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

Canada

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

—Public Health Agency of Canada

Également disponible en français sous le titre :
Recommandations pour les programmes de vaccination antirotavirus
To obtain additional copies, please contact:

Canadian Immunization Committee (CIC)
Public Health Agency of Canada
Ottawa, ON K1A 0K9
E-mail: cic-cci@phac-aspc.gc.ca

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

Publication date: January 2014

Cat.: HP40-95/2014E-PDF
ISBN: 978-1-100-23153-2
Pub.: 130542

TABLE OF CONTENTS

ROTAVIRUS: BURDEN OF DISEASE

NATURE AND CHARACTERISTICS OF THE INFECTIVE AGENT

Rotavirus is a virus in the family Reoviridae. It has a double stranded RNA genome composed of 11 segments contained within three concentric shells. The outermost shell is composed of two proteins, VP4 (P Protein) and VP7 (G Protein). These proteins are important for vaccine development and immune response as they are the target of neutralizing antibodies (1). Since the P and G proteins can segregate independently, serotype is determined by antigenic difference in both proteins. Although the prevalence of rotavirus serotypes varies from year to year and by region (Table 1), G1P[8] has been detected consistently and is often the predominant strain in developed regions (i.e. North America, Europe and Australia) (1,2).

Rotavirus is transmitted via the fecal-oral route, through person-to-person contact and contaminated environmental surfaces (2). The virus' ability to persist on environmental surfaces facilitates the dissemination of rotavirus in certain settings (*i.*e. hospitals and daycares). There is also some evidence that rotavirus can be transmitted through the respiratory route (1).

Table 1: Selection of recent North American studies tracking the prevalence of rotavirus strains.

Study Site	Public Health Laboratories (3)	Physician offices and pediatric clinics (4)	Community samples submitted to Public Health Laboratory (5)	Emergency Departments (6)
Study Timing	1996-2005	2005	2004-2009	2007-2009
Region	U.S. urban centres	Across Canada	Alberta	Canadian urban centres
Most prevalent serotypes	G1P[8] (78.5%) G2P[4] (9.2%) G9P[8] (3.6%) G9P[6] (1.8%) G3P[8] (1.7%) G4P[8] (0.8%)	G1P[8] (55%) G4P[8] (22%) G3P[8] (10%) G9P[6] (8%) G2P[4] (3%)	G1P[8] (48%) G3P[8] (21%) G2P[4] (15%) G2P[8] (3.4%) G1P[4] (3.3%) G9P[8] (2.5%)	G1P[8] (68%) G3P[8] (17%) G2P[4] (8%) G9P[8] (6%) G4P[8] (1%)

CLINICAL MANIFESTATIONS AND COMPLICATIONS

Rotavirus infections have a wide range of clinical presentations from asymptomatic infection or mild disease to severe infection which can lead to severe dehydration and death. Severity of infection is age-dependent, with clinically significant disease occurring most frequently in infants and young children. Illness is self-limiting, rarely resulting in long-term sequelae or death in healthy children in Canada. Death due to rotavirus is a rare outcome in Canada. Immunodeficient children can develop a chronic symptomatic infection. Adults are commonly infected with rotavirus, but symptoms are usually minimal or subclinical (1).

Following a 1-3 day incubation period, symptomatic children develop fever, diarrhea and vomiting, either alone or in combination (2). A Canadian community based study found that 62% of children with rotavirus gastroenteritis (RVGE) experienced all three symptoms of fever,

diarrhea and vomiting, with the majority of children manifesting all three symptoms concurrently for at least one day. The average duration of illness was 8 days, and ranged from 6-10 days (7).

Rotavirus infections in children are often more severe than illness associated with other viral gastroenteritis. Rotavirus cases are comparatively more likely to experience dehydration, hospitalization and if left untreated, shock, electrolyte imbalance and death (2). Health-care utilization among children with rotavirus-associated diarrhea is higher and accounts for a greater proportion of hospitalization compared to cases of diarrhea due to other viral pathogens. It is estimated that one in seven children with rotavirus gastroenteritis will seek health care, 1 in 20 will visit an emergency department or be hospitalized and 1 in 62 will be hospitalized (8). The Immunization Monitoring Program ACTive (IMPACT) study, which tracks rotavirus-related hospital stays in children's hospitals across Canada, found hospitalized children had serious clinical symptoms: 48.6% were assessed with significant dehydration, 19% had clinical sepsis, 7% experienced seizures and 8% presented with other serious signs. The majority of these children did not have underlying health problems. The median hospital stay for children with a rotavirus infection was 3.4 days, with a range of 1 to 46 days (9).

EPIDEMIOLOGY OF ROTAVIRUS

Rotavirus infections are not nationally notifiable. Therefore there is no one monitoring system that captures the occurrence of rotavirus cases in Canadian communities. Data are available through several laboratory and hospital-based surveillance programs. The National Enteric Surveillance Program (NESP) and Canadian Virus Report (CVR) track the number of laboratory confirmed rotavirus cases. Provincial public health laboratories report the positive results to NESP while CVR receives data from select hospitals and regional public health laboratories. The Canadian Institutes for Health Information (CIHI) provides information on hospital admissions across Canada. Patients' medical conditions during hospitalization are classified according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10) since 2002. The IMPACT study provides extensive case data from children hospitalized with rotavirus in the 12 participating paediatric hospitals across Canada from 2005 to 2007.

These four monitoring systems encompass different populations with differing magnitudes of illness. However, all demonstrate a distinct seasonal trend with the majority of cases occurring during the winter and spring months (Figure 1). This seasonal distribution of rotavirus gastroenteritis is well-established and occurs in most temperate zones (1).

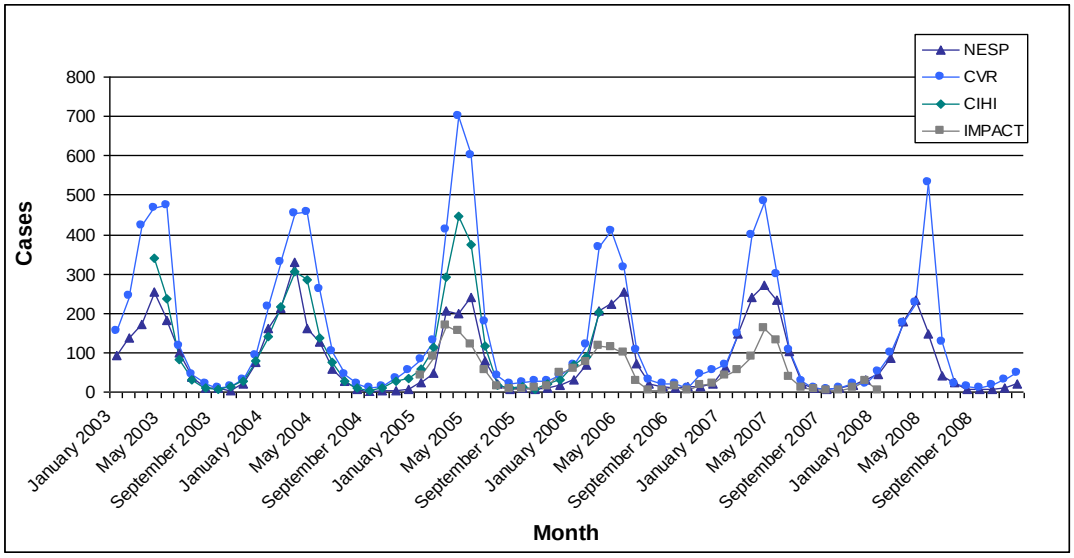


Figure 1: Seasonal trends of community rotavirus infections and hospitalizations as reported between January 2003 and December 2008 to the National Enteric Surveillance Program (NESP), Canadian Virus Report (CVR), Canadian Institute for Health Information (CIHI), and the Immunization Monitoring Program ACTive (IMPACT).

Despite similar seasonal trends, incidence rates based on NESP reports vary substantially from province to province (Figure 2). Given the ubiquitous distribution of rotavirus, the provincial cases observed in NESP are likely an under-representation of the true incidence, and more reflective of presentation to medical practitioners, notification practices and testing procedures. Laboratory-confirmed rotavirus cases from the CVR exemplify a similar range in provincial incidence rates (Figure 2).

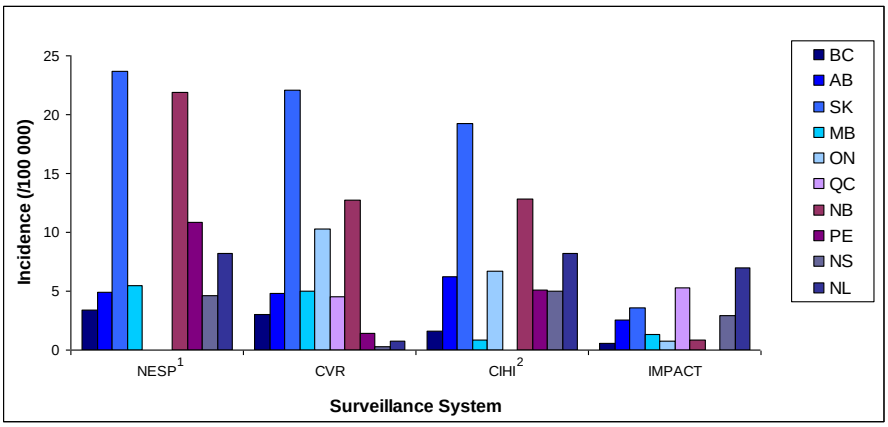


Figure 2: Incidence rate of rotavirus cases by province in 2005 as reported to the National Enteric Surveillance Program (NESP), the Canadian Virus Report (CVR) the Canadian Institute for Health Information (CIHI) and the Immunization Monitoring Program ACTive (IMPACT).

[1]Ontario and Quebec did not report rotavirus results to NESP in 2005.
[2]Quebec used a different coding scheme (ICD-9) in 2005 and thus was not included

Rotavirus hospitalization trends like those of community cases show a large variation in the provincial incidence rate (Figure 2). Access to medical care and/or misclassification of true rotavirus cases may account for some of the provincial differences in hospitalizations. A review

of CIHI records showed that several non-specific gastroenteritis codes had strikingly parallel seasonal distribution to rotavirus in children less than 5 years of age (Figure 3), suggesting that a large number of rotavirus hospitalizations may be attributed to non-specific gastroenteritis. One study in the United States (U.S.) estimated that only 47% of hospital discharge records were correctly coded as rotavirus. The authors ascribed the discrepancy to 3 possible scenarios: testing for rotavirus does not affect treatment and therefore may not be routinely done; specific guidelines do not exist for diagnostic testing of rotavirus in the U.S.; and variation exists between institutions in testing and coding practices (2).

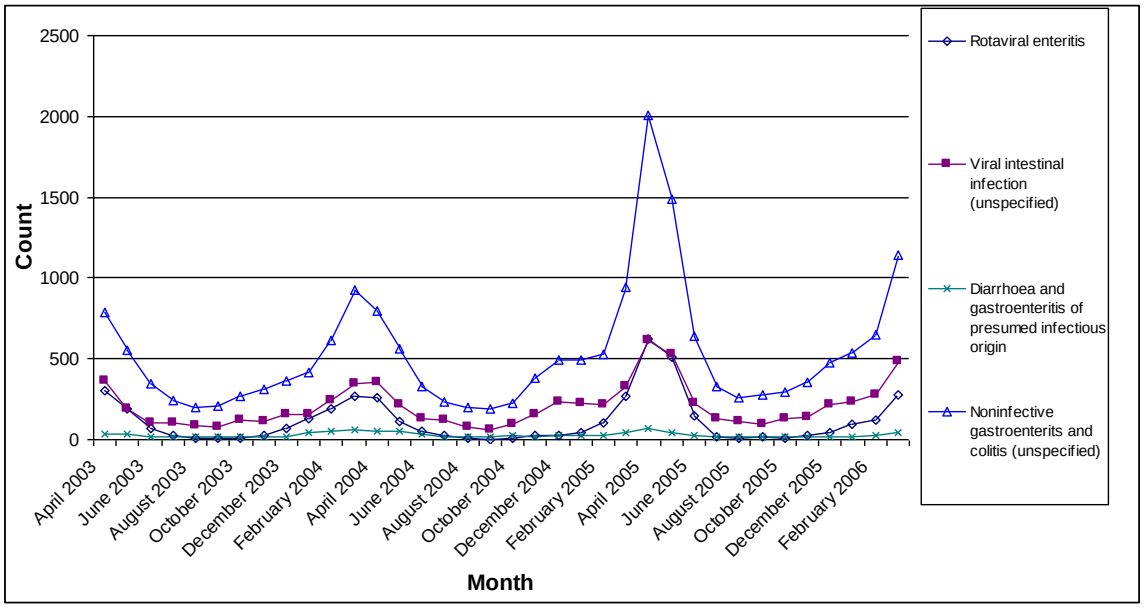


Figure 3: Seasonal trends of hospital admissions due to “rotaviral enteritis” and “other non-specific gastroenteritis” conditions in children less than 5 years of age as reported to the Canadian Institute for Health Information (CIHI) between April 2003 and February 2006.

Deaths due to rotavirus are relatively rare in Canada. A review of the vital statistics database (2000-2007) revealed that 6 deaths were attributed to rotavirus infection. These deaths occurred among the very young (≤ 1 year of age) and the elderly (> 85 years of age). During this timeframe, all provinces except Quebec reported deaths to vital statistics.

SPECIFIC POPULATIONS AFFECTED AND RISK FACTORS

Rotavirus infections are extremely common worldwide. By five years of age, most children will have experienced an infection of rotavirus. This is true in both developed and developing countries, suggesting that improved sanitation does not decrease rotavirus transmission. However, mortality due to rotavirus infection is much higher in developing countries (1). There are an estimated 600, 000 deaths each year attributable to rotavirus infection, occurring primarily in Africa and Asia (2).

Infection with rotavirus does not always confer lifelong immunity and individuals can therefore experience multiple infections throughout their lifetime. The severity of disease, however, is age dependent. Infants less than 3 months undergo a mild illness, possibly due to passive maternal immunity. The first infection subsequent to this period is usually the most clinically significant. Severe rotavirus gastroenteritis occurs most frequently in children 3 to 35 months of age (2).

Immunocompromised children are at an increased risk of severe, prolonged and even fatal rotavirus infections (10). Other risk factors associated with developing severe illness with a rotavirus infection are unclear. In a U.S. study, risk factors associated with severe illness included: low birth weight (<2500 g), attending a child care facility, recipients of Medicaid or being without health insurance, another child less than 24 months of age in the household, maternal age less than 25 years, and a mother with less than a high school education (11). In contrast, a study of children in the Toronto area found that socioeconomic factors, parental and marital status, daycare attendance and ethnicity did not influence the rate of rotavirus hospitalizations (12).

One study in the early 1980s suggests that Inuit and First Nations infants in remote northern Manitoban communities have a higher rate of rotavirus diarrhea in the first 6 months of life (1.07 and 0.73 infections per child per year, respectively) than infants in an urban area (0.36 infections per child per year) (13).

CURRENT DISEASE TREATMENT

There are currently no antiviral agents effective at treating rotavirus infections (2). Treatment is supportive and includes oral rehydration to replace lost fluids and electrolytes. Intravenous rehydration may be required in cases of severe dehydration (1, 2).

IMPACT OF THE DISEASE

The ubiquitous nature and distribution of rotavirus infections suggests that many individuals and families are impacted each year during rotavirus season. However, the relative rarity of mortality and sequalae limits the impact to the period of acute illness. The majority of cases do not require medical attention and assessing the burden of illness is difficult. For cases of illness severe enough to require medical attention, parents report disruption to family and work schedules (7, 14). In approximately 50% of families at least one other household member also experienced gastroenteritis within two weeks of the index case seeking medical attention for rotavirus infection (7). The quality of life lost due to rotavirus gastroenteritis is comparable to that experienced with children afflicted with chickenpox, pneumonia or otitis media (15).

The impact on the Canadian health care system is considerable with the majority (>90%) of hospitalizations occurring in the winter and spring months (9). During this time period, approximately 55% of children seeking medical attention for gastroenteritis tested positive for rotavirus (7). Nosocomial cases of rotavirus are a significant burden to the health care system. The IMPACT study found that 27% of rotavirus cases were hospital-acquired (16). These nosocomial cases resulted in increased health care costs and prolonged hospital stays. Exact figures are not available for Canada. However, data available from France found that hospital-acquired rotavirus infections increased the mean length of hospital stay by 4.9 days and increased costs by €1930 (approximately $3054 CAD) (17).

VACCINE CHARACTERISTICS

Data on the two available rotavirus vaccines have been reviewed by the National Advisory Committee on Immunization and are contained in the 2008 and 2010 statements of this committee (18, 19). A review of studies summarizing the key parameters was conducted for the preparation of this statement and is enclosed in Appendix A.

EFFICACY

Immune correlates of protection for rotavirus have not been established, and therefore both vaccines were approved based on large-scale clinical trials demonstrating efficacy against acute gastroenteritis end points. Each trial involved over 60,000 infant participants. In the RotaTeq® trials, efficacy against rotavirus gastroenteritis of any severity was 74% and against severe rotavirus gastroenteritis was 98% in the first season following immunization (20). Efficacy could not be reliably demonstrated against serotypes G3-5 because the number of observations were small. In the RotarixTM trials efficacy ranged from 85 to 100% in the first season and 72 to 92% in the second season in the Latin American and European country analysis for the three outcomes assessed of any rotavirus gastroenteritis, severe rotavirus gastroenteritis and hospitalized rotavirus gastroenteritis. Efficacy of RotarixTM was high for all strains assessed with the exception of the G2[P4] serotype, which had low efficacy and with wide confidence intervals spanning 0 for some analyses. Details of these studies are well summarized in the NACI statements previously referenced and in a NACI literature review published recently (21).

SAFETY

Two rotavirus vaccines have been approved for use in Canada: RotaTeq®, Merck Frosst Canada Ltd., approved in August 2006, and RotarixTM, GlaxoSmithKline Inc., approved in October 2007. Both vaccines have been approved in over 100 countries worldwide, and these products have been incorporated into routine infant immunization programs in a number of countries, including the U.S. and Australia. In Canada, these vaccines have also been incorporated into routine infant immunization programs in some provinces and territories, and in those provinces and territories that do not have rotavirus immunization programs, are available for private purchase.

Both products are administered by the oral route, a clear advantage in considering a vaccine for addition to the routine infant schedule. The formulation of the two products differs in that RotaTeq® is a bovine human reassortant vaccine consisting of the P1A[8] genotype and serotypes G1, G2, G3 and G4 each present at 2-2.8×106 infectious forming units per dose. In contrast, RotarixTM is a live attenuated human rotavirus G1P1A[8] strain (RIX4414) present at not less than 106.0 CCID50 per dose. This difference may be important to consider when information is available about circulating serotypes of the virus, and is reflected in the Health Canada indications for these two vaccines in the current product monographs, with RotaTeq® approved for prevention of rotavirus gastroenteritis (RVGE) caused by the serotypes G1, G2, G3, G4, and G-serotypes that contain P1A[8] (24) (51), and RotarixTM approved for prevention of rotavirus gastroenteritis (RVGE) caused by rotavirus types G1P[8], G2P[4], G3P[8], G4P[8] and G9P[8] (22).

The initial National Advisory Committee on Immunization (NACI) statement on rotavirus vaccine reviewed RotaTeq®, the only rotavirus vaccine available in Canada at that time. It concluded that while the vaccine may be of individual benefit for infants and their families, its incorporation into public health programs could not be recommended because the virus accounts for only 20% of diarrheal illness in children. There was inadequate information about the burden of illness due to rotavirus in Canada and circulating serotypes, and there was lack of information about the vaccine's cost effectiveness (18). NACI updated its recommendations for rotavirus vaccine in 2010 (19). These recommendations now include information about the RotarixTM vaccine. This recent statement recommends that either vaccine should be used for routine infant immunization of healthy infants beginning at 6 weeks of age and the series completed by 8 months of age. The vaccine should not be administered to infants with known or suspected immunodeficiency and to infants with a history of intussusception. The vaccines are not interchangeable and the series should be completed with the product used for the first dose. The vaccine schedules differ in that RotaTeq® is recommended in a three dose series, and RotarixTM in a two dose series and the minimum interval between doses is 4 weeks for both products.

Both vaccines are refrigerator stable and storage recommendations are standard at 2˚-8˚C. The Merck product is provided as a 2 ml dose in a squeezable plastic tube. The GSK product is provided as a 1.5 ml dose that is contained in a syringe with a plunger for oral administration. Neither product requires reconstitution and the containers are latex-free. For details of additives and excipients, the reader is referred to the product monographs.

An earlier rotavirus vaccine, Rotashield® (Wyeth-Lederle Vaccines), was withdrawn from the U.S. market in 1999 due to an association with intussusception. This vaccine was a rhesus-human reassortant vaccine, and the risk of intussusception was assessed as 20-fold within 3-14 days following the first dose and 5-fold for the same interval following the second dose. The clinical trials for both RotaTeq® and RotarixTM were powered to detect risk of this magnitude, and this event was not observed pre-marketing. Nevertheless, the limitations on use of this vaccine after 8 months of age are related to likely age-based increase in risk of intussusception. In post-marketing surveillance in the U.S., intussusception has not been observed at higher than expected levels following use of RotaTeq®, which has been the predominant vaccine in use in that country (23, 24). However, in two separate post-marketing studies conducted in Mexico, clustering of this event was observed in the period 1–7 days and 30 days after the first dose, with estimates of risk of intussusception about 4–5 times and 1.8 times higher, respectively, than in later periods after vaccination after adjusting for age. No clustering was observed after the first dose in similar studies being conducted in Brazil. In Australian post-marketing studies, a possible risk of intussusception was observed after both vaccines in the first week after the first dose, although the numbers observed are smaller than in Mexico. An elevated risk of intussusception has not been observed in the U.S. where more than 27 million doses of RotaTeq® have been distributed since its approval, although the analyses conducted through the Vaccine Safety Datalink program of 800,000 recipients may not be able to detect a risk of the size observed in Mexico, as the calculated incidence of intussusception attributable to RotaTeq® using the Mexican data would be 1 case per 100,000 vaccine recipients. Too few doses of RotarixTM have been distributed in the U.S. to examine this risk. Based on the results of these studies presented to the Advisory Committee on Immunization Practices (ACIP) at its October 2010 meeting, the Centers for Disease Control and Prevention continues to recommend the use of these vaccines in infants, as the benefits far outweigh the possible risk (25).

In late 2010, the World Health Organization (WHO) vaccine safety monitoring centre reported receipt of 4 reports of RotarixTM administration by the intramuscular route by health care providers who mistook the oral syringe for a pre-filled syringe for parenteral use. A non-syringe format of this vaccine is available outside of Canada but not presently within the country (26).

No other serious adverse events have been noted to occur in association with RotaTeq® vaccine in post-marketing surveillance; specifically hematochezia, meningitis, encephalitis, seizures, Kawasaki disease, myocarditis, or Gram negative sepsis have not been observed at elevated rates. In clinical trials of RotarixTM, serious adverse events occurred slightly less frequently in vaccine than placebo recipients. There are no published studies on the safety of RotarixTM in post-marketing use at this time. Both vaccines were well tolerated in infants in clinical trials. There were no statistically significant differences in solicited adverse events between vaccine and placebo groups for either vaccine.

IMMUNIZATION STRATEGIES

Publicly funded immunization programs have traditionally been thought of as either 'universal', that is, offered to entire population or age-defined cohort therein, or 'targeted', that is offered to a defined segment of the population deemed to be at high risk for the vaccine preventable disease. Both approaches can be utilized to attain public health objectives (27).

At the time of writing, where publicly funded rotavirus programs exist globally, all have been implemented using the former or universal approach (28, 29). The CIC-led cost effectiveness analysis assumed universality. A targeted high risk program is not contemplated by either NACI (19) or the Advisory Committee on Immunization Practice (ACIP) in the U. S. (30). Further, a literature search using terms rotavirus vaccine, program, targeted, high risk, yielded no examples of targeted or high risk programs. It would therefore seem reasonable to recommend a universal infant rotavirus vaccine program in the Canadian context.

The approved schedules for the two vaccines differ significantly, with 2 or 3 doses recommended based on the product. As well, NACI recommends series completion with either product by 8 months of age. All provinces/territories offer routine immunizations at 2, 4 and 6 months which could accommodate either a two or three dose schedule given at the same time as the first two or three doses of the infant vaccines. Completion rates with two dose schedules are expected to be higher than those with three doses. A 2009 survey of provincial and national 3rd dose DPT completion rates by 8 months of age indicated that 2 doses have been received by this milestone in 86.4%, 79.8% and 94% in BC, Manitoba and Quebec infants and national survey data indicate 82.4% 2-dose completion, but for three doses, this declines to 68.9%, 67.4%, 65% and 70.2%, for the same jurisdictions, respectively (31). Best practices designed to ensure timely administration, such as through use of recall reminder systems, are particularly important to optimize the protection offered by this childhood vaccine. This is especially important for children at high risk for hospitalization due to rotavirus such as infants with chronic gastrointestinal disease, and infants with conditions more likely to expose them to nosocomial infection and those from remote/isolated communities.

Rotavirus vaccine is recommended as follows by the National Advisory Committee on Immunization:

1. Healthy infants: Rotavirus vaccines are recommended for infants starting at 6 weeks (6 weeks and 0 days) and up to 15 weeks (14 weeks plus 6 days of age). The vaccination series should be completed by 8 months (8 months plus 0 days of age). (Recommendation - Grade A - good evidence to recommend immunization). To optimize protection from rotavirus, rotavirus vaccine should be initiated as soon after 6 weeks of age as feasible. If catch-up vaccination of infants who missed receiving the dose earlier is needed, the Rotarix™ product monograph allows for administration of the first dose by 20 weeks of age.

2. Preterm infants: Infants who are between 6 weeks (6 weeks and 0 days) and 8 months (8 months plus 0 days) of chronological age who are healthy and not hospitalized, can receive RotaTeq® or Rotarix™. The vaccine should be given on the same schedule as above for healthy infants. (Recommendation - Grade A - good evidence to recommend immunization)

3. Immunocompromised Infants: Based on the theoretical risk of live attenuated viral vaccines in immunocompromised infants, and very minimal data in this population, NACI recommends

that infants with suspected or known immunocompromising conditions should not receive RotaTeq® or Rotarix™ without consultation with a physician specialist or expert in these conditions. (Recommendation - Grade E - Good evidence to recommend against immunization)

4. Infants with a history of intussusception: NACI recommends, based on current evidence, that infants with a history of intussusception should not be given rotavirus vaccines. (Recommendation - Grade E - good evidence to recommend against immunization)

Routine childhood immunization using an orally administered vaccine has not occurred in Canada since oral polio vaccine was discontinued in the early to mid-1990s. In addition to education about administration of an oral vaccine, provinces/territories employing fee for service administration models may have to consider remuneration/billing issues for orally administered vaccines.

NACI cites the absence of data regarding administration of rotavirus vaccinations in home settings and the need to maintain cold chain as considerations in recommending provision of these vaccines in a clinic/office setting under the direction of a healthcare provider.

In summary, provinces/territories contemplating routine rotavirus vaccine programs should administer the vaccine at the 2 and 4 month visits or the 2, 4 and 6 month visits depending on the product used. Rotavirus vaccines should be administered in a health care clinic setting with special attention to timely administration.

COST-EFFECTIVENESS

ECONOMIC IMPACT OF THE DISEASE

The economic burden of rotavirus to society in Canada is estimated to be $125 million over five years for each birth cohort (32). This compares to estimates from the U.S. which put the total cost to society per year at $893 million of which $319 million represents health care costs (33).

The total cost associated with rotavirus gastroenteritis cases varies based on the severity of the disease. One Canadian study estimated the total societal cost at $366 for a child not requiring medical attention, $396 for a child seen at a physician's office, $809 for a child seen in an emergency room and $2690 for a hospitalized child. These estimates considered direct costs, (i.e. medical care, rehydration fluids, diapers and transportation) and the cost of lost work (34).

Cost-effectiveness analysis is an integral component of evidence based decision-making for publicly-funded rotavirus vaccination programs. According to Erickson et al., cost-effectiveness is a necessary category in the vaccine analysis framework to justify new vaccination programs due to potential long-term and recurrent expenditures (27). Cost-effectiveness of vaccination programs is assessed using economic evaluations that synthesize clinical, epidemiological and economic information. The outcomes of cost effectiveness analyses are expressed as incremental cost ratios relative to the current practice (no immunization program) per health effect (i.e. RVGE case/hospitalization/death averted, quality adjusted life years (QALY) gained or disability-adjusted life-year (DALY) averted) (35).

Although the WHO defines interventions to be cost-effective if a DALY is averted at a cost less than three times the gross domestic product (GDP) per capita, a universally agreed upon threshold for an acceptable cost-effectiveness ratio for vaccination programs does not exist (36). Some countries such as the UK have set a national threshold in incremental cost-effectiveness ratio of £20,000-30,000/QALY on interventions that are publicly funded (37).

A systematic review of 19 cost-effectiveness evaluations of rotavirus vaccination programs demonstrated that most studies utilize static deterministic models, which exclude herd effects (38). While such models may underestimate the economic impact of rotavirus vaccination programs with high coverage, they were deemed appropriate at the time as there was no convincing evidence of herd immunity and indirect protection of susceptible individuals via fecal shedding of vaccinated children is rare (35, 38). Herd immunity has now been demonstrated in several jurisdictions where routine rotavirus immunization programs have been implemented (see Vaccine Characteristics section).

INTERNATIONAL COST-EFFECTIVENESS ANALYSES

The two vaccines approved for use in Canada, RotarixTM and RotaTeq®, are administered to infants in two and three-dose courses, respectively. In high income countries, rotavirus vaccines confer 85–100% protection against severe disease whereas rotavirus vaccine efficacy is significantly lower in low income countries at 46–77% (35). For generalizability and comparative purposes, only published rotavirus cost-effectiveness evaluations in high income countries were reviewed.

Ten cost-effectiveness evaluations that were selected span eight countries. The results of these studies vary across and within countries due to the differences in model design and parameter inputs (38). Most inputs that determine cost-effectiveness (the cost of the immunization program with administration and wastage, vaccine coverage, the incidence and prevalence of rotavirus gastroenteritis (RVGE), and the morbidity and mortality associated with RVGE) are country or region specific (35). As such, the specific model parameters vary widely in the selected cost-effectiveness evaluations (Table 2). Most notable differences are: i) in the measurable costs of RVGE, which range from $1,071-$3,258 for direct health care cost of hospitalization due to RVGE (39, 40); ii) the cost of the vaccine program per complete dose range from $123 – $259 for RotarixTM and $138 - $282 for RotaTeq® (40, 41); and iii) the impact of RVGE on the quality of life (some studies included lifetime productivity losses whereas others examined quality of life effects on one or two caregivers).

The main outcomes of the studies in terms of the incremental cost-effectiveness ratio (ICER) also differ across the countries: i) from healthcare perspective for RotarixTM, $25,250 – $170,511/QALY and for RotaTeq®, $36,450 - $220,915/QALY; and ii) from societal perspective, RotarixTM, $11,812 – $92,851/QALY and for RotaTeq®, $47,154 - $120,336/QALY (7, 8, 33, 39-50) (Table 2). The results diverged for cost-effectiveness evaluations within a country as well: i) for Belgium, the ICER ranged from $79,607 - $86,400/QALY for RotarixTM and $101,250- $102,597/QALY for RotaTeq® (42, 45); ii) for England and Wales, the incremental ICER ranged from $40,772- 106,624/QALY for RotarixTM and $139,834 - $202,500/QALY for RotaTeq® (39, 45, 47); and iii) for Finland, the ICER ranged from $20,250 - $38,340/QALY for RotarixTM and $36,450 – $70,510 for RotaTeq® (41, 45).

Seven of the ten selected studies compared the cost-effectiveness of RotarixTM versus RotaTeq® (39-42, 45, 46, 50). In all of these studies, RotarixTM was found to be more cost-effective (dominant). In the Australian context, both vaccines were found to be cost-saving when indirect costs were included in the analysis (50). The dynamic economic model from the U.S. found the vaccines to be cost-saving for a case of RVGE prevented from the societal perspective (40).

Table 2: Overview of Economic Evaluations of Rotavirus Vaccination[a].

	Type of Model	Model Parameters			Main Outcomes (CAD)		
		RR	**RT**	**Other**	**Healthcare Perspective**	**Societal Perspective**	**D**
Australia (2007) [50]	Markov	Eff: 76.3-100% Cov: 92% C: $148	Eff: 86-95.8% Cov: 92% C: $167	BOI: 0.45 (GP), 0.09 (ED), 0.07 (H) HC C: $38 (GP), $288 (ED), $1,701 (H) SC C: $244 (GP), $401 (ED), $601 (H)	RR: 54,065/QALY RT: 60,913/QALY	RR: Cost-saving RT: Cost-saving	RR
Belgium (2009) (42)	Markov				RR: 79,607 - 86,400/QALY [45] RT: 101,250/QALY [45] - 102,597/QALY	RR: 11,812/QALY RT: 47,154/QALY	RR
England and Wales (2007) (39**)**	Markov	Eff: 85.2% Cov: 95% C: $140	Eff: 66-94% Cov: 95% C: $158	BOI: 0.28 (GP), 0.09 (ED), 0.04 (H) HC C: $45 (GP), $99 (ED), $1,071 (H) SC C: $111 (GP), $111 (ED), $111 (H)	RR: 684/RVGE, 6,382/hosp, 40,772/QALY [47] - 106,624/QALY RT: 919/RVGE, 6,655/hosp, 139,834/QALY - 202,500/QALY [45]	RR: 20,071/QALY [47]	RR
Finland (2009) (41**)**	Regression	C: $123	C: $138	N/A	RR: 20,250/QALY [45] - 38,340/QALY RT: 36,450/QALY [45] - 70,510		RR
France (2007) (48**)**	Markov	Eff: 70 – 85% Cov: 75% C: $218	Eff: 70 – 85% Cov: 75% C: $218	BOI: 0.24-0.65 (GP), 0.04 (ED) HC C: $60 (GP), $100 (ED), $1,798 (H)	RR or RT: 432,100/LY 200,100/QALY RR: 87,750/QALY [45] RT: 113,400/QALY [45]	N/A	RR

Netherlands (2010) [46]	Markov	Eff: 80-84% Cov: 97% C: $142	Eff: 67-91% Cov: 97% C: $148	BOI: 0.33 (GP), 0.07 - 0. 09 (H) HC C: $28 (GP), $2,538 (H)	RR: 351/RVGE; 5,130/hosp; 71,550/DALY; 118,800/QALY [45] RT: 405/RVGE; 5,535/hosp; 78,300/DALY; 126,900/QALY [45]	RR: 324/RVGE; 4,860/hosp; 66,150/DALY RT: 378/RVGE; 5,130/hosp; 72,900/DALY	RR
New Zealand (2009) [49]	Static Equilibrium	N/A	Eff: 70 – 85% Cov: 85% C: $108	BOI: 0.43 (GP), 0.01 (ED), 0.005 (H) HC C: $29 (GP), $421 (ED), $1,089 - 1,360 (H) SC C: $73 (GP), $76 (ED), $176 (H)	RT: 1,807/hosp; 33,187/QALY; 103,030/LY		-
U.S. (2007) [33]	Markov	N/A	Eff: 65 – 90% Cov: 71% C: $239	BOI: 0.10 (GP), 0.05 (ED), 0.01 (H) HC C: $69 (GP), $365 (ED), $3,258 (H) SC C: $187 (GP, ED), $374 (H)	RT: 386/RVGE; 3,478/hosp; 470,730/LY	RT: 159/RVGE; 3031/hosp; 226,769/LY	-
U.S. (2009) [40]	Dynamic	C: $259	C: $282	BOI: 0.11 (GP), 0.06 (ED), 0.02 (H) HC C: $138 (GP), $634 (ED), $4,552 (H) SC C: $271	RR: 170,511/QALY RT: 89/RVGE; 366/hosp; 220,915/QALY; 8,604,300/LY	RR: 92,851/QALY RT: cost-saving/RVGE; 167/hosp; 120,336/QALY; 8,987,250/LY	RR

BOI = Burden of RVGE for medical care; **C** = cost; **Cov** = vaccine coverage; **D** = dominance; **DALY** = disability-adjusted life-year averted; **ED** = % of RVGE requiring emergency department; **Eff** = efficacy; **LY** = life year saved; **RVGE** = RVGE case prevented; **GP** = % of RVGE requiring general practitioner; **H** = % of RVGE requiring hospitalization; **HC** = healthcare; **hosp** = hospitalization prevented; **QALY** = quality-adjusted life-year gained; **RR** = Rotarix™; **RT** = RotaTeq®; **SC** = societal

[a]all currencies were converted to CAD using an average exchange rate for the publication year

CANADIAN COST-EFFECTIVENESS ANALYSES

Two Canadian cost-effectiveness evaluations were included in this review (43, 44). Both used Markov cohort design that conceptualizes health and disease as a series of mutually exclusive and collectively exhaustive health states and included probabilistic sensitivity analyses (43). The studies followed a hypothetical birth cohort in Canada from birth to 5 years. One considered both healthcare and societal perspectives (44) while the other only included direct costs in the cost-effectiveness evaluations (43).

Diverging cost-effectiveness results found between evaluations in one country can be largely explained by differences in disease incidence estimates and related healthcare costs (38). There are several studies from various parts of Canada for RVGE related health care encounters with children that were seen in family physician or paediatric clinics, emergency departments and admitted to hospitals (7-9, 12). However, due to the lack of a national surveillance system and the relative paucity of Canadian population-based studies on RVGE, it is difficult to decipher the true burden in the Canadian context.

Accordingly, varying assumptions were found for the burden of illness parameters between the two studies (Table 3). The two studies derived rotavirus vaccine efficacy values from clinical trials of Rotarix™ and RotaTeq®, but Fisman et al. (43) considered reduced efficacy of incomplete vaccination in the model, while Coyle (44) did not (7-9, 12). Vaccine coverage parameters differed as Coyle (44) used the WHO report for a similar vaccine schedule (DPT) while Fisman et al. (43) utilized data collected from the provincial/territorial and federal members of the Canadian Immunization Registry Network (CIRN) for 2007 annual as well as BC's iPHIS vaccine coverage data for 2002-2008 on completion rates by age milestone for the infant DaPT-Polio/Hib series (43, 44). Healthcare costs were based on Ontario physician billing rates for the Coyle (44) analysis compared to the British Columbia's counterpart for Fisman et al. (43). Vaccine costs were relatively similar for both of the analyses. As Coyle (44) included societal costs, the quality of life impact was also considered in the evaluation (43) (Table 3).

Table 3: Model Parameters for the Canadian Cost Effectiveness Evaluations.

	Coyle (44)	**Fisman et al. (43)**
Model Type	Markov	Markov
Time Horizon	Birth-5 years	Birth-5 years
BOI	No medical care – 80.7% Medical care – 19.3% GP – 70.8% ED – 16.4% H – 12.9%	5-yr cumulative incidence of RVGE – 75% Medical care – 19.3% GP – 40% ED – 13% H – 2%
Efficacy	RR: RVGE – 76.3% GP – 83.8% ED – 83.8% H – 96% RT: RVGE – 73.8% GP – 86% ED – 93.7% H – 95.8%	RR: RVGE – 84% (dose 1) and 87% (dose 2) GP – 89% (dose 1) and 92% (dose 2) ED – 89% (dose 1) and 92% (dose 2) H – 100% RT: RVGE – 60% (dose 1); 64% (dose 2); 74% (dose 3) GP – 70% (dose 1); 76% (dose 2); 86% (dose 3) ED – 76% (dose 1); 82% (dose 2); 94% (dose 3) H – 78% (dose 1); 84% (dose 2); 96% (dose 3)
Vaccine Coverage	94%	1 dose: 93.2% 2 doses: 86.4% 3 doses: 68.9%
Vaccine Costs	RR: $189.97 RT: $209.54	RR: $189.51 RT: $183.60
Healthcare Costs	GP - $62.65 ED - $367.22 H – 3,057.12	GP - $62.64 ED - $169 H – $4,582
Societal Costs (patient, caregiver and lost productivity)	No visit - $31.37 GP – $426.70 ED - $170.76 H - $3,267.69	Not assessed
Utility Values	Healthy child – 0.986 Healthy caregiver – 0.967 Child with RV – 0.927 Utility for caregiver of child with RV – 0.910	Not assessed

BOI = Burden of RVGE for medical care; **RVGE** = RVGE case; **ED** = % of RVGE requiring emergency department visit; **GP** = % of RVGE requiring general practitioner visit; **H** = % of RVGE requiring hospitalization; **RR** = Rotarix™; **RT** = RotaTeq®

The two studies found that per 100 infants vaccinated with Rotarix™ or RotaTeq® the following were prevented: 48-66 RVGE gastroenteritis infections; 8.4-15 outpatient general practitioner visits; 2.3-10 emergency department visits, and 1-2 hospitalizations (43, 44) (Table 4). Neither vaccine reduced total costs from the health care perspective; the net cost of a RotaTeq® vaccination program relative to no vaccination was $74-$138 per vaccinated individual (43, 44). The studies found Rotarix™ to be more cost-effective in comparison to RotaTeq® ($108,000/QALY gained or $101/infection prevented). Fisman et al. (43) found that a universal program of Rotarix™ became cost-saving at a vaccine cost of between $25-$27.50 per dose, and that at $70.13 per dose, the program is cost-effective at the $30,000/QALY gained level.

Table 4: Main Outcomes of the Canadian Cost Effectiveness Evaluations.

	Coyle (44)		**Fisman et al. (43)**	
	Rotarix™	**RotaTeq®**	**Rotarix™**	**RotaTeq®**
RVGE prevented (per 100 vaccinated)	53		66	48
RVGE GP prevented (per 100 vaccinated)	8.4		12-15	
RVGE ER prevented (per 100 vaccinated)	2.3		7-10	
RVGE H prevented (per 100 vaccinated)	1.9		1-2	
Net HC Costs/vaccinated	$130.21	$137.56	$82	$74
Net SC costs	Cost-saving	Cost-saving	-	-
ICER – HC	$108,000/QALY	$122,000/QALY	$101/infection prevented	Eliminated by extended dominance
ICER – SC	Cost-saving	Cost-saving	-	-

HC = net cost to the health care system of vaccination relative to no vaccination program; **SC** = net cost from societal perspective comparing vaccination relative to no vaccination program

Post-licensure effectiveness studies have demonstrated that rotavirus vaccines may provide herd immunity through reduced rotavirus transmission thus resulting in reduced rates of rotavirus diarrhea in older and unimmunized children (35, 38). If these indirect benefits from herd immunity are confirmed and dynamic rather than static models are utilized to evaluate the cost-effectiveness of rotavirus vaccination programs, the results could be even more favourable for vaccination.

ACCEPTABILITY AND FEASIBILITY

PROGRAM ACCEPTABILITY

In the context where rotavirus vaccination is recommended, but not publicly funded, vaccine uptake depends largely upon whether health professionals recommend it to parents (51-53). In the U.S., rotavirus vaccines were recommended for routine vaccination of all U.S. infants in February 2006 and 2008 and results of the 2010 national coverage survey of 19-35 month old children indicated that uptake of 2 or more doses of rotavirus vaccine had increased to 59.2% from 43.9% in 2009 (25). The negative publicity associated with the withdrawal of a previous rotavirus vaccine did not seem to have a major impact on the adoption of new rotavirus vaccines, as it had been anticipated by studies done before their reintroduction (54-57).

Few psychosocial studies have been conducted after the reintroduction of rotavirus vaccines. Two studies were carried out right after the licensure of RotaTeqTM in the U.S. (52, 58). One survey of sentinel physicians (n =360 paediatricians, 331 family physicians) was conducted before the publication of the ACIP recommendations on rotavirus vaccine use (58). In this survey, rates of offering the rotavirus vaccine were high among paediatricians (85%), but down to 45% for family physicians. Barriers to vaccine use included reported lack of coverage by insurance companies, costs of purchasing the vaccine and lack of adequate reimbursements and concerns about safety and about adding another vaccine to the schedule. Whether or not they actually administered the vaccine in their offices, paediatricians were more likely to recommend the vaccine strongly (70%) than family physicians (22%) (58). Another qualitative study was conducted among 57 parents and 10 physicians in spring 2006 (52). In this study, physicians expressed a high likelihood of adopting rotavirus vaccine, particularly if recommended by their professional organizations and expressed specific interest in post-marketing safety data (52). Results of another brief U.S. survey handed out to 105 health professionals (mostly paediatricians) after a lecture on the epidemiology and immunology of rotavirus infection indicated a high level of endorsement of the rotavirus vaccination program (84% of respondents agreed with the Center for Diseases Control recommendations for routine rotavirus vaccination). However, only 49% of respondents were strongly encouraging the vaccine to their patients. The most frequent reasons for not offering the vaccine were “safety concerns” (55%) and “costs” (45%) (59).

In contrast, in an internet-based survey conducted in 2007 among family physicians and paediatricians in Switzerland, only 48% of respondents agreed to recommend rotavirus vaccine if it was officially recommended by federal authorities and reimbursed by insurance companies (60).

Few studies regarding the acceptability of rotavirus vaccination among parents have been published. In the previously cited U.S. qualitative study (52), a lack of awareness about rotavirus disease and need for more information about the disease and the vaccine was found among parents. Parents generally deemed the vaccine to be acceptable and commented positively on several aspects of the vaccine (oral formulation, high efficacy in preventing severe disease). Most parents also reported that they would rely on their physician’s recommendation on whether their child should receive the rotavirus vaccine (52). Results of a telephone survey conducted in France in 2008 indicated that, among the 1002 mothers of at least one child aged < 2 years, respectively 43% and 51% considered gastroenteritis as a severe or very severe pathology for young children (61).

CANADIAN STUDIES

Three Canadian studies on health professionals' knowledge, attitudes and practices regarding rotavirus vaccination were identified (62-64). In a questionnaire-based survey conducted among Canadian paediatricians (n=912) and family physicians (n=371), the majority of respondents rated consequences of rotavirus infection for young patients as moderate (72% of paediatricians and 67% of family physicians) (62). Sixty-six percent of paediatricians and 50% of family physicians considered that rotavirus disease occurs frequently without vaccination and 62% of paediatricians and 45% of family physicians estimated that the disease generates a significant economic burden. Sixty-nine percent (69%) of paediatricians and 73% of family physicians considered rotavirus vaccines to be safe and 61% of paediatricians and 58% of family physicians considered it to be effective. The reduction of severe gastroenteritis cases was seen as the main benefit of rotavirus vaccination, while the risk of adverse events was the principal perceived barrier. Fifty-three percent (53%) of paediatricians and 44% of family physicians indicated a strong intention to recommend rotavirus vaccines. Fifty-nine percent (59%) of paediatricians and 45% of family physicians perceived that it would be useful to introduce a publicly-funded rotavirus vaccination program. In a multivariate analysis, the main determinants of physicians' intention to recommend rotavirus vaccines were the perceived benefits of the vaccines (partial $R2=0.56$, $p<0.0001$), the perceived acceptability of the vaccines by health professionals who administer vaccines (partial $R2=0.05$, $p<0.0001$) and the self-estimated sufficiency of knowledge about the vaccines (partial $R2=0.02$, $p<0.0001$) (62).

Less than half of the nurses (43%) who participated (n=299) in a questionnaire survey conducted in 2008 in Quebec indicated a strong willingness to recommend the rotavirus vaccines to their patients (63). In this study, 57% of nurses agreed about rotavirus vaccine efficacy and 52% agreed about rotavirus vaccine safety, while respectively 39% and 44% of nurses chose the answer "Do not know" for these two questions. Only 35% of nurses self-estimated the information they had received on rotavirus vaccine to be sufficient. Finally, 40% of nurses strongly agreed and 39% somewhat agreed that it would be very useful to introduce a publicly funded rotavirus vaccination program (63).

Another survey was conducted in 2006 among 101 Regional Medical Officers of Health (MOH), communicable diseases control coordinators and/or immunization program managers in 3 provinces (NS, QC, ON) (64) for an overall participation rate of 74%. In this survey, 54% of respondents perceived the rotavirus vaccine to be effective and 56%, to be safe. Respectively 65% and 67% of respondents thought that rotavirus vaccine would be well accepted by the public and by the health professionals who administer vaccines. Less than 20% of respondents felt that the self-acquired information on rotavirus vaccine met their needs. Sixty percent (60%) of respondents perceived that it would be useful to introduce a publicly funded rotavirus vaccination (65). Similar findings were made in a survey of primary care physicians providing services to pediatric patients in British Columbia (66). Support for publicly funded rotavirus vaccine among GPs and pediatricians was high. A knowledge gap was identified, with paediatricians more knowledgeable about rotavirus infection and the vaccine, suggesting value of an education program, particularly targeting family physicians (66).

Few studies on Canadian parents' opinions regarding rotavirus vaccination were identified. Results of an Internet survey conducted by the Canadian Institute of Child Health in 2007 indicate that over 90% of the 822 surveyed Canadian mothers (with at least one child under the age of three) agreed on the seriousness of severe gastroenteritis. However, only 48% of those mothers had ever heard of rotavirus. No outcomes regarding demand for or acceptability of rotavirus vaccines among Canadian mothers were reported (67).

Another longitudinal study was conducted in 3 Canadian cities (Quebec City, QC; Vancouver, BC; Halifax, NS) among parents of newborns (68). Data were collected by telephone interviews in two phases and main outcome measures were (I) parents' intention to have their child immunized against rotavirus (n=413) and (II) children's immunization status (n=394). In this study, 67% of parents had a firm intention to have their child vaccinated against rotavirus (phase I) and 42% of children were effectively vaccinated (phase II). Having a doctor or a nurse recommendation was an important determinant of parents' decision to vaccinate their child against rotavirus. The cost of the rotavirus vaccine, the fear of side effects and the fact that the vaccine will not protect the child against all diarrhea were the main barriers perceived by parents who decided not to vaccinate their child (68).

PRIORITY FOR A NEW ROTAVIRUS PROGRAM WITH RESPECT TO OTHER POTENTIAL / APPROVED VACCINATION PROGRAMS

Three of the previously cited Canadian studies have assessed health professionals' perceived priority for new immunization program implementation, including rotavirus (63, 64,69). Differences in terms of the methodology used, the target population and the new vaccines included in these studies do not allow direct comparison of the findings. However, in all these studies, rotavirus vaccines received the lowest ratings (Table 6).

Table 5: Results of 3 Canadian studies on health professionals perceptions of the priority for a publicly funded rotavirus vaccination program with respect to other potential / approved vaccination programs.

VACCINES	**STUDIES AND PRIORITY SCORES**			
	Nurses* (63)	**Physicians†** (69)		**Public Health Professionals*** (64)
		Paediatricians	Family Physicians	
Measles, mumps, rubella and varicella (MMRV)	5.2	77.8	74.3	7.3
Hexavalent (DTaP-Polio-Hepatitis B-Hib)	5.0	75.7	72.9	7.0
New pneumococcal conjugate vaccines (PCV-10, PCV-13)	4.7	74.7	66.2	-
Meningococcal ACYW135	4.3	71.0	63.8	5.4
Hepatitis A and B (combined vaccine)	5.3	68.9	66.8	-
Human papillomavirus (HPV)	63.8	64.3	59.0	4.8
Rotavirus	**2.8**	**57.8**	**52.0**	**1.6**

* Priority scores range from 0 to 10 (10= the highest potential score)
† Priority scores range from 0 to 100 (100= the highest potential score)

In summary, most health professionals surveyed estimated that the health and economic burden of rotavirus infection is important in Canada and agreed that rotavirus vaccines are safe and effective. However, the proportion of health professionals who had a strong intention to

recommend rotavirus vaccines to their patients remains low when compared to several other new vaccines (63, 64, 69). Results of published studies also indicated that most parents of young children perceived gastroenteritis as severe disease and held positive attitudes toward rotavirus vaccination. Health professionals' recommendation was also identified as an important determinant of parental intention to vaccinate their child against rotavirus.

PROGRAM FEASIBILITY: UNIVERSAL ROTAVIRUS FEASIBILITY ISSUES

The NACI has recommended universal rotavirus vaccine immunization for Canadian infants. These vaccines are administered in infancy starting at the two month immunization visit in a series of 2 or 3 doses depending on the product used and given in conjunction with other infant vaccines.

All Canadian provinces and territories have well established vaccination programs for these infant visits. Since this vaccine requires no extra injections and is orally given, it is well accepted by health care providers and parents alike. It also does not result in extra or new visits, as infants are already presenting for immunizations at these ages. Though the exact rates of vaccine coverage for the routine infant schedule are unknown across Canada as a whole, the vaccine programs are successful, and excellent vaccine coverage is presumed by known data from certain populations and by number of doses distributed in provinces. Many other comparable countries, like Australia and the U.S., have universal programs for rotavirus vaccination with no substantive issues with regards to the feasibility of the implementation of public programs.

These vaccines require adherence to the cold chain, and can use systems already established and in place. In the practitioner's clinic, the vaccine is easily stored in the same fridge already containing other vaccines. However, this vaccine does take up much more space, so some practitioners may find its storage problematic. The delivery system is intended to be oral, so there is little chance of incorrect administration. There have been rare inadvertent intramuscular injections with the current RotarixTM delivery system reported globally and this potential error should be highlighted in education provided to immunizers.

This vaccine differs from other infant vaccines with respect to strict age limits related to its initiation and series completion. The limit of 14 weeks plus six days was set both in the product monograph and in the NACI statement as a precautionary principle in light of previous rotavirus vaccines being associated with intussusception. The natural rate in infant intussusception increases after this point, and also there is a suggestion that some of the increased rate of intussusception occurred because the vaccine was given later. There are reports of an increase in intussusception in universal programs in Mexico and Australia. There would need to be appropriate education of individuals administering this vaccine to give the first dose before 14 weeks, six days, or not to give it at all. Enhanced surveillance of cases of intussusception would be prudent to ascertain, including its relationship to timing of the vaccine.

Vaccine availability and long term supply are also consideration when addressing feasibility of a universal program. As there are two vaccines, any manufacturing issue with one supplier is partially offset by availability of another supplier. The two vaccines are not interchangeable, so jurisdictions will choose one or the other. While from a security of supply perspective a dual award of the two products may be considered, price points will be a key driver or purchasing

decisions. As many large countries now have universal programs, global supply has not been an issue, and it is unlikely that a manufacturer could not meet Canadian demand.

EVALUATION

ROTAVIRUS EVALUATION FRAMEWORK

The introduction of two rotavirus vaccines into the Canadian market and provincial implementation of publicly-funded immunization programs for Canadian infants will require an evaluation framework that measures the impact of the vaccine on the burden of rotavirus in Canada. The evaluation of the rotavirus immunization program is necessary to document the success of program implementation and effectiveness.

The objectives of the rotavirus surveillance strategy are to 1) monitor burden of disease in Canada, 2) assess severity of infections, 3) track vaccine coverage in the target population, and 4) monitor vaccine safety. Results from each of these components will contribute to ascertaining the impact of vaccination.

SURVEILLANCE OF ROTAVIRUS

There are currently several surveillance systems in place which when combined provide a comprehensive picture of the burden of illness and severity of disease related to rotavirus gastroenteritis in Canada.

- Data are available through the following laboratory and hospital-based surveillance programs:
- The National Enteric Surveillance Program (NESP) receives reports of positive results from provincial public health laboratories;
- The Canadian Virus Report (CVR) tracks the number of laboratory confirmed rotavirus cases from select hospitals and provincial laboratories;
- The Canadian Institute for Health Information (CIHI) provides information on hospital admissions across Canada.
- IMPACT (Immunization Monitoring Program Active) surveillance provided extensive case data from children hospitalized with rotavirus in 12 participating paediatric hospitals across Canada between 2005 and 2009 and will continue to assess vaccine safety including occurrences of intussusception.

These four surveillance systems cover different populations; however the trends they report are very similar. These systems also provide valuable historical baseline information related to both case counts and severity of disease. Collectively, data captured through the existing programs (NESP, CVR and CIHI) are sufficient to monitor changes or trends that occur as a result of vaccination programs.

Due to the nature of the virus and vaccine, systematic laboratory surveillance of circulating rotavirus genotypes should be considered. This will ensure that new strains of the virus are not evolving potentially as a result of vaccine pressure, which could reduce the effectiveness of the vaccination program.

The Public Health Agency of Canada (PHAC) will be collaborating with provincial and territorial authorities to enhance understanding of testing and reporting practices and how these practices impact the reporting of rotavirus related trends.

VACCINE COVERAGE

Evaluation of rotavirus vaccine coverage is primarily a provincial or territorial responsibility. Therefore, in provinces and territories where publicly funded immunization is implemented, assessment of coverage will be conducted through methods in place for infant coverage assessment, which is typically reported out at the 2nd birthday. PHAC collects national level data on vaccine coverage through the National Immunization Coverage Surveys (NICS). These surveys include immunization coverage assessment of children who are 2 years old and are conducted every two years with the future cycle beginning in fall 2011. The 2013 survey will include assessment of coverage in provinces with publicly funded rotavirus programs and will provide useful data to evaluate the coverage of rotavirus vaccine in Canada.

OTHER EVALUATION AREAS

Other worthwhile areas of evaluation include the impact of the use of infant rotavirus vaccines on health care utilization for acute gastroenteritis, and changes in knowledge among the public and health care professionals.

RESEARCH QUESTIONS

VACCINE UPTAKE

Concrete steps should be taken to assess rotavirus vaccine uptake (including partial series completion) in jurisdictions where publically funded rotavirus vaccine programs have been initiated. Data should ideally include provider type, prematurity, and socioeconomic status and the impact on uptake of other routinely recommended childhood vaccines.

INDIRECT PROTECTION THROUGH HERD IMMUNITY

Data on rotavirus infection from jurisdictions such as the US are suggestive of indirect protection of unvaccinated older individuals (70). These benefits have not been considered in Canadian cost effectiveness analyses and are important to evaluate as these further increase the favourability of use of the vaccine in infants.

PREMATURE INFANTS

There is inadequate information and reluctance to use vaccine in this population especially in nurseries. Further studies should address this area.

BURDEN OF DISEASE

Rotavirus surveillance in all provinces should be a priority to see the change over time in provinces that are early implementers (PEI, Ontario, Québec, BC), later implementers and non-implementers.

In addition, Canada does not have population-based burden of illness data for rotavirus gastrointestinal illness. Selected sentinel sites could be chosen to define this incidence. This would contribute significantly towards data that could be used by provincial and territorial authorities considering public funding of vaccines. This should include the Aboriginal population including those living on reserves or remote areas. As a proof of principle, in provinces that have adopted vaccines, pilot projects demonstrating burden of illness incidence data should be undertaken in selected sites with the ability to track disease both in the inpatient and outpatient arenas. Burden of illness assessment could be conducted in a variety of ways including sentinel site surveillance, use of administrative data, IMPACT surveillance through pediatric tertiary care hospitals, including identification of nosocomial infections, and a combination of laboratory confirmed rotavirus infection and clinically diagnosed gastroenteritis.

ROTAVIRUS GENOTYPE INFORMATION

Systematic collection of rotavirus positive stool samples to enable genotype testing for surveillance purposes will be imperative in order to detect shifts in genotype over time. This

process will enhance surveillance. Given the mobility of the Canadian population, it will not be surprising to see genotypes found in other jurisdictions around the world in Canada.

INTUSSUSCEPTION AND OTHER SERIOUS ADVERSE EVENTS

Given the 'risk adverse' climate that exists for vaccines in Canada and the signal of a weak association with intussusception and both vaccines, a robust intussusception surveillance program should continue to be supported across the country. Intussusception is now an adverse event captured through the passive reporting system for adverse events following immunization in Canada (the Canadian Adverse Event Following Immunization Surveillance System or CAEFISS) (71). Active surveillance through IMPACT for intussusception is also conducted and cases of intussusception managed in the emergency room setting or hospitalized will be identified through this program operating in 12 pediatric tertiary care centers in Canada.

Priority should also be given to reporting of any events such as prolonged shedding of rotavirus or side effects in immunocompromised children.

OTHER CONSIDERATIONS

EQUITY CONSIDERATIONS

As of the time of writing of this statement and between July 2011 through January 2012, routine rotavirus vaccination has been launched in Ontario, Quebec and British Columbia. As well, a feasibility study is ongoing in PEI and Nova Scotia of public health nursing versus physician delivery. PEI has reported excellent uptake 94-5% for first dose and 2nd dose uptake above 91-2% as of December 2010 (72). In other Canadian jurisdictions, the vaccine is available for purchase, resulting in inequities of access across the country. Within a jurisdiction with a publicly funded program, inequities are minimal because unlike many other vaccine programs introduced under specific criteria of eligibility, the limitations on use of rotavirus vaccine in young infants ensure that inequities in access exist only in the early stages of program introduction.

ETHICAL CONSIDERATIONS

As other vaccines, rotavirus immunization service delivery should be under the usual provisions of informed consent with appropriate identification of infants with known contraindications to receipt of these vaccines.

Results of cost effectiveness analyses using information based on Canadian health data including current government contract pricing indicates that routine infant rotavirus is favourable using direct medical costs.

Although rotavirus affects those older than infancy, current rotavirus vaccines are not approved for use outside of infancy. Routine infant rotavirus vaccine programs appear to have resulted in reductions of rotavirus burden among age groups not targeted for direct protection. These findings improve the benefit profile of rotavirus vaccines beyond those anticipated prior to their wide scale introduction.

LEGAL CONSIDERATIONS

In jurisdictions with legal mandates related to immunization, it is likely that considerations of rotavirus immunization will not be relevant with respect to ensuring compliance with immunization recommendations related to school entry or employment in health care settings because of the age of individuals who can be immunized. The exception may be day nurseries attended by infants young enough to be immunized in jurisdictions with documentation requirements related to immunization for children attending day nurseries. The potential value of rotavirus vaccines in the control of outbreaks of rotavirus in day nurseries is not known.

CIC RECOMMENDATION FOR USE OF ROTAVIRUS VACCINES

The Canadian Immunization Committee supports the recommendations of the National Advisory Committee on Immunization for routine use of rotavirus vaccines in infants without contraindications. Results of cost-effectiveness analysis at current pricing available through Canadian government purchasing contracts indicate that rotavirus vaccination is cost saving, and in these models public funding of rotavirus vaccine programs can be recommended.

APPENDIX A: SUMMARY OF KEY VACCINE RELATED PARAMETERS FOR THE TWO AVAILABLE ROTAVIRUS VACCINES

	RotaTeq®	**Rotarix™**
Duration of protection: season 2 and 3	A detailed analysis of the vaccine efficacy of RotaTeq® was performed through 3 rotavirus seasons. The analysis included participants in REST and the Finnish Extension Study (FES) which comprised Finnish infants enrolled in REST (21,000) who were followed through 2 additional rotavirus seasons upon conclusion of REST. During the 2nd rotavirus season there were sustained reductions in ED visits and hospitalizations. Vaccine efficacy (reported as rate reductions) for the pooled REST+FES participants was 97.7% (95% CI: 86.6-99.9) for ED visits; 90.8% (95% CI: 76.9-97.1) for hospitalizations and 93.9% (95% CI: 86.1-97.8) for ED visits and hospitalizations combined. The rate reductions reported in the 2nd season were not significantly different from those reported for the 1st season. The FES study followed ~6100 subjects through the 3rd rotavirus season and there were no reports of ED visits or hospitalizations among RotaTeq® recipients while only 1 ED visit was reported from a child that had received placebo during the trial (73). The VE of RotaTeq® was reported through 2 rotavirus seasons for a subset of European infants enrolled in REST. During the 2nd season the VE against severe or any RVGE (Vesikari clinical scoring scale) was 94.3% (95% CI: 64.0-99.9) and 58.5% (95% CI: 40.1-71.7), respectively. The VE during the 2nd season was lower for both outcomes compared to the first season where VE was 100% (95% CI: 90.7-100) and 72% (95% CI: 63.2-78.9) for severe and any RVGE, respectively (74).	Clinical trials have evaluated the efficacy of Rotarix™ through 2 rotavirus seasons but there is no available data beyond the second season. A trial in Latin America involving ~14,000 infants evaluated the efficacy of Rotarix™ over two consecutive rotavirus seasons. VE against severe RVGE (Vesikari clinical scoring scale ≥11) was 79% (95% CI: 66.4-87.4) for the second season compared to 83.1% (95% CI 66.6-92.3) for the first season (75). The efficacy of Rotarix™ was followed for 2 seasons in 5 European countries. VE was determined for RVGE severity (Vesikari clinical scoring scale), hospitalization and medical attention (medical personnel or ED contact or visit). During the 2nd rotavirus season, VE against RVGE of any severity was 71.9% (95% CI: 61.2-79.8) and 85.6% (95% CI: 75.8-91.9) for severe RVGE. VE for hospitalization and medical attention were 92.2% (95% CI: 65.6-99.1) and 76.2% (95% CI: 63.0-85.0); respectively. VE during the 2nd rotavirus season were moderately lower for all outcomes compared with the 1st season (reductions in VE ranging from 8-16% depending on the outcome) (76). A study of Finnish infants receiving 2 doses of rotavirus vaccine showed sustained vaccine efficacy against either severe or any RVGE (Vesikari clinical scoring scale) across two rotavirus seasons. During the second season VE was 73% (95% CI: 20-92) for RVGE of any severity and 83% (95% CI: 7-95) for severe RVGE. The VE in the 2nd season was comparable to the VE in the first season in which VE was 73% (95% CI: 27-91) and 90% (95% CI: 10-100) against any or severe RVGE respectively (77).

	RotaTeq®	**Rotarix™**
Effectiveness in postmarketing use	Studies from the USA, Australia and Nicaragua describe the effectiveness of RotaTeq® against RVGE in postmarketing use. An earlier study reporting the decline and change in seasonality of rotavirus activity in the USA is described briefly in the section below addressing herd immunity. The effectiveness of RotaTeq® (full or partial series) vaccination against RVGE in children 15 days-23 month of age was conducted in an ED in Houston Texas from February through June 2008. Controls were drawn from age-matched children with rotavirus negative GE or children admitted for acute respiratory infection (ARI). Identified circulating strains of rotavirus were 50% G3P[8] and 26% G1P[8] with the remainder being mixed strains. VE against hospitalization and ED visits in fully vaccinated children was 88% (95% CI: 68-96) with the combined rotavirus negative GE and ARI control groups. VE with 2 and 1 doses using the combined control groups were 81% (95% CI: 13-96) and 69% (95% CI: 13-89) respectively. By comparison, when Vesikari clinical severity scores ≥11 were assessed VE was 87% (95% CI: 63-95), 89% (95% CI: 15-99), and 79% (95% CI: 25-94) for 3, 2 and 1 doses respectively using the combined control groups. When hospitalization for severe RVGE was assessed, VE for ≥1 dose of RotaTeq® was 100% (95% CI: 72-100). For children receiving intravenous hydration, the 3 dose VE was 96% (95% CI: 72-99) with the combined control groups (78). In another study out of the USA, a large national health insurance claim database was used to assess the effectiveness of RotaTeq® during the first 2 rotavirus vaccine seasons post-licensure (2007 and 2008). Two cohorts of infants were followed, those receiving 3 doses of RotaTeq® (33 140 participants) and another cohort receiving DTaP but not RotaTeq® (26, 167 participants) (18). RVGE cases were identified using diagnostic codes. VE effectiveness was 100% (95% CI: 87-100) against hospitalization and ED visits RVGE and	The effectiveness of one or two doses of Rotarix™ was examined in a case-control study conducted in El Salvador. The study spanned January 2007 to June 2009 and evaluated the effectiveness of Rotarix against hospital admission for dehydrating rotavirus diarrhoea in children less than 2 years of age. VE following 2 doses of vaccine was 76% (95% CI: 64-84) and 51% (95% CI: 26-67) after one dose. A VE of 67% (95% CI: 54-77) was reported for the intention to vaccinate population (one or more doses of vaccine). In determining the VE based on the severity of illness (using the Vesikari clinical scoring scale); Rotarix™ was found to have a VE of 83% (95% CI: 54-77) for rotavirus diarrhoea with a severity of ≥15 and 73% (95% CI: 56-84) for a severity score of ≥11. The possibility of vaccine waning was suggested by the higher protection afforded to children 6-11 months of age (83% reduction in hospital admissions compared with controls; 95% CI: 68-91) relative children 12 or more months of age (59% reduction in admission; 95% CI: 27-77) (81). The effect of the phased introduction of Rotarix™ (from February 2006-May 2007) on deaths due to diarrhoea in children during 2008 and 2009 was evaluated in Mexico. Diarrhoea related mortality (regardless of cause) in 2008 and the 2008 and 2009 rotavirus seasons was compared to the baseline period from 2003-2006 prior to Rotarix™ introduction. Prior to the study period, first dose vaccine coverage was estimated to be 74% of children ≤11 months of age. During 2008, a relative reduction of 41% (95% CI: 36-47) was observed for the mortality rate due to diarrhoea (decreasing from 61.5 to 36 per 100,000 children). The absolute number of deaths in children ≤11 months of age during the 2008 and 2009 rotavirus seasons decreased by 45% and 66% respectively. No significant reduction in diarrhoea related mortality was reported for unvaccinated children aged 24 to 59 months. This contrasts with the 29% reduction diarrhoea mortality for children aged 12-23 months of whom most were

	RotaTeq®	**Rotarix™**
	96% (95% CI: 76-100) against outpatient visits for RVGE during the two combined rotavirus seasons. The effect of RotaTeq® on healthcare utilization was also examined. RotaTeq® vaccination resulted in relative reductions in both days (100%; 95% CI: 96-100) and costs (100%; 95% CI: 100-100) of ED and hospitalization visits compared with DTaP vaccination (34). The study out of Australia described the effectiveness of 3 doses of RotaTeq® in preventing hospitalization due to RVGE in the first 12 month birth cohort eligible for RotaTeq® vaccination. Hospital records were used to identify admissions for RVGE. VE was 93.9% (95% CI: 83.1-98.1) for primary and 89.3% (95% CI: 75.9-95.4) for any rotavirus diagnosis in fully vaccinated children relative to unvaccinated children (79). A case control study was performed in 4 hospitals in Nicaragua between June 2007 and June 2008 to evaluate the effectiveness of the introduction of RotaTeq® on the primary outcome of laboratory confirmed RVGE in age-eligible children requiring overnight admission or intravenous hydration and the secondary outcome of severe and very severe disease (Vesikari clinical scoring system). Control participants were age-matched neighbourhood residents or hospital admissions (unrelated to diarrhoea or other VPDs). The predominant identified rotavirus strain (88% of cases) was G2P[4]. The VE against hospitalization or intravenous hydration was 46% (95%CI: 18-64) for 3 doses of RotaTeq®; 51% (95% CI: 18-70) for 2 doses; and 52% (95% CI: 18-72) for 1 dose recipients using the combined controls (no differences were observed when controls were considered independently). VE for 3 doses of RotaTeq® against very severe and severe rotavirus diarrhoea was 77% (95% CI: 39-92) and 58% (95% CI: 30-74) respectively using the combined controls (80).	not age-eligible for vaccination (82). The effectiveness of Rotarix™ against severe rotavirus diarrhoea caused by the serotypically unrelated G2P[4] strains has been reported in a study from in Brazil. A case-control study was conducted from March 2006 through September 2008. Cases were children presenting to hospital with severe G2P[4] rotavirus diarrhoea. Case controls were children with rotavirus negative severe acute diarrhoea and children admitted for acute respiratory infection (ARI). The effectiveness of 2 doses of Rotarix™ against severe rotavirus disease (requiring hospital admission or ED treatment) in 6-11 month old children was 77% (95% CI: 42-91) using the rotavirus negative control subjects and 77% (95% CI: 43-90) using the ARI control subjects. Vaccination did not alter the risk for G2P[4] rotavirus diarrhoea in children ≥12 months of age. Rotarix™ was also highly effective in preventing severe G2P[4] rotavirus diarrhoea requiring hospitalization in 6-11 month olds. VE was 85% (95% CI: 54-95) using rotavirus negative control participants and 83% (95% CI: 51-94) using ARI control participants. No effect of vaccination was seen for the risk of hospitalization from G2P[4] rotavirus diarrhea in children ≥12 months of age (83).
Herd immunity	Evidence for herd immunity following the introduction of RotaTeq® has come from studies in both the USA and Australia.	Evidence for herd immunity following the introduction of Rotarix™ has come from studies in El Salvador and Mexico.

	RotaTeq®	**Rotarix™**
	RotaTeq® was licensed for use in the USA in February of 2006. The National Respiratory and Enteric Virus Surveillance System (NREVSS) was used to assess the impact of the introduction of RotaTeq® by comparing the level of rotavirus activity post-introduction of the vaccine relative to the pre-vaccine period. Although the number of tests performed in the 2007-2008 rotavirus season (July to June) increased 11% compared to the pre-vaccine period (2000-2006) there was a decrease in both the number (67%) and proportion (69%) of rotavirus positive samples. The observed reduction in rotavirus activity was greater than what would be expected based on estimates of vaccine coverage (84). RotaTeq® was included as part of the infant immunization program in Queensland, Australia on July 1, 2007. Hospital admission records for RVGE indicated an immediate decrease in the mean annual hospitalization rate for those under 20 years of age in 2007 compared to the mean annual rate from 2000-2006. The rate ratio for 2007 was 0.5 (95%CI: 0.5-0.6) in those 0-4 years of age and 0.4 (95% CI: 0.3-0.6) for those aged 5-19 years. Similar rate ratios were observed in 2008, indicative of a sustained reduction in RVGE in the unvaccinated population (79).	Following the introduction (October 2006) of Rotarix™ into the national childhood immunization program in El Salvador reductions in both acute all cause diarrhoea and confirmed rotavirus diarrhoea were observed in children under 5 years of age in 7 sentinel hospitals. During the rotavirus season, admissions for all cause diarrhoea decreased by 40% in 2008 and 51% in 2009 in children less than 5 years of age and laboratory confirmed rotavirus related admissions decreased by 84% in 2008 and 69% in 2009. Note that the incidence of confirmed rotavirus diarrhoea in 2008 (18%) was considerably lower than that seen in 2009 (40%) and 2006 (62%). The authors suggest that the reductions observed in all cause diarrhoea in the unvaccinated population (those >2 years but <5 yrs) is indicative of an indirect benefit of interruption of rotavirus transmission as few children >2 years of age were vaccinated during the study period (81). A study from Mexico reported diarrhoea related deaths in children in 2008 following the phased introduction of Rotarix™ from February 2006 through May 2007. In 2008, there was a significant reduction in the number of diarrhoea related deaths amongst children age 12-23 months relative to the annual median for the baseline period of 2003-2006. A reduction of 29% (95% CI: 17-30) in the mortality rate (deaths/100 000 children) was reported. The 29% decrease in the mortality rate in this population exceeded the estimated percentages of age-eligible children for rotavirus immunization of 10-15% and is supportive of herd immunity effects attributable to Rotarix™ immunization. A reduction in diarrhoea related deaths in children 24-59 months of age was also observed but the relative rate reduction from 2.9 to 2.7 per 100,000 or 7% (95% CI: -14 to 26) was not statistically significant (82).

REFERENCES

1. Estes MK, Kapikian AZ. Rotaviruses. In: Knipe DM, Howley PM, Griffin DE, Lamb RA, Martin MA, Roizman B, et al., editors. Fields' Virology. 5th ed. Philadelphia, Pennsylvania: Lippincott, Williams and Wilkins; 2007. p. 1917-74.

2. Bernstein DI. Rotavirus overview. Pediatr Infect Dis J. 2009 Mar;28(3 Suppl):S50-3.

3. Gentsch JR, Hull JJ, Teel EN, Kerin TK, Freeman MM, Esona MD, et al. G and P types of circulating rotavirus strains in the United States during 1996-2005: nine years of prevaccine data. J Infect Dis. 2009 Nov 1;200 Suppl 1:S99-S105.

4. Senecal M, Lebel MH, Yaremko J, Wong R, Gallant LA, Garfield H, et al. Serotype distribution of rotavirus associated gastroenteritis in Canada: a community-based study. Canadian Journal of Infectious Diseases and Medical Microbiology, Abstract P98 7th Canadian Immunization Conference, December 3 to 6, 2006, Winnipeg Convention Centre, Winnipeg, Manitoba. 2006;17(6):347-87.

5. Pang XL, Lee BE. Personal communication. 2011.

6. McDermid A, Grudeski E, Surinicz K, Le Saux N, Bettinger J, Halperin S, et al., editors. Genetic characterization of Canadian rotaviruses from 2007-2009: results from an IMPACT emergency department study in Canada. Epigenetics Neuroscience and Mental Health; June 7-9, 2011; Winnipeg, Manitoba: University of Manitoba.

7. Senecal M, Brisson M, Lebel MH, Yaremko J, Wong R, Gallant LA, et al. Measuring the Impact of Rotavirus Acute Gastroenteritis Episodes (MIRAGE): A prospective community-based study. Can J Infect Dis Med Microbiol. 2008 Nov;19(6):397-404.

8. Senecal M, Quach C, Brisson M, editors. The burden of rotavirus associated gastroenteritis in young Canadian children: a cohort model. Canadian Public Health Association 97th Annual Conference; 2006; Vancouver, British Columbia: Canadian Public Health Association.

9. Le Saux N, Bettinger JA, Halperin SA, Vaudry W, Scheifele DW, for Members of the Canadian Immunization Monitoring Program A. Substantial morbidity for hospitalized children with community-acquired rotavirus infections: 2005-2007 IMPACT surveillance in Canadian hospitals. Pediatr Infect Dis J. 2010 Sep;29(9):879-82.

10. Salvadori M, Le Saux N. Recommendations for the use of rotavirus vaccines in infants. Paediatr Child Health. 2010 Oct;15(8):519-28.

11. Dennehy PH, Cortese MM, Begue RE, Jaeger JL, Roberts NE, Zhang R, et al. A case-control study to determine risk factors for hospitalization for rotavirus gastroenteritis in U.S. children. Pediatr Infect Dis J. 2006 Dec;25(12):1123-31.

12. Ford-Jones EL, Wang E, Petric M, Corey P, Moineddin R, Fearon M. Hospitalization for community-acquired, rotavirus-associated diarrhea: a prospective, longitudinal, population-based study during the seasonal outbreak. The Greater Toronto Area/Peel Region PRESI Study

Group. Pediatric Rotavirus Epidemiology Study for Immunization. Arch Pediatr Adolesc Med. 2000 Jun;154(6):578-85.

13. Gurwith M, Wenman W, Gurwith D, Brunton J, Feltham S, Greenberg H. Diarrhea among infants and young children in Canada: a longitudinal study in three northern communities. Journal of Infectious Diseases. 1983;147(4):685-92.

14. Mast TC, DeMuro-Mercon C, Kelly CM, Floyd LE, Walter EB. The impact of rotavirus gastroenteritis on the family. BMC Pediatr. 2009;9:11.

15. Brisson M, Senecal M, Drolet M, Mansi JA. Health-related quality of life lost to rotavirus-associated gastroenteritis in children and their parents: a Canadian prospective study. Pediatr Infect Dis J. 2010 Jan;29(1):73-5.

16. Le Saux N, Bettinger J, Halperin S, Vaudry W, Scheifele D. Hospital acquired rotavirus infections: burden in Canadian paediatric hospitals. J Infect Prev. 2011;12(4):159-62.

17. Piednoir E, Bessaci K, Bureau-Chalot F, Sabouraud P, Brodard V, Andreoletti L, et al. Economic impact of healthcare-associated rotavirus infection in a paediatric hospital. J Hosp Infect. 2003 Nov;55(3):190-5.

18. National Advisory Committee on I. Statement on the recommended use of pentavalent human-bovine reassortant rotavirus vaccine. An Advisory Committee Statement (ACS). Can Commun Dis Rep. 2008 Jan;34(ACS-1):1-33.

19. National Advisory Committee on Immunization (NACI). Updated statement on the use of rotavirus vaccines. Canada Communicable Disease Report. 2010;36(ACS-4):1-37.

20. Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, Rodriguez Z, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med. 2006 Jan 5;354(1):23-33.

21. National Adivsory Committee on Immunization (NACI). Literature review on rotavirus: disease and vaccine characteristics. Canada Communicable Disease Report. 2010;36(ACS-14):1-31.

22. GlaxoSmithKline. Rotarix(TM) Product Monograph. London: GlaxoSmithKline; 2011.

23. Haber P, Patel M, Pan Y, Baggs J, Haber M, Museru O, et al. Intussusception after rotavirus vaccines reported to US VAERS, 2006-2012. Pediatrics. 2013 Jun;131(6):1042-9.

24. Shui IM, Baggs J, Patel M, Parashar UD, Rett M, Belongia EA, et al. Risk of intussusception following administration of a pentavalent rotavirus vaccine in US infants. JAMA. 2012 Feb 8;307(6):598-604.

25. Centers for Disease C, Prevention. National and state vaccination coverage among children aged 19-35 months--United States, 2010. MMWR Morb Mortal Wkly Rep. 2011 Sep 2;60(34):1157-63.

26. Uppsala Monitoring Centre. Rotavirus vaccine and incorrect administration route – a patient safety signal. WHO Signal. 2010;December:13-4.

27. Erickson LJ, De Wals P, Farand L. An analytical framework for immunization programs in Canada. Vaccine. 2005 Mar 31;23(19):2470-6.

28. Merck Frosst Canada. Personal communication. 2012.

29. GlaxoSmithKline. Unpublished data. 2012.

30. Cortese MM, Parashar UD, Centers for Disease C, Prevention. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2009 Feb 6;58(RR-2):1-25.

31. Laroche J, Frescura AM, Belzak L. Results from the 2006 and 2009 Childhood National Immunization Coverage Surveys. Canadian Journal of Infectious Diseases and Medical Microbiology. 2010;21(4):173-230.

32. Coyle D, Coyle K, Bettinger JA, Halperin SA, Vaudry W, Scheifele DW, et al. Cost effectiveness of infant vaccination for rotavirus in Canada. Canadian Journal of Infectious Diseases & Medical Microbiology. 2012;23(2):71-7.

33. Widdowson MA, Meltzer MI, Zhang X, Bresee JS, Parashar UD, Glass RI. Cost-effectiveness and potential impact of rotavirus vaccination in the United States. Pediatrics. 2007 Apr;119(4):684-97.

34. Jacobs P, Shane L, Fassbender K, Wang E, Moineddin R, Ford-Jones E. Economic analysis of rotavirus-associated diarrhea in the metropolitan Toronto and Peel regions of Ontario. Can J Infect Dis. 2002 May;13(3):167-74.

35. Grimwood K, Lambert SB, Milne RJ. Rotavirus infections and vaccines: burden of illness and potential impact of vaccination. Paediatr Drugs. 2010 Aug 1;12(4):235-56.

36. World Health Organization. Report on Macroeconomics and Health: Investing in Health for Economic Development. Geneva: World Health Organization, 2001.

37. McCabe C, Claxton K, Culyer AJ. The NICE cost-effectiveness threshold: what it is and what that means. Pharmacoeconomics. 2008;26(9):733-44.

38. Bilcke J, Beutels P. Reviewing the cost effectiveness of rotavirus vaccination: the importance of uncertainty in the choice of data sources. Pharmacoeconomics. 2009;27(4):281-97.

39. Jit M, Edmunds WJ. Evaluating rotavirus vaccination in England and Wales. Part II. The potential cost-effectiveness of vaccination. Vaccine. 2007 May 16;25(20):3971-9.

40. Shim E, Galvani AP. Impact of transmission dynamics on the cost-effectiveness of rotavirus vaccination. Vaccine. 2009 Jun 19;27(30):4025-30.

41. Nohynek H, Salo H, Renko M, Leino T. Finland introduces rotavirus vaccine into the national vaccination programme in September 2009. Euro Surveill. 2009;14(35).

42. Bilcke J, Van Damme P, Beutels P. Cost-effectiveness of rotavirus vaccination: exploring caregiver(s) and "no medical care" disease impact in Belgium. Med Decis Making. 2009 Jan-Feb;29(1):33-50.

43. Fisman DN, Chan CH, Lee V, Lowcock E, Naus M. Economic Effectiveness of Pediatric Rotavirus Vaccination in British Columbia. Vancouver, British Columbia: Presented to the Canadian Immunization Committee Task Group on Rotavirus Vaccine, 2012.

44. Coyle D. Economic Burden of Illness of Rotavirus in Canada and an Assessment of the Cost Effectiveness of Childhood Vaccination. Ottawa, Ontario: University of Ottawa, Presented to the Canadian Immunization Committee Task Group on Rotavirus Vaccine, Medicine DoEaC; 2010.

45. Jit M, Mangen MJ, Melliez H, Yazdanpanah Y, Bilcke J, Salo H, et al. An update to "The cost-effectiveness of rotavirus vaccination: comparative analyses for five European countries and transferability in Europe". Vaccine. 2010 Nov 3;28(47):7457-9.

46. Mangen MJ, Van Duynhoven YT, Vennema H, Van Pelt W, Havelaar AH, De Melker HE. Is it cost-effective to introduce rotavirus vaccination in the Dutch national immunization program? Vaccine. 2010;28(14):2624-35.

47. Martin A, Batty A, Roberts JA, Standaert B. Cost-effectiveness of infant vaccination with RIX4414 (Rotarix) in the UK. Vaccine. 2009 Jul 16;27(33):4520-8.

48. Melliez H, Levybruhl D, Boelle PY, Dervaux B, Baron S, Yazdanpanah Y. Cost and cost-effectiveness of childhood vaccination against rotavirus in France. Vaccine. 2008 Jan 30;26(5):706-15.

49. Milne RJ, Grimwood K. Budget impact and cost-effectiveness of including a pentavalent rotavirus vaccine in the New Zealand childhood immunization schedule. Value Health. 2009 Sep;12(6):888-98.

50. Newall AT, Beutels P, Macartney K, Wood J, MacIntyre CR. The cost-effectiveness of rotavirus vaccination in Australia. Vaccine. 2007 Dec 17;25(52):8851-60.

51. Lagarde F. Summary of Public Opinion on Immunization in Canada. Ottawa, Ontario: Public Health Agency of Canada; 2005. p. 19.

52. Patel MM, Janssen AP, Tardif RR, Herring M, Parashar UD. A qualitative assessment of factors influencing acceptance of a new rotavirus vaccine among health care providers and consumers. BMC Pediatr. 2007;7:32.

53. Zimet GD, Liddon N, Rosenthal SL, Lazcano-Ponce E, Allen B. Chapter 24: Psychosocial aspects of vaccine acceptability. Vaccine. 2006 Aug 31;24 Suppl 3:S3/201-9.

54. Iwamoto M, Saari TN, McMahon SR, Yusuf HR, Massoudi MS, Stevenson JM, et al. A survey of pediatricians on the reintroduction of a rotavirus vaccine. Pediatrics. 2003 Jul;112(1 Pt 1):e6-10.

55. Kempe A, Daley MF, Parashar UD, Crane LA, Beaty BL, Stokley S, et al. Will pediatricians adopt the new rotavirus vaccine? Pediatrics. 2007 Jan;119(1):1-10.

56. McPhillips HA, Davis RL, Marcuse EK, Taylor JA. The rotavirus vaccine's withdrawal and physicians' trust in vaccine safety mechanisms. Arch Pediatr Adolesc Med. 2001 Sep;155(9):1051-6.

57. Sansom SL, Barker L, Corso PS, Brown C, Deuson R. Rotavirus vaccine and intussusception: how much risk will parents in the United States accept to obtain vaccine benefits? Am J Epidemiol. 2001 Dec 1;154(11):1077-85.

58. Kempe A, Patel MM, Daley MF, Crane LA, Beaty B, Stokley S, et al. Adoption of rotavirus vaccination by pediatricians and family medicine physicians in the United States. Pediatrics. 2009 Nov;124(5):e809-16.

59. Jacobson LM, Santosham M, Milstone AM. Pediatric providers' acceptance of recommendations for routine rotavirus vaccination. Clin Pediatr (Phila). 2008 Jun;47(5):500-3.

60. Agyeman P, Desgrandchamps D, Vaudaux B, Berger C, Diana A, Heininger U, et al. Interpretation of primary care physicians' attitude regarding rotavirus immunisation using diffusion of innovation theories. Vaccine. 2009 Jul 30;27(35):4771-5.

61. Haas H, Olives JP, Virey B, Klein P. [Survey about the perception of the gastroenteritis and the infection due to rotavirus by the mothers in France]. Pathol Biol (Paris). 2010 Apr;58(2):e43-7.

62. Dube E, Bradet R, Gilca V, Sauvageau C, Boulianne N, Boucher FD, et al. Rotavirus vaccination: results of a survey on Canadian physicians' knowledge, attitudes and practices. Canadian Journal of Infectious Diseases and Medical Microbiology. 2010;21(4):173-230.

63. Gilca V, Boulianne N, Dube E, Sauvageau C, Ouakki M. Attitudes of nurses toward current and proposed vaccines for public programs: a questionnaire survey. Int J Nurs Stud. 2009 Sep;46(9):1219-35.

64. Gilca V, Sauvageau C, McNeil S, Gemmill IM, Dionne M, Dobson S, et al. Setting priorities for new vaccination programs by using public health officers and immunization managers opinions. Vaccine. 2008 Aug 5;26(33):4204-9.

65. Wang FT, Mast TC, Glass RJ, Loughlin J, Seeger JD. Effectiveness of the pentavalent rotavirus vaccine in preventing gastroenteritis in the United States. Pediatrics. 2010 Feb;125(2):e208-13.

66. Chan J, Sahni V, Donovan T, Naus M. Rotavirus immunization: knowledge, attitudes, beliefs and practices of BC physicians. Canadian Journal of Infectious Diseases and Medical Microbiology. 2010;21(4):173-230.

67. Campbell J, Sogbanmu E. The Canadian Institute of Child Health Conducts National Survey on Rotavirus. Canadian Institute of Child Health [Internet]. 2007. Available from: http://www.cich.ca/News/news_May17_07.html.

68. Dube E, Bettinger JA, Halperin B, Bradet R, Lavoie F, Sauvageau C, et al. Rotavirus vaccination: results of a longitudinal study on determinants of Canadian parents' decision. Canadian Journal of Infectious Diseases and Medical Microbiology. 2010;21(4):173-230.

69. Dube E, Gilca V, Sauvageau C, Boulianne N, Boucher FD, Bettinger JA, et al. Priorities for new vaccination programs implementation: paediatricians' and family physicians' opinions. Canadian Journal of Infectious Diseases and Medical Microbiology. 2010;21(4):173-230.

70. Lopman BA, Curns AT, Yen C, Parashar UD. Infant rotavirus vaccination may provide indirect protection to older children and adults in the United States. J Infect Dis. 2011 Oct 1;204(7):980-6.

71. Public Health Agency of Canada (PHAC). Canadian Adverse Event Following Immunization Surveillance System (CAEFISS)2006. Available from: http://www.phac-aspc.gc.ca/im/vs-sv/caefiss-eng.php.

72. Zelman M. Personal communication. 2011.

73. Vesikari T, Itzler R, Karvonen A, Korhonen T, Van Damme P, Behre U, et al. RotaTeq, a pentavalent rotavirus vaccine: efficacy and safety among infants in Europe. Vaccine. 2009 Dec 11;28(2):345-51.

74. Vesikari T, Karvonen A, Ferrante SA, Kuter BJ, Ciarlet M. Sustained efficacy of the pentavalent rotavirus vaccine, RV5, up to 3.1 years following the last dose of vaccine. Pediatr Infect Dis J. 2010 Oct;29(10):957-63.

75. Linhares AC, Velazquez FR, Perez-Schael I, Saez-Llorens X, Abate H, Espinoza F, et al. Efficacy and safety of an oral live attenuated human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in Latin American infants: a randomised, double-blind, placebo-controlled phase III study. Lancet. 2008 Apr 5;371(9619):1181-9.

76. Vesikari T, Karvonen A, Prymula R, Schuster V, Tejedor JC, Cohen R, et al. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. Lancet. 2007 Nov 24;370(9601):1757-63.

77. Vesikari T, Karvonen A, Puustinen L, Zeng SQ, Szakal ED, Delem A, et al. Efficacy of RIX4414 live attenuated human rotavirus vaccine in Finnish infants. Pediatr Infect Dis J. 2004 Oct;23(10):937-43.

78. Boom JA, Tate JE, Sahni LC, Rench MA, Hull JJ, Gentsch JR, et al. Effectiveness of pentavalent rotavirus vaccine in a large urban population in the United States. Pediatrics. 2010 Feb;125(2):e199-207.

79. Field EJ, Vally H, Grimwood K, Lambert SB. Pentavalent rotavirus vaccine and prevention of gastroenteritis hospitalizations in Australia. Pediatrics. 2010 Sep;126(3):e506-12.

80. Patel M, Pedreira C, De Oliveira LH, Tate J, Orozco M, Mercado J, et al. Association between pentavalent rotavirus vaccine and severe rotavirus diarrhea among children in Nicaragua. JAMA. 2009 Jun 3;301(21):2243-51.

81. de Palma O, Cruz L, Ramos H, de Baires A, Villatoro N, Pastor D, et al. Effectiveness of rotavirus vaccination against childhood diarrhoea in El Salvador: case-control study. BMJ. 2010;340:c2825.

82. Richardson V, Hernandez-Pichardo J, Quintanar-Solares M, Esparza-Aguilar M, Johnson B, Gomez-Altamirano CM, et al. Effect of rotavirus vaccination on death from childhood diarrhea in Mexico. N Engl J Med. 2010 Jan 28;362(4):299-305.

83. Correia JB, Patel MM, Nakagomi O, Montenegro FM, Germano EM, Correia NB, et al. Effectiveness of monovalent rotavirus vaccine (Rotarix) against severe diarrhea caused by serotypically unrelated G2P[4] strains in Brazil. J Infect Dis. 2010 Feb 1;201(3):363-9.

84. Tate JE, Panozzo CA, Payne DC, Patel MM, Cortese MM, Fowlkes AL, et al. Decline and change in seasonality of US rotavirus activity after the introduction of rotavirus vaccine. Pediatrics. 2009 Aug;124(2):465-71.