Evaluation of Universal Rotavirus Vaccination

Study Participant Training Materials
November 3rd, 2010

Dear Colleague:

We write this letter to inform you of an exciting opportunity to provide rotavirus vaccine to infant patients born after October 1st 2010, free of charge, starting December 1st, 2010. As you know, Rotavirus is the most frequent cause of diarrheal infection in children in Canada and the most common cause of diarrhea that leads to hospitalization in infants. Two rotavirus vaccines are now available for use in Canada to prevent severe diarrhea caused by this virus. The National Advisory Committee on Immunization recommends that all infants receive rotavirus vaccine during infancy at 2 and 4 months of age (Rotarix, GlaxoSmithKline) or 2, 4 and 6 months of age (Rotateq, Merck and Co). A decision on whether rotavirus vaccine should be included in the publicly funded, universal infant immunization schedule has not yet been made.

Capital District Health Authority 9, Prince Edward Island Department of Health and Wellness and the Canadian Center for Vaccinology at Dalhousie University, Capital Health, and the IWK Health Centre, with support from GlaxoSmithKline, are undertaking a universal rotavirus vaccination demonstration project whereby Rotarix will be provided free of charge to all infants born after October 1, 2010, along with their publicly funded routine vaccines. The purpose of the demonstration project is to evaluate the effectiveness of a universal rotavirus immunization program by measuring the burden of illness including the impact on hospitalizations due to rotavirus gastroenteritis and economic factors related to hospitalization and emergency department visits for diarrhea, the acceptance of the program by the public and health care providers, and the logistics of implementing a universal immunization program.

This binder contains materials that will assist you as a health care provider in implementing this program:

- An orientation slide deck
- A summary of the pivotal clinical trials with Rotarix
- Epidemiology of rotavirus in Canada (IMPACT publications/abstracts)
• Rotarix Product Monograph

• National Advisory Committee on Immunization Rotavirus statement

• Advisory Committee on Immunization Practices of the United States Centers for Disease Control Rotavirus statement

• A letter from GlaxoSmithKline outlining Rotarix Commercial materials available for ordering and a sample of each.

We look forward to working with you on this exciting universal rotavirus vaccine immunization program demonstration project which will provide great benefit to the populations that we serve.

Sincerely,

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Deputy Chief Health Officer  
Department of Health & Wellness  
Chief Health Office  
Charlottetown, PEI

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Professor of Pediatrics and Microbiology & Immunology  
Head, Pediatric Infectious Diseases  
Director, Canadian Center for Vaccinology  
Dalhousie University, IWK Health Centre
Items for Rotarix™ Training Binder:

1. Public Health Presentation
2. Rotarix™ Clinical Papers
   - Vesikeri
   - Linhars
   - 2010 Efficacy in Africa
3. IMPACT Canadian Surveillance
   - PIDJ Lesaux
4. Product Monograph
5. NACI Statement
6. CPS Recommendations
7. ACIP statement
8. Q&A on PCV1
9. Health Canada
10. Rotavirus Promotional Materials
    - Fact Sheet
    - Patient Brochure
Rotavirus & Rotarix™
Contents

• Epidemiology
  • IMPACT data
  • Global Epidemiology
• The Rotavirus
• Rotavirus Gastroenteritis Disease
• Rotavirus Vaccines
• Rotavirus Effectiveness
• Rotavirus Vaccine Safety
• Implementation
• Health Economics
• Recommendations

Rotarix is a trade mark of the GlaxoSmithKline group of companies
IMPACT Data
Rotavirus:

- All children under 5 years will have rotavirus infection
- Most important cause of severe childhood diarrhea and annually causes more than 500,000 deaths in children < 5 years worldwide

- **US data** Children < 3 years  Payne D. Pediatr 2008 122(6)
  - 1 in 11 children will have Outpatient visits
  - 1 in 11 children will have Emergency Department visits
  - 1 in 150 will be hospitalized for rotavirus

- **Canadian Data**
  - 1:20 will require Emergency Department visit
  - 1:160 will be hospitalized for rotavirus < 5 years

*Slide Source - CPS 2010 Presentation by Nicole LeSaux
Sénécal M, CPHA abstract 2006
ROT-2009-007 (DEC)*
Rotavirus is the most common diarrhoeal pathogen

Over 475 million cases of infantile gastroenteritis (GE) each year\(^1\) – with rotavirus (RV) the most common pathogen\(^2,3\)

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- 1856 hospitalized children
  - 1359 Community acquired
  - 497 Hospital acquired
- none received rotavirus vaccine
- 1020 (45.4%) females

*Slide Source - CPS 2010 Presentation by Nicole LeSaux
Children Hospitalized for Community Acquired Rotavirus

**General Health**

- Healthy
- Underlying disease
- Premature or <4 wks

**Presence of altered immunity**

- Normal Immunity
- Immune compromise
- Premature or <4 weeks

*Slide Source - CPS 2010 Presentation by Nicole LeSaux*
How different is it from other common causes of diarrhea?

![Bar chart showing comparison between Rotavirus and Non Rotavirus diarrhea, vomiting, and fever.]

IMPACT 70

*Slide Source - CPS 2010 Presentation by Nicole LeSaux

ROT-2009-007 (DEC)
### Severity of Illness: IMPACT admissions

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>% of children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent vomiting/diarrhea</td>
<td>47.2%</td>
</tr>
<tr>
<td>Dehydration</td>
<td>48.6%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>4.4%</td>
</tr>
<tr>
<td>Sepsis</td>
<td>19%</td>
</tr>
<tr>
<td>Seizures</td>
<td>7%</td>
</tr>
</tbody>
</table>

*50% of children 0-3 months present with clinical sepsis.*

*Slide Source - CPS 2010 Presentation by Nicole LeSaux*
Younger children have higher incidence of sepsis associated with rotavirus infection

- Children under 2 years were significantly more likely to present with a clinical picture suggestive of sepsis (22.1%) compared with children between 2 and 16 years (13.7%) \((P < 0.001)\)

- 50% of children 0 to 3 months of age presenting with sepsis-like picture, a rate significantly higher than among children 4 to 23 months of age \((P < 0.001)\).
What impact will a rotavirus infection have on the family and the child?

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of ED visits per case</td>
<td>1.3</td>
<td>1</td>
</tr>
<tr>
<td>Duration of stay in ED per case</td>
<td>7.9 hours</td>
<td>7.0</td>
</tr>
<tr>
<td>Duration of Hospital stay</td>
<td>3.4 days</td>
<td>3.0</td>
</tr>
<tr>
<td>Requiring ICU care n=48 (3.5%)</td>
<td>2.4 days</td>
<td>2</td>
</tr>
</tbody>
</table>

26% had 2 visits

Health related quality of life lost to Rotavirus

- 8 days mean duration of entire episode
- Significantly impacts the quality of life of child and parents, similar to varicella, pneumonia and otitis media
Hospital Acquired Rotavirus = 497

Accounted for 27% of all children in hospital with rotavirus infections

Median age 9.6 months
Rotaviruses are one of the most common hospital acquired infections in pediatrics. 30% in hospital for another infection.
Rotavirus Serotypes (291 samples): ED study 2007-2009

Of 102 negative samples, 40 (39.6%) were positive using molecular testing.

Data from Dr. T. Booth, National Microbiology Lab

Slide Source - CPS 2010 Presentation Nicole LeSaux
Rotavirus Serotype Prevalence - Canada

- Of the 14 G types, most strains belong to G1, G2, G3 or G4
- Serotype prevalence varies by region & can change from one season to the next
- G9: Emergent strains, maybe a fifth common serotype worldwide
Global distribution of RV strains

- G1P[8] is the most common strain, causing 65% of RVGE cases worldwide\(^1\)

- Globally, the same five RV strains cause >90% of RVGE episodes\(^1\)
  - G1P[8]
  - G2P[4]
  - G3P[8]
  - G4P[8]
  - G9P[8]

- Global and regional fluctuations in RV strain distribution occur year by year\(^1\)

Global serotype prevalence 1989–2004\(^1\)

- G1P[8] 65%
  - G9P[8] 3%
  - G4P[8] 9%
  - G3P[8] 3%
  - G2P[4] 12%

Strain distribution by WHO region worldwide 2001–2008

*The category ‘Other’ includes non-typeable strains. SE, southeast; E, east.
Summary of serotype distribution

- Of the 14 G types, most strains belong to G1, G2, G3 or G4.
- Serotype prevalence varies by region & can change from one season to the next.
- G9: Emergent strains, maybe a fifth common serotype worldwide.
Rotavirus
Rotavirus

- Rotavirus belongs to the family Reoviridae
- Rotavirus was identified for the 1st time in 1973
- They have a distinct morphologic wheel-like appearance by negative-stain electron microscopy. (Latin, rota = wheel)
- Rotaviruses are non-enveloped, segmented, double-stranded RNA viruses
Rotavirus

- The 70 nm viral particle has a characteristic double-shelled outer capsid enclosing a third layer or core, comprising the genome. \(^1\)
- Outer layer made of VP7 and VP4 neutralizing proteins
  - VP7 determines G-serotypes
  - VP4 determines P-serotypes
  - 14 G serotypes and 8 P serotypes identified in humans
- VP6 (used for diagnosis) located in middle capsid
- Both G and P serotypes elicit specific neutralizing antibodies and they are important targets for vaccines.

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\(^1\) Plotkin, Orenstein eds. Vaccines. 4th ed. 2004: 1327-1345

Bloom, Lambert eds. The Vaccine Book. 2003: 225-243

Rotavirus Gastroenteritis Disease
Pathogenesis

Rotaviruses adhere to the GI tract epithelia (jejunal mucosa)

↓

Atrophy of the villi of the gut

↓

Loss of absorptive area

↓

Flux of water and electrolytes

↓

NSP4 viral enterotoxin

↓

Enteric nervous system activation

VOMITING AND diarrhoea

Rotavirus Gastroenteritis; Severity / Symptoms / Duration

- Incubation period is typically 1-3 days, during which virus is present in stools
- Severity ranges from asymptomatic infection to dehydrating gastroenteritis that can occasionally be fatal
- The most typical symptoms of illness are:
  - Sudden onset watery diarrhea (85% - 100%)
  - Preceded or accompanied by vomiting (89% - 97%)
  - Fever (53% - 89%)
- Duration of illness: 4 to 8 days
Symptoms of RGE

M. Sénécal, M. Brisson, M. H. Lebel, J. Yaremko et al. for the MIRAGE group.- 2006
Primary infection with RV is usually the most severe

Primary infection protects against subsequent infections (symptomatic and asymptomatic)\(^1\)

Secondary infections are clinically milder or asymptomatic\(^1\)

*defined as no diarrhoea 5 days before or after detection of RV or during the interval in which a serological response detected

Rotavirus Vaccines
The two principal commercial vaccines

**Rotarix™**
A live-attenuated vaccine comprising the G1P[8] human strain (RIX4414)¹
Liquid formulation to be given orally in two doses¹

**RotaTeq®**
A 5-valent bovine-derived reassortant attenuated vaccine
Comprises five bovine–human RV strains
Liquid formulation to be given orally in three doses²

The Next Generation of Rotavirus Vaccines

Rotarix™
GlaxoSmithKline

RotaTeq™
Merck Frosst

Human rotavirus
G1P[8]

Bovine rotavirus with single human rotavirus gene substitution
G1
G3
G2
P[8]
G4

Rotarix™
GlaxoSmithKline

RotaTeq™
Merck Frosst
Rotarix™ – product profile

- Live-attenuated human virus, G1P[8] strain (RIX4414)
- Oral vaccine: liquid (1.5 mL)
- Vaccine concentration: 106 median Cell Culture Infective Dose (CCID50)
- Two doses:
  - First dose as early as 6 weeks of age
  - Second dose completed by 24 weeks (preferably before 16 weeks)
  - Minimum interval between doses: 4 weeks
- Co-administration with other vaccines
  - Diphtheria-tetanus-whole cell pertussis (DTPw), diphtheria-tetanus-acellular cell pertussis (DTPa), hepatitis B vaccine (HBV), Haemophilus influenzae type B (Hib), inactivated polio vaccine (IPV), oral polio vaccine (OPV), meningitis C, Streptococcus pneumoniae

Rotarix™ Indication and Contraindications

- **INDICATIONS AND CLINICAL USE**

  ROTARIX™ is indicated for active immunization of infants from the age of 6 weeks for the prevention of gastroenteritis caused by rotavirus types G1P[8], G2P[4], G3P[8], G4P[8] and G9P[8].

- **CONTRAINDICATIONS**

  ROTARIX™ should not be administered in:

  - Infants who are hypersensitive to this drug or to any ingredient in the formulation or component of the container.
  - Infants who experienced hypersensitivity after previous administration of rotavirus vaccines.
  - Infants with uncorrected congenital malformation (such as Meckel’s diverticulum) of the gastrointestinal tract that would predispose for intussusception.
Vesikari 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.

# Rotarix™ study 036 – overview

## Key efficacy study for Rotarix™

<table>
<thead>
<tr>
<th>Study setting</th>
<th>3994 infants from 6 European countries:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy cohort</td>
<td>Rotarix™ (N=2646) vs placebo (N=1348)</td>
</tr>
<tr>
<td>Design</td>
<td>Phase IIIb, double-blind, placebo-controlled, randomised</td>
</tr>
<tr>
<td>Main efficacy endpoints</td>
<td>Efficacy against:</td>
</tr>
<tr>
<td></td>
<td>• Any RVGE caused by circulating RV strains</td>
</tr>
<tr>
<td></td>
<td>• Severe RVGE</td>
</tr>
<tr>
<td></td>
<td>• RVGE-related hospitalisations</td>
</tr>
<tr>
<td></td>
<td>• RVGE caused by G1 and non-G1 types</td>
</tr>
<tr>
<td>Efficacy population</td>
<td>Per-protocol</td>
</tr>
<tr>
<td></td>
<td>• All infants who received both vaccine doses</td>
</tr>
<tr>
<td></td>
<td>Intent-to-treat</td>
</tr>
<tr>
<td></td>
<td>• All infants who received ≥1 vaccine dose</td>
</tr>
<tr>
<td>Efficacy instrument</td>
<td>Vesikari 20-point scale</td>
</tr>
<tr>
<td>Follow up</td>
<td>2 years</td>
</tr>
</tbody>
</table>

Study design

n=3994 infants enrolled and randomised (2:1)

- **1st dose**: n=1348
  - Month 0: Age 6–14 weeks
- **2nd dose**: n=2646
  - Months 1–2: Age 10–24 weeks
  - Months 7–9: Age 10–11 months
  - Months 19–21: Age 22–23 months

**Rotarix™**

**Placebo**

Year 1 efficacy
Year 2 efficacy
Vaccine efficacy [95% CI] against any RVGE

From 2 weeks post-dose two to end of the first and second RV seasons (ATP cohort)*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Vaccine Efficacy (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any RVGE</td>
<td>87%</td>
<td>[80;92]</td>
</tr>
<tr>
<td>Severe RVGE</td>
<td>96%</td>
<td>[90;99]</td>
</tr>
<tr>
<td>RVGE hospitalisations</td>
<td>100%</td>
<td>[82;100]</td>
</tr>
</tbody>
</table>

*All p<0.0001 for Rotarix™ vs placebo.

Efficacy between doses

- Rotarix™ provides 90% protection against any episode of RVGE between the first and second dose.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rotarix™</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Efficacy</td>
</tr>
<tr>
<td>RVGE (any severity)</td>
<td>90%</td>
</tr>
</tbody>
</table>

Strain-specific vaccine efficacy [95% CI] against any and severe RVGE

From 2 weeks post-dose two to the end of the second year of life*

- Statistically significant protection against any and severe RVGE caused by each of the 5 main circulating strains over the first 2 years of life

All comparisons significant at the 5% level.

Vaccine efficacy against hospitalisations due to GE of any cause

From 2 weeks post-dose two to end of the first or second RV season

<table>
<thead>
<tr>
<th>Hospitalisation for GE</th>
<th>Vaccine n (%)</th>
<th>Placebo n (%)</th>
<th>Vaccine efficacy [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1 year)</td>
<td>11 (&lt;1)</td>
<td>22 (2)</td>
<td>75 [45; 89]</td>
<td>0.0001</td>
</tr>
<tr>
<td>(2 year)</td>
<td>27 (1)</td>
<td>48 (4)</td>
<td>72 [53; 83]</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Cross-protection: Rotarix™

- Statistically significant efficacy against each of the 5 main circulating G-types up to 2 years post-dose 2
- Demonstrates cross-protection, mimicking natural infection

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Type</th>
<th>Follow-up</th>
<th>Efficacy</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any RVGE</td>
<td>G1</td>
<td>Up to 2 years following</td>
<td>90%</td>
<td>83–94</td>
</tr>
<tr>
<td></td>
<td>G2</td>
<td>dose 2</td>
<td>58%</td>
<td>10–81</td>
</tr>
<tr>
<td></td>
<td>G3</td>
<td></td>
<td>85%</td>
<td>41–97</td>
</tr>
<tr>
<td></td>
<td>G4</td>
<td></td>
<td>83%</td>
<td>56–95</td>
</tr>
<tr>
<td></td>
<td>G9</td>
<td></td>
<td>73%</td>
<td>59–82</td>
</tr>
<tr>
<td>Severe RVGE</td>
<td>G1</td>
<td>Up to 2 years following</td>
<td>96%</td>
<td>90–99</td>
</tr>
<tr>
<td></td>
<td>G2</td>
<td>dose 2</td>
<td>86%</td>
<td>24–99</td>
</tr>
<tr>
<td></td>
<td>G3</td>
<td></td>
<td>94%</td>
<td>53–100</td>
</tr>
<tr>
<td></td>
<td>G4</td>
<td></td>
<td>95%</td>
<td>68–100</td>
</tr>
<tr>
<td></td>
<td>G9</td>
<td></td>
<td>85%</td>
<td>72–93</td>
</tr>
</tbody>
</table>

‡ ≥11 Vesikari score; RVGE, rotavirus gastroenteritis; CI, confidence interval

Conclusion

- Over the first 2 years of life, two doses of Rotarix™ provide sustained protection against:

- Rotarix™ demonstrates protection against any and severe RVGE caused by each of the five main circulating strains over the first 2 years of life

<table>
<thead>
<tr>
<th>Vaccine efficacy</th>
<th>1 year</th>
<th>2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any RVGE</td>
<td>87%</td>
<td>79%</td>
</tr>
<tr>
<td>Severe RVGE (≥11 Vesikari score)</td>
<td>96%</td>
<td>90%</td>
</tr>
<tr>
<td>RVGE hospitalisations</td>
<td>100%</td>
<td>96%</td>
</tr>
<tr>
<td>All cause GE hospitalisation</td>
<td>75%</td>
<td>72%</td>
</tr>
</tbody>
</table>

Europe: **efficacy** summary

- Over the first 2 years of life, two doses of Rotarix™ provide high and sustained protection against:

<table>
<thead>
<tr>
<th>Rota-023 Study</th>
<th>VE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 year</td>
</tr>
<tr>
<td>Any RVGE</td>
<td>87%</td>
</tr>
<tr>
<td>Severe RVGE (Vesikari score ≥11)</td>
<td>96%</td>
</tr>
<tr>
<td>RVGE hospitalisations</td>
<td>100%</td>
</tr>
<tr>
<td>All-cause GE hospitalisation</td>
<td>75%</td>
</tr>
</tbody>
</table>

- Rotarix™ demonstrates high protection against any and severe RVGE caused by each of the five main circulating strains over the first 2 years of life
Rotarix™ Co administration

Co-administration with other vaccines
1–3
- Diphtheria-tetanus-whole cell pertussis (DTPw)
- Diphtheria-tetanus-acellular cell pertussis (DTPa)
- hepatitis B vaccine (HBV)
- Hib
- inactivated polio vaccine (IPV)
- oral polio vaccine (OPV)
- MenC
- Streptococcus pneumoniae

Rotavirus Effectiveness Data
Vaccine Terminology for Rotavirus

- **Immunogenicity** – level of antibody measured in blood - no known correlate of protection for rotavirus /the property enabling a substance to provoke an immune response, or the degree to which a substance possesses this property.

- **Vaccine Efficacy** – measure of effect in a clinical trial setting/ the reduction in the incidence of a disease among people who have received a vaccine compared to the incidence in unvaccinated people.

- **Vaccine Effectiveness** – measure of effect in a real life setting; also takes into consideration herd immunity.
Impact of RV vaccination in the USA


Parashar U, 27th ESPID Brussels Belgium 9–13 June, and personal communication.
Impact of RV vaccination in the USA

Percentage of RV-positive tests from NREVSS laboratories, by week of year

Parashar U, 27th ESPID Brussels Belgium 9–13 June, and personal communication.

ROT-2009-007 (DEC)
RV vaccination impact: Belgium (Flanders and Brussels)

- Rotarix™ introduced in Belgium at the end of 2006
- Weekly number of RV-positive laboratory diagnoses decreased by >50% in post-vaccine period (2007–2009) compared with pre-vaccine period (2005–2006)

Effectiveness of RV vaccines in Belgium 2006–2008

- RV vaccination implemented in Belgium in 2006
- A significant decrease in the weekly RV case rate (particularly during the winter disease peak) was seen in Flanders and Wallonia (Belgium’s two largest regions) after vaccine introduction.
Rotavirus Vaccine Safety
Rotavirus Vaccine Safety

- RotaShield and history of intussusception
- PCV1
RV vaccination history – *RotaShield™* and IS

- First RV vaccine licensed in the USA by FDA in 1998
  - Rhesus-based tetravalent reassortant vaccine (RRV-TV; RotaShield™)
  - Withdrawn in 1999 due to an epidemiological link with IS
  - Estimated risk between 1/10,000 and 1/32,000 vaccinees (age-dependent)

Striking temporal association of IS with *RotaShield™*²

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What is IS?

- Bowel obstruction:
  - One segment of intestine folds inside the other
  - Intestine wall swells and bleeds
- Most common cause of intestinal obstruction in children less than 2 years old:
  - 90% unknown cause (idiopathic)
  - 10% related to intestinal mass
  - Male infants aged 3–9 months most at risk
  - Death rare if access to treatment prompt

Symptoms, diagnosis and treatment of IS

- Symptoms:¹
  - Vomiting
  - Rectal bleeding or bloody stool
  - Abdominal pain
  - Shock
  - Fever
  - Progressive weakness, lethargy, dehydration
  - Diarrhoea
  - Constipation

- Diagnosis by sonography or radiography²

- Treatment:²
  - Diagnostic enema (75% of cases)
  - Surgical reduction (25% of cases)
    - ~10% of surgical cases require bowel resection

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Intussusception The risk of intussusception has been evaluated in a large safety trial conducted in Latin America and Finland where 63,225 infants were enrolled. No increased risk of intussusception in the ROTARIX™ group was observed and observed rates were comparable to the placebo group. Data are shown below in Tables 1 and 2. **Table 1**

**Rate of intussusception within 31 days after administration**

<table>
<thead>
<tr>
<th>Intussusception</th>
<th>ROTARIX™</th>
<th>Placebo</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=31,673</td>
<td>N=31,552</td>
<td></td>
</tr>
<tr>
<td>First dose</td>
<td>1</td>
<td>2</td>
<td>0.50 (0.07;3.80)</td>
</tr>
<tr>
<td>Second dose</td>
<td>5</td>
<td>5</td>
<td>0.99 (0.31;3.21)</td>
</tr>
</tbody>
</table>

CI: Confidence Interval **Table 2 Rate of intussusception up to one year of age**

<table>
<thead>
<tr>
<th>Intussusception</th>
<th>ROTARIX™</th>
<th>Placebo</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=10,159</td>
<td>N=10,010</td>
<td></td>
</tr>
<tr>
<td>First dose up to one year</td>
<td>4</td>
<td>14</td>
<td>0.28 (0.10;0.81)</td>
</tr>
</tbody>
</table>

In 11 other clinical studies (N =12,220) there were 7 cases of intussusception reported, 5 IS cases in HRV vaccinees and 2 cases in placebo recipient. It is to be highlighted that none of these studies were powered to compare the incidence of intussusception in the ROTARIX™ and placebo groups.
Intussusception Data with Rotarix™

- In clinical trials, no increase in intussusception was seen with Rotarix™

- Recent data from a post-marketing study in Mexico using Rotarix has been made available recently and the WHO and the FDA have updated the statements on their websites with this new information

- The US Product Monograph has been updated incorporated this new data from the Mexican PASS study

http://www.who.int/vaccine_safety/topics/rotavirus/rotarix_and_rotateq/intussusception_sep2010/en/
http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm133920.htm
On May 7, 2010 Health Canada issued an advisory indicating ongoing review of information regarding the presence of porcine circovirus (PCV-1/PCV-2).

While porcine circovirus is considered a contaminant in these vaccines, it is not known to cause illness in humans.

Health Canada stated that there is no evidence that the presence of PCV-1 or PCV2 in rotavirus vaccines poses a safety risk to patients and highlighted the fact that rotavirus vaccines have a strong safety record both in clinical trials and in clinical experience with millions of patients.
Health Economics of Rotavirus Vaccination
Diseases such as RVGE have many different types of cost

**Direct (medical) costs**
- Hospitalisations
- Medical care
- Pharmaceuticals
- and vaccines...

**Indirect (social) costs**
- Lost work-productivity for care givers
- Transport costs
- Cost of additional nappies
- Lost earnings from premature death

**Intangible costs**
- RVGE distressing for the child
- Distressing for the parents
- Disruption to family life

The direct and indirect costs of RVGE vary from country to country due to the pattern of disease and the nature of the medical system
# Physician Billing for Immunization

<table>
<thead>
<tr>
<th>Province</th>
<th>Well Baby Visit: GP</th>
<th>Well Baby Visit: Paed</th>
<th>First Dose</th>
<th>Additional Doses</th>
<th>Vaccination sole reason for visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>ON¹</td>
<td>$32.35</td>
<td>$40.30</td>
<td>$4.10</td>
<td>$4.10</td>
<td>$9.00</td>
</tr>
<tr>
<td>BC²</td>
<td>$32.59</td>
<td>-</td>
<td>$4.09</td>
<td>$4.09</td>
<td>-</td>
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<tr>
<td>SK³</td>
<td>$31.20</td>
<td>$32.10</td>
<td>$14.10</td>
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<td>-</td>
</tr>
<tr>
<td>MB⁴</td>
<td>$31.85</td>
<td>$43.05</td>
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</tr>
<tr>
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<td>$29.00</td>
<td>$8.00</td>
<td>$8.00</td>
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</tr>
<tr>
<td>NS⁶</td>
<td>$13.00</td>
<td>$8.00</td>
<td>$6.00</td>
<td>$6.00</td>
<td>-</td>
</tr>
</tbody>
</table>

## Total Cost of Vaccination

<table>
<thead>
<tr>
<th>Study</th>
<th>Family Practices</th>
<th>Pediatric Practices</th>
<th>Public Health Dept. / Nursing Services</th>
<th>School-based Programs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glazner et al. (Pediatric Practices)¹</td>
<td>$7.57</td>
<td>$10.67</td>
<td>$5.41</td>
<td></td>
</tr>
<tr>
<td>Glazner et al. (Different Provider Types)²</td>
<td></td>
<td>$9.90-$11.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bauch et al.³</td>
<td></td>
<td>$36.48</td>
<td>Or $18.46 if administered with other vaccines</td>
<td>$10.00 Or $3.80 if administered with other vaccines</td>
</tr>
</tbody>
</table>

**Serotype coverage matters - Rotarix™ protects against a broad range of RV types**

<table>
<thead>
<tr>
<th>Source</th>
<th>VE [95% CI] against severe RVGE 1-year follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G1</td>
</tr>
<tr>
<td>Ruiz-Palacios et al. 2006¹</td>
<td>Latina</td>
</tr>
<tr>
<td></td>
<td>[74;98]</td>
</tr>
<tr>
<td>Tregnaghi et al. 2008²</td>
<td>Latina</td>
</tr>
<tr>
<td></td>
<td>[&lt;0;100]</td>
</tr>
<tr>
<td>Neuzil et al. 2009³</td>
<td>Africa</td>
</tr>
<tr>
<td></td>
<td>[30;82]</td>
</tr>
<tr>
<td>Vesikari et al. 2007⁴</td>
<td>Europe</td>
</tr>
<tr>
<td></td>
<td>[86;100]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source</th>
<th>VE [95% CI] against severe RVGE 2-year follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G1</td>
</tr>
<tr>
<td>Linhares et al. 2008⁵</td>
<td>Latina</td>
</tr>
<tr>
<td></td>
<td>[64;92]</td>
</tr>
<tr>
<td>Phua et al. 2009⁶</td>
<td>Asia</td>
</tr>
<tr>
<td></td>
<td>[81;100]</td>
</tr>
<tr>
<td>Vesikari et al. 2007⁴</td>
<td>Europe</td>
</tr>
<tr>
<td></td>
<td>[90;99]</td>
</tr>
</tbody>
</table>

*Pooled data for G3, G4 and G9. References in speaker notes.*
Health Economics of Rotavirus Vaccination
Diseases such as RVGE have many different types of cost.

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The direct and indirect costs of RVGE vary from country to country due to the pattern of disease and the nature of the medical system.

RV vaccination is recommended globally by the World Health Organization\(^1\)

In 2009, SAGE recommended the global inclusion of RV vaccination into **all** national immunisation programmes for all infants

“the introduction of the vaccine is **strongly** recommended in regions where diarrhoeal deaths account for \(\geq 10\%\) of mortality among children aged \(<5\) years”

Countries with rotavirus vaccination in UMV

- **Countries with Rotateq UMV**
  - USA* (2006)

- **Countries with Rotarix UMV**
  - Belgium (2006)
  - Austria* (2006)
  - Luxemburg (2007)
  - Germany# (2008)
  - Finland* (2009)
  - **Latvia (2011 planned)**

- **Countries with both products used**
  - Morocco (2010)
  - Nigeria (Akwa Ibom only, 2009)

- **Countries without UMV**
  - Australia* (2006)
  - Bahrain, Qatar, Oman, Russia
  - South Africa (2008)

---

**Rotavirus UMV in GAVI countries**: Latina: Nicaragua (Rotateq), Guyana (Rotateq), Bolivia (Rotarix), Honduras (Rotarix), Colombia, Paraguay (2010 planned)

**ROT-2009-007 (DEC)**
NACI recommendations

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). The vaccination series should be completed by 8 months (8 months plus 0 days).

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 first dose should be given between 6 weeks (6 weeks and 0 days) and up to 15 weeks (14 weeks plus 6 days). The vaccination series should be completed by 8 months (8 months plus 0 days).

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.

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.
Liquid formulation of Rotarix™ available from 2008¹
  - Simplified administration
    - Ready to use – no reconstitution required
    - Prefilled oral applicator
  - Lower shipping and storage costs due to space-saving packaging²
  - Higher manufacturing capacity²

Storage and Stability

- Store in a refrigerator (2°C to 8°C).
- Do not freeze.
- In order to protect the vaccine from light it is recommended that the vaccine is stored in the original package.
- The expiry date of the vaccine is indicated on the label and packaging.
Special Handling Instructions

- The vaccine is presented as a clear, colorless liquid, free of visible particles, for oral administration.
- The vaccine is ready to use (no reconstitution or dilution is required).
- The vaccine is to be administered orally without mixing with any other vaccines or solutions.
- The vaccine should also be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, discard the vaccine.
- Any unused vaccine or waste material should be disposed of in accordance with local requirements.
- This medicinal product must not be mixed with other medicinal products.
Administration

Remove the protective tip cap from the oral applicator

This vaccine is for **oral administration only**. The child should be seated in a reclining position. Administer orally (i.e. into the child’s mouth towards the inner cheek) the entire content of the oral applicator.

**Do not inject**
ROTARIX™ is available in an oral applicator (Type 1, Ph. Eur.) with a plunger stopper (butyl rubber) in pack sizes of 1, 5, 10, 25, 50 or 100.
Packaging – Peel & Stick Label

Rotarix

TM/MC

Glanzmann's disease

LOT: EXP: LOT: EXP:

456025

NLT 10^6.0 CCID50, 6 weeks and up. Single dose. See PI. Do not freeze.

Pas moins de 10^6.0 DICT50, 6 semaines et plus. Dose unique. Voir notice.

Ne pas congeler.

ORAL / ADMINISTRATION ORALE
ROTARIX™ is available in an oral applicator (Type 1, Ph. Eur.) with a plunger stopper (butyl rubber) in pack sizes of 1, 5, 10, 25, 50 or 100.
Countries with rotavirus vaccination in UMV

- **Countries with Rotateq UMV**: Belgium (2006), Austria* (2006), Luxembourg (2007), Germany* (2008), Finland* (2009), Latvia (2011 planned)
- **Countries with Rotarix UMV**: Morocco (2010 planned)
- **Both products used**: Nigeria (Akwa Ibom only, 2009), Paraguay (2010 planned)

**Rotavirus UMV in GAVI countries**: Latina: Nicaragua (Rotateq), Guyana (Rotateq), Bolivia (Rotarix), Honduras (Rotarix)
Rotarix™
Clinical Papers
Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study

T Vesikari, A Karvonen, R Prymula, V Schuster, J C Tejedor, R Cohen, F Meurice, H H Han, S Damaso, A Bouckenooghe

Summary

Background We aimed to assess the efficacy of the oral live attenuated human rotavirus vaccine Rotarix (RIX4414) for prevention of rotavirus gastroenteritis in European infants during their first 2 years of life.

Methods 3994 study participants were enrolled from six countries and were randomly assigned two oral doses of either RIX4414 (n=2646) or placebo (n=1348), which were coadministered with the first two doses of specific childhood vaccinations. Follow-up for gastroenteritis episodes was undertaken from 2 weeks post-dose two through the two consecutive rotavirus seasons following vaccinations (combined efficacy follow-up period; mean duration 17 months [SD 1·6]). Our primary endpoint was vaccine efficacy against rotavirus gastroenteritis of any severity during the first efficacy follow-up period (2 weeks post-dose two to the end of the first rotavirus season). Stool specimens obtained during gastroenteritis episodes were tested for rotavirus by ELISA and typed by RT-PCR. Episodes scoring 11 or greater on the 20-point Vesikari scale were classified as severe. Analysis was according to protocol. This study is registered with ClinicalTrials.gov, number NCT00140686 (eTrack102247).

Findings 120 infants were excluded from the according-to-protocol analysis. During the first efficacy follow-up period (mean duration 5·7 months [SD 1·2]), 24 of 2572 infants allocated RIX4414 versus 94 of 1302 given placebo had rotavirus gastroenteritis episodes of any severity, resulting in a vaccine efficacy of 87·1% (95% CI 79·6–92·1; p<0·0001). For the combined efficacy follow-up period (2 weeks post-dose two to the end of the first rotavirus season), 24 of 4774 infants given RIX4414 versus 94 of 2604 given placebo had rotavirus gastroenteritis episodes of any severity, resulting in vaccine efficacy of 87·0% (95% CI 79·6–92·1; p<0·0001). For the combined efficacy follow-up period, vaccine efficacy against severe rotavirus gastroenteritis was 90·4% (85·1–94·1; p<0·0001), for admission owing to rotavirus gastroenteritis 96·0% (83·8–99·5; p<0·0001), and significant protection against severe rotavirus gastroenteritis was shown. Findings of the safety trial in 63 225 infants showed no increased risk of intussusception in vaccinated infants versus placebo.

Interpretation In a European setting, two doses of RIX4414 coadministered with childhood vaccines provided high protection against any and severe rotavirus gastroenteritis, with an overall reduction of admissions for gastroenteritis over two consecutive rotavirus epidemic seasons.

Introduction

Worldwide, an estimated 611 000 children die every year from rotavirus disease, mainly in low-income countries.1 In the European Union, the annual burden of rotavirus disease is estimated at more than 200 deaths, over 87 000 admissions, and almost 700 000 outpatient visits in children younger than 5 years of age.1 An oral live attenuated human rotavirus vaccine Rotarix (RIX4414) containing the G1P[8] strain, derived from the 89-12 parent candidate,3–5 has been developed by GlaxoSmithKline (GSK) Biologicals. Two doses of the vaccine tested at different concentrations in phase II clinical trials were immunogenic, well-tolerated, and protective against rotavirus gastroenteritis.6–9 In a multicentre phase III trial in Latin America (n=17 867), 85% vaccine efficacy was noted in the first efficacy follow-up period (from 2 weeks post-dose two until 1 year of age) against severe rotavirus gastroenteritis and rotavirus-related admissions, reaching 100% efficacy against the most severe episodes.10 Findings of the safety trial in 63 225 infants showed no increased risk of intussusception in vaccinated infants versus placebo.11

We aimed to investigate the efficacy of RIX4414 at the titre level and composition corresponding to the licensed Rotarix vaccine when administered concomitantly with other routine childhood vaccines, following typical European routine immunisation schedules. We report vaccine efficacy recorded during follow-up of infants over two consecutive rotavirus epidemic seasons after vaccination.

Methods

Participants

We undertook a phase IIIb, double-blind, randomised, placebo-controlled trial in six European countries. The protocol, amendments, and consent forms were reviewed and approved by the independent ethics committee for every centre and country. The study was done according to good clinical practice guidelines and the 1996 version of the Declaration of Helsinki.

We enrolled healthy infants aged 6–14 weeks who weighed more than 2000 g at birth and whose parent or legal guardian signed an informed consent form. Infants were not eligible for the study if they had an acute disease at the time of enrolment, a history of chronic administration of immunosuppressants since birth, had received
any vaccines or treatments prohibited by the protocol, or had any disorders or illnesses excluded by the protocol (for exclusion criteria see webpanel).

**Procedures**

GSK Biologicals provided vaccine supplies that were numbered with a computer-generated randomisation list. Randomisation was done by a central internet randomisation system. Infants were randomly allocated in a 2/1 ratio two doses of either RIX4414 or placebo. Treatment allocation remained concealed from investigators and the parents of participating infants throughout the study.

The Rotarix (RIX4414) vaccine contained $10^{6.5}$ median cell culture infectious dose of the vaccine strain per vaccine dose. The placebo had the same constituents as the active vaccine but without the vaccine virus and was identical in appearance to the vaccine. The lyophilised vaccine and placebo were reconstituted with the supplied liquid calcium carbonate buffer before oral administration. Infants received the two oral doses of either RIX4414 or placebo according to a schedule of 0, 1, or 2 months at the same time as the first two doses of their primary childhood vaccination series, respecting national immunisation calendars. Vaccination was postponed if the baby either had a temperature of 37.5°C or greater (axillary) or of 38.0°C or greater (rectal) or had gastroenteritis within 7 days before planned vaccination.

Concomitant vaccines provided free of charge were: diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus and *Haemophilus influenzae* type b (Infanrix hexa; GSK Biologicals, Rixensart, Belgium); diphtheria-tetanus-acellular pertussis-inactivated poliovirus and *Haemophilus influenzae* type b (Infanrixiquinta; GSK Biologicals); seven-valent pneumococcal polysaccharide conjugate vaccine (Prevenar; Wyeth Pharmaceuticals, Maidenhead, UK); and meningococcal group C conjugate vaccine (Meningitec; Wyeth Pharmaceuticals). Infants in every country received three doses of Infanrix hexa, except in France, where Infanrixiquinta was given at dose two. Babies in Spain received three doses of Meningitec, and infants in France and Germany received three doses of Prevenar.

We did active surveillance for gastroenteritis episodes and serious adverse events from the day of the first vaccine or placebo dose (Sept 8, 2004) until the follow-up visit at the end of the second rotavirus epidemic season (Aug 10, 2006). We defined gastroenteritis as diarrhoea characterised by at least three looser than normal stools within a day, with or without vomiting. Two occurrences of gastroenteritis were classified as separate episodes if 5 or more symptom-free days fell between them. We analysed all gastroenteritis episodes reported until the follow-up visit. Study staff contacted parents every week, starting from first vaccination until the end of May, 2005, and from December, 2005, until the end of May, 2006. Contacts every 2 weeks took place from June, 2005, until December, 2005, and from June, 2006, until the end of the study (Aug 10, 2006). Parents were asked to collect a stool sample during every gastroenteritis episode, preferably within 7 days of onset. During every episode, we asked parents to record in a daily diary card the number of looser than normal stools, axillary or rectal temperature, number of vomiting episodes, any rehydration or other medication, contact with medical personnel, and emergency room contact or visit; or admission). We used the information from the diary card to assess severity with the

![Figure 1: Trial profile](Image)
Vesikari 20-point scale. A score less than 7 was defined prospectively as mild, a score of 7–10 as moderate, and a score of 11 or more as severe.

We tested for the presence of rotavirus in stool specimens with the ELISA test RotaClone (Meridian Bioscience, Cincinnati, OH, USA) at GSK Biologicals, Rixensart, Belgium—a test also used in several previous studies. Rotavirus-positive samples were analysed by RT-PCR and reverse hybridisation assay at Delft Diagnostic Laboratory, Delft, Netherlands, to ascertain the G and P types and discriminate between vaccine virus and wild-type G1 rotavirus. We deemed a gastroenteritis episode to be attributable to rotavirus if a rotavirus strain was identified in a stool sample collected during the episode or within 7 days after resolution of symptoms, or before the next episode if fewer than 7 days had fallen between the end of one episode and the start of the next, in cases of multiple episodes. We analysed prevaccination seropositivity for anti-rotavirus IgA antibody in an immunogenicity and reactogenicity subset of infants (n=1404) with an in-house ELISA test (cutoff 20 U/mL), adapted from a published method.

### Statistical analysis
The primary endpoint of our study was vaccine efficacy against rotavirus gastroenteritis of any severity during the first efficacy follow-up period.

We did efficacy analysis of the according-to-protocol cohort, which included participants who completed the full two-dose vaccination course and adhered to the protocol. Efficacy analysis was undertaken for three periods: first, from 2 weeks post-dose two (Nov 3, 2004) up to the visit at the end of the first rotavirus epidemic season (Sept 7, 2005); second, from the visit at the end of the first rotavirus epidemic season (Sept 7, 2005) to the visit at the end of the second rotavirus epidemic season (Aug 10, 2006); and third, the combined period, from 2 weeks post-dose two up to the visit at the end of the second rotavirus epidemic season. Only gastroenteritis episodes in which wild-type rotavirus (ie, other than the vaccine strain) was identified in a stool specimen were included in the efficacy analysis. We used the total vaccinated cohort to calculate vaccine efficacy starting from the first dose onwards, and we included all participants who received at least one dose. Data analysis was done at GSK Biologicals, according to the reporting and analysis plan established for this study.

This trial was designed with the assumption that rate of rotavirus gastroenteritis during the first efficacy follow-up period in the placebo group was 10% and true vaccine efficacy was 70%. Taking into account that 15% of participants could be non-assessable, we calculated that a sample size of 3990 infants would provide at least 90% power to detect a lower limit of the 95% CI for vaccine efficacy above 50%.

Further, the number of rotavirus gastroenteritis episodes (any severity, severe, leading to admission, and needing medical attention) per 1000 infant-years was calculated by group. Vaccine efficacy (95% CI) was ascertained with the formula: 1-incidence of rotavirus gastroenteritis in the vaccine group/incidence of rotavirus gastroenteritis in the placebo group. We derived 95% CIs for vaccine efficacy from the exact CI for Poisson rate ratio. When

<table>
<thead>
<tr>
<th>Country (n [%])</th>
<th>RIX4414 (n=2572)</th>
<th>Placebo (n=1302)</th>
<th>Total (n=3874)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Czech Republic</td>
<td>193 (8%)</td>
<td>97 (7%)</td>
<td>290 (7%)</td>
</tr>
<tr>
<td>Finland</td>
<td>1893 (74%)</td>
<td>956 (73%)</td>
<td>2849 (74%)</td>
</tr>
<tr>
<td>France</td>
<td>95 (4%)</td>
<td>50 (4%)</td>
<td>145 (4%)</td>
</tr>
<tr>
<td>Germany</td>
<td>179 (7%)</td>
<td>94 (7%)</td>
<td>273 (7%)</td>
</tr>
<tr>
<td>Italy</td>
<td>15 (1%)</td>
<td>10 (1%)</td>
<td>25 (1%)</td>
</tr>
<tr>
<td>Spain</td>
<td>197 (8%)</td>
<td>95 (7%)</td>
<td>292 (8%)</td>
</tr>
</tbody>
</table>

Table 1: Demographic characteristics of according-to-protocol cohort (pooled countries)

Figure 2: Seasonal distribution of rotavirus gastroenteritis (RVGE) episodes reported during the combined efficacy follow-up period (according-to-protocol cohort for efficacy)
more than one G type was isolated for an episode, the child was counted in every G-type category for analysis of vaccine efficacy by G type. We judged p<0·05 significant.

This study is registered with ClinicalTrials.gov, number NCT00140686 (e-Track102247).

Role of the funding source
This study was funded by GSK Biologicals. The sponsor was involved in all study stages, from study design to data analysis and writing of the report, and did rotavirus ELISA testing. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Between Sept 8, 2004, and Feb 1, 2005, 3994 infants were enrolled into the study (figure 1), from the Czech Republic (n=299), Finland (2890), France (146), Germany (289), Italy (25), and Spain (345). All enrolled infants received the first dose of vaccine or placebo and 3959 (99%) received both doses. The two treatment arms were similar for demographic characteristics in terms of age, sex, race, height, and weight (table 1). The study population was predominantly white. One infant received dose one of RIX4414 early (at age 5 weeks) and 32 infants (1%) received dose two of the vaccine or placebo after the recommended age of 24 weeks (at age 25–30 weeks). Of 3994 infants enrolled and vaccinated, 3883 (97%) completed the follow-up visit at the end of the second rotavirus epidemic season. Annual rotavirus epidemic seasons were predefined from December to the end of May.3 3271 infants (82%) received the first dose of RIX4414 or placebo before December, 2004, and 723 (18%) received the dose during the first rotavirus epidemic season.

From administration of dose one until the follow-up visit at the end of the first rotavirus epidemic season, a total of 1446 episodes of gastroenteritis were reported in 1156 infants, with rotavirus detected in 130 episodes. In the according-to-protocol cohort, 1060 gastroenteritis episodes were reported during the first efficacy follow-up period (mean duration 5·7 months [SD 1·2]). Stool analysis results were available for 962 (91%) of these episodes. Unavailable results—attributable to insufficient quantity of stool specimens or specimen not collected—were distributed equally between the treatment arms. Rotavirus was detected in stool samples from 118 episodes of gastroenteritis: G1P[8] wild-type (n=49), G2P[4] (7), G3P[8] (6), G4P[8] (15), G9P[8] (40), and both G1 wild-type and G4 type (1).

In the second efficacy follow-up period (mean duration 12 months [SD 0·8]), a total of 1489 episodes of gastroenteritis were reported in 1157 children in the according-to-protocol cohort. Stool analysis results were available for 1308 (88%) of these episodes. Similar to the first efficacy period, unavailable results were distributed equally between groups. Rotavirus was detected in stool samples from 171 episodes of gastroenteritis: G1P[8] wild-type (n=54), G2P[4] (22), G3P[8] (7), G4P[8] (8), G9P[8] (67), G12P[8] (2), G1 wild-type and G9 type (1), both G2 and G9 type (1), both G1 and G2 type (1), G1 wild-type and non-typable P type (1), non-typable G type (2), and non-typable G and P type (5).

No infant was detected with more than one episode of wild-type rotavirus gastroenteritis during the combined efficacy follow-up period (mean duration 17 months [SD 1·6]). Figure 2 shows seasonal distribution of rotavirus gastroenteritis episodes.

Table 2 shows vaccine efficacy data for any and severe rotavirus gastroenteritis episodes in the according-to-protocol cohort. In the first efficacy follow-up period, 24 of 2572 infants allocated RIX4414 versus 94 of 1302 assigned placebo had rotavirus gastroenteritis episodes of any severity caused by the circulating wild-type rotavirus, resulting in a vaccine efficacy of 87·1% (95% CI 79·6–92·1; p<0·0001). Five episodes of severe rotavirus gastroenteritis arose in vaccine recipients versus 60 in placebo. Over the two consecutive rotavirus seasons (combined efficacy follow-up period), vaccine efficacy was 78·9% (72·7–83·8; p<0·0001) against any and 90·4% (85·1–94·1; p<0·0001) against severe episodes of rotavirus gastroenteritis.

Although this study was not powered to assess vaccine efficacy for every individual country, post-hoc analysis for Finland (73% of infants) showed that the 95% CIs for vaccine efficacy were 74·3–85·6 against rotavirus gastroenteritis of any severity and 85·4–94·5 against severe rotavirus gastroenteritis during the combined efficacy follow-up period. Other participating European countries (pooled cohort, 1025 infants) had 95% CIs for vaccine efficacy of 33·3–83·1 against any and 47·4–97·5 against severe rotavirus gastroenteritis.

<table>
<thead>
<tr>
<th>RIX4414</th>
<th>Placebo</th>
<th>Vaccine efficacy (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Incidence (episodes per 1000 infants per year)</td>
<td>n</td>
<td>Incidence (episodes per 1000 infants per year)</td>
</tr>
<tr>
<td>Any severity</td>
<td>24</td>
<td>19.7</td>
<td>94</td>
</tr>
<tr>
<td>Severe</td>
<td>5</td>
<td>4.1</td>
<td>60</td>
</tr>
<tr>
<td>Admission</td>
<td>0</td>
<td>0.0</td>
<td>12</td>
</tr>
<tr>
<td>Medical attention</td>
<td>10</td>
<td>8.2</td>
<td>62</td>
</tr>
<tr>
<td>Second efficacy follow-up period (RIX4414, n=2572; placebo, n=1302)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any severity</td>
<td>61</td>
<td>24.4</td>
<td>110</td>
</tr>
<tr>
<td>Severe</td>
<td>19</td>
<td>7.6</td>
<td>67</td>
</tr>
<tr>
<td>Admission</td>
<td>2</td>
<td>0.8</td>
<td>13</td>
</tr>
<tr>
<td>Medical attention</td>
<td>31</td>
<td>12.4</td>
<td>66</td>
</tr>
<tr>
<td>Combined efficacy follow-up period (RIX4414, n=2572; placebo, n=1302)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any severity</td>
<td>85</td>
<td>22.9</td>
<td>204</td>
</tr>
<tr>
<td>Severe</td>
<td>24</td>
<td>6.5</td>
<td>127</td>
</tr>
<tr>
<td>Admission</td>
<td>2</td>
<td>0.5</td>
<td>25</td>
</tr>
<tr>
<td>Medical attention</td>
<td>41</td>
<td>11.0</td>
<td>128</td>
</tr>
</tbody>
</table>

Table 2: Vaccine efficacy against any and severe rotavirus gastroenteritis, admission, and medical attention (according-to-protocol cohort)
against severe rotavirus gastroenteritis, which did not differ significantly from the Finnish data.

Vaccine efficacy analysed in the period after dose one until the follow-up visit at the end of the first rotavirus epidemic season (total vaccinated cohort) was 87.3% (95% CI 80.3–92.0) against any rotavirus gastroenteritis episode and 96.0% (95% CI 89.8–99.6) against severe episodes. Vaccine efficacy for the period after dose one until the follow-up visit at the end of the second rotavirus epidemic season (total vaccinated cohort) was 79.4% (95% CI 73.4–84.1) against any rotavirus gastroenteritis episode and 96.0% (95% CI 90.2–98.8) against severe episodes.

Table 3: Vaccine efficacy against any and severe rotavirus gastroenteritis according to detected rotavirus G-type category

<table>
<thead>
<tr>
<th>G type</th>
<th>Any rotavirus gastroenteritis</th>
<th>Severe rotavirus gastroenteritis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RIX4414</td>
<td>Placebo</td>
</tr>
<tr>
<td>G1*</td>
<td>4 (2)</td>
<td>46 (3)</td>
</tr>
<tr>
<td>G3</td>
<td>1 (0)</td>
<td>5 (0)</td>
</tr>
<tr>
<td>G4</td>
<td>3 (0)</td>
<td>33 (10)</td>
</tr>
<tr>
<td>G9</td>
<td>13 (0.5)</td>
<td>27 (2.1)</td>
</tr>
<tr>
<td>G2†</td>
<td>3 (0)</td>
<td>4 (0.3)</td>
</tr>
</tbody>
</table>

| G1*    | 2 (0.1) | 28 (2.2) | 96.4% (85.7–99.6) | <0.0001 | 2 (0.1) | 29 (2.2) | 96.5% (86.2–99.6) | <0.0001 |
| G3     | 0 (0.0) | 5 (0.4)  | 100% (44.8–100)  | 0.0043  | 1 (0.0) | 3 (0.2)  | 83.1% (99.9–99.7)| 0.1136  |
| G4     | 0 (0.0) | 7 (0.5)  | 100% (64.9–100)  | 0.0005  | 1 (0.0) | 4 (0.3)  | 87.3% (99.9–99.7)| 0.0466  |
| G9     | 2 (0.1) | 19 (1.5)| 94.7% (77.9–99.4) | <0.0001 | 11 (0.4)| 25 (1.9)| 77.7% (53.0–90.1)| <0.0001 |
| G2†    | 1 (0.0) | 2 (0.2)  | 74.7% (<0–99.6)  | 0.2629  | 1 (0.0) | 5 (0.4)  | 89.9% (94.9–99.6)| 0.0185  |

Participants with episodes in which more than one isolated G type was identified were counted in every relevant detected rotavirus G-type category. *All G1 types isolated were wild-type rotavirus. †Rotavirus gastroenteritis due to G2 type has been detected in various centres.

Table 4: Vaccine efficacy against all-cause severe gastroenteritis and admission (according-to-protocol cohort for efficacy)

<table>
<thead>
<tr>
<th>G type</th>
<th>RIX4414</th>
<th>Placebo</th>
<th>Vaccine efficacy (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>First efficacy follow-up period (RIX4414, n=2572; placebo, n=1302)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe gastroenteritis</td>
<td>116 (5%)</td>
<td>123 (9%)</td>
<td>52.3% (38.0–66.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Admission</td>
<td>11 (1%)</td>
<td>22 (2%)</td>
<td>74.7% (45.5–88.9)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Second efficacy follow-up period (RIX4414, n=2554; placebo, n=1294)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe gastroenteritis</td>
<td>149 (6%)</td>
<td>153 (12%)</td>
<td>50.7% (37.8–60.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Admission</td>
<td>18 (1%)</td>
<td>26 (2%)</td>
<td>64.9% (33.5–81.9)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Combined efficacy follow-up period (RIX4414, n=2572; placebo, n=1302)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe gastroenteritis</td>
<td>256 (10%)</td>
<td>257 (20%)</td>
<td>49.6% (39.8–57.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Admission</td>
<td>27 (1%)</td>
<td>48 (4%)</td>
<td>71.5% (53.4–82.9)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Table 3 shows vaccine efficacy data for any and severe rotavirus gastroenteritis episodes according to detected rotavirus G types for the according-to-protocol cohort. During the first efficacy follow-up period, significant protection was recorded against G1, G3, G4, and G9 rotavirus types for any and severe episodes of rotavirus-related gastroenteritis. Vaccine efficacy against any and severe rotavirus gastroenteritis caused by all rotavirus G types was noted during the combined efficacy follow-up period.

Over the combined efficacy follow-up period, a significant reduction of about 50% in episodes of severe gastroenteritis of any cause was noted. Further, a 71.5% decrease was recorded in admissions for all-cause gastroenteritis (table 4).

During the entire study period, serious adverse events were reported in 290 of 2646 vaccine recipients (11%) and 176 of 1348 infants given placebo (13%). One case of intussusception arose 8 days after the second dose of RIX4414. The child underwent surgery and recovered well. Two cases of intussusception (one in each group) were recorded during the second rotavirus season after vaccination.

Discussion

Our findings confirm the high incidence of rotavirus gastroenteritis during the first 2 years of life and, hence, a need for long-term protection induced by rotavirus vaccination. The human rotavirus vaccine RIX4414 showed high and sustained efficacy against severe rotavirus gastroenteritis and admission for rotavirus gastroenteritis. Efficacy against rotavirus gastroenteritis of any severity was high in the first year after vaccination but fell in the second year, which is in line with previously reported data for other rotavirus vaccines.8,9,10 Nevertheless, during the combined efficacy follow-up period, vaccine efficacy was well maintained. The high vaccine efficacy in the first year might be attributable to administration of RIX4414 shortly before the beginning of the rotavirus epidemic season,29 but sustained efficacy through two rotavirus seasons is probably independent of this timing, giving a realistic picture of the performance of the vaccine.

Sustained significant vaccine efficacy against G1 and non-G1 rotavirus types was noted over the two rotavirus seasons. Efficacy against G9 (representative of a non-G1 type) is especially important because this G type has become frequent in Europe and elsewhere.21–23 Evidence that G type is not the only important factor for protective immunity has been reported previously in various studies of rotavirus vaccine.30,31 Moreover, data from different RIX4414 clinical trials32,33,34,35 have shown that the vaccine provides good and sustained homotypic protection against all encountered non-G1 strains (G3, G4, G9) sharing the same P type (P[8]). Our findings lend support to these data again over two consecutive rotavirus seasons. The noted variability in protection against G9 type during the first and second rotavirus season follow-up period does not contradict the finding, since the 95% CIs of vaccine efficacy largely overlap.

The vaccine efficacy against G2P[4] rotavirus strain is of particular interest, because this strain is heterotypic to the RIX4414 vaccine strain, according to G and P types. Our findings show that RIX4414 protects over two consecutive rotavirus epidemic seasons against any and severe rotavirus gastroenteritis caused by the G2 type. Vaccine efficacy for G2 rotavirus gastroenteritis of any severity was lower compared with other G types, whereas efficacy against severe G2 rotavirus gastroenteritis was as high as for other rotavirus types. In previous work39,40 circulation of G2P[4] strains was low, which is in line with epidemiological findings.21–23 Therefore, an integrated analysis of vaccine efficacy39 (follow-up of one rotavirus season or until age 1 year) against the G2P[4] strain was done. These results accord with our clinical evidence of protection against rotavirus gastroenteritis due to G2 type.

The protection seen against any and severe rotavirus gastroenteritis between dose one and dose two is an important finding, apparently related to good uptake of RIX4414 after the first dose.6 The benefit of early protection could be especially relevant when vaccine is given during a rotavirus epidemic season.

In a large Latin American phase III study of RIX4414 in 14,286 children followed up for 2 years, two doses of vaccine prevented 39% of admissions related to acute gastroenteritis of any cause (mean duration of follow-up, 20 months [SD 1·6]). In our study, RIX4414 prevented 72% of all admissions attributable to acute all-cause gastroenteritis during two consecutive rotavirus epidemic seasons, showing the importance of rotavirus as a causative agent of severe gastroenteritis and the potential effect of rotavirus vaccination on all severe paediatric gastroenteritis cases in Europe.

The recorded case of intussusception at 4 months of age—8 days after administration of dose two—was an isolated event and does not, as such, allow for any conclusions. Two other cases of intussusception were reported remote from vaccination during the second rotavirus season. Findings of a large-scale safety trial of RIX4414 in 63,225 infants, with vaccinations at 2 and 4 months of age, did not indicate an increased risk for intussusception.39

In conclusion, our study findings show that, if integrated into routine infant immunisation schedules, vaccination with RIX4414 could result in significant reduction not only of rotavirus disease burden but also of severe paediatric gastroenteritis during the first 2 years of life.

Contributors

All authors participated in design or implementation of the study and analysis and interpretation of findings. TV, AK, RP, AB, SD, and FM were involved in all phases of the study. AB, FM, and HHH led the clinical team at GSK Biologicals. SD did statistical analysis. TV was the principal investigator for Finland and coordinating principal investigator for the study. AK was an investigator in Finland. RC was the principal investigator for France. RP was the principal investigator in the
Czech Republic. JCT was the principal investigator for Spain. VS was the principal investigator for Germany. The study report was written by Dipl.-Ing. Shringmankar (GSK Biologics).

Conflicts of interest statement
FM, HHH, SD, and AB are employees of GSK Biologics. FM owns Dipali Shirgaonkar (GSK Biologicals).

References
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


Summary

Background Peak incidence of rotavirus gastroenteritis is seen in infants between 6 and 24 months of age. We therefore aimed to assess the 2-year efficacy and safety of an oral live attenuated human rotavirus vaccine for prevention of severe gastroenteritis in infants.

Methods 15183 healthy infants aged 6–13 weeks from ten Latin American countries randomly assigned in a 1 to 1 ratio to receive two oral doses of RIX4414 or placebo at about 2 and 4 months of age in a double-blind, placebo-controlled phase III study were followed up until about 2 years of age. Primary endpoint was vaccine efficacy from 2 weeks after dose two until 1 year of age. Treatment allocation was concealed from investigators and parents of participating infants. Efficacy follow-up for gastroenteritis episodes was undertaken from 2 weeks after dose two until about 2 years of age. Analysis was according to protocol. This study is registered with ClinicalTrials.gov, number NCT00140673 (eTrack444563–023).

Findings 897 infants were excluded from the according-to-protocol analysis. Fewer cases (p<0.0001) of severe rotavirus gastroenteritis were recorded for the combined 2-year period in the RIX4414 group (32 [0.4%] of 7205; 95% CI 0.3–0.6) than in the placebo group (161 [2.3%] of 7081; 1.9–2.6), resulting in a vaccine efficacy of 80.5% (71.3–87.1) to 82.1% (64.6–91.9) against wild-type G1, 77.5% (64.7–86.2) against pooled non-G1 strains, and 80.5% (67.9–88.8) against pooled non-G1 P[8] strains. Vaccine efficacy for hospital admission for rotavirus gastroenteritis was 83.0% (73.1–89.7) and for admission for diarrhoea of any cause was 39.3% (29.1–48.1). No cases of intussusception were reported during the second year of follow-up.

Interpretation Two doses of RIX4414 were effective against severe rotavirus gastroenteritis during the first 2 years of life in a Latin American setting. Inclusion of RIX4414 in routine paediatric immunisations should reduce the burden of rotavirus gastroenteritis worldwide.

Funding GlaxoSmithKline.

Introduction

Rotavirus is the leading recognised cause of severe gastroenteritis in infants and young children worldwide. Estimates suggest that it accounts for more than a third of all diarrhoea-related hospital admissions and causes about 527000 deaths per year in children aged less than 5 years, with most deaths occurring in developing countries. Vaccination is thought to be the most effective approach to reduce the worldwide burden associated with rotavirus gastroenteritis, and the development of a safe and effective vaccine has been given priority by WHO. Although infections can arise early in life (ie, in infants aged <6 months), epidemiological studies in Latin America showed that the peak incidence of rotavirus gastroenteritis occurred between 6 and 24 months of age. Therefore, early and persistent vaccine-induced protection is clearly needed during the first 2 years of life.

A classification system has been established for group A rotavirus serotypes on the basis of outer surface VP7 glycoprotein and the protease-sensitive VP4 protein, defining the G and P types, respectively. At least 15 G types and 26 P types have thus far been identified; however, the five worldwide prevalent VP7 and VP4 combinations include G1, G3, G4, and G9 with P[8] strains and G2 P[4] strains. A live attenuated human rotavirus vaccine RIX4414 (Rotarix, GlaxoSmithKline Biologicals, Rixensart, Belgium) derived from the most common circulating wild-type strain G1P[8], has now been licensed in many parts of the world. Its efficacy during the first 2 years of life in a large European phase III study was 90.4% (95% CI 85.1–94.1) against severe rotavirus gastroenteritis and...
96.0% (83.8–99.5) against admission. For severe illness, high vaccine efficacy was shown against the most common virus types: 96.4% (90.4–99.1) for G1, 93.7% (52.8–99.9) for G3, 95.4% (68.3–99.9) for G4, 85.0% (71.7–92.6) for the emerging G9 type, and 85.5% (24.0–98.5) for G2.11 In a large Latin American study,12 two oral doses of RIX4414 given at about 2 and 4 months of age proved to have a good safety profile and were highly efficacious for prevention of rotavirus gastroenteritis in healthy infants during the first year of life. Vaccine efficacy against severe illness was 84.7% (95% CI 71.7–92.4), with vaccination affording substantial reductions in hospitalisation for both severe rotavirus gastroenteritis (85.0%; 69.6–93.5) and gastroenteritis of any cause (42.4%; 28.6–53.1). Protection was shown against both G1 and non-G1P[8] strains, with efficacy of 91.8% (74.1–98.4) against G1 wild-type and 87.3% (64.1–96.7) against pooled non-G1P[8] strains (G3, G4, and G9). Protection was shown individually against G1P[8], G3P[8], and G9P[8] strains but not against the G4P[8] strain because of low circulation; a non-significant trend towards protection against G2P[4] strain was noted. Importantly, RIX4414 was not associated with an increased risk of intussusception compared with placebo after either vaccine dose.13 We report a large subset of infants participating in this initial study who were followed up to 24 months of age to assess the safety and protective efficacy of the human rotavirus vaccine during the second year of life.

Methods
Participants and study design
We undertook a large, multicountry, randomised, double-blind, placebo-controlled, multicentre phase III study in Latin America between Aug 5, 2003, and Oct 20, 2005. Inclusion and exclusion criteria were as previously described.12 The study was approved by the research ethics committees at all participating centres and was done in accordance with the Declaration of Helsinki and guidelines for good clinical practice. Written informed consent was obtained from parents or guardians before study entry. Parents or guardians had to sign a supplementary informed consent to continue participation during the second year.

GlaxoSmithKline Biologicals provided vaccine supplies that were numbered with a computer-generated randomisation list. We used a blocking scheme randomisation. Randomisation was done by a central internet randomisation system. Infants were randomly assigned in a 1 to 1 ratio to receive two doses either of RIX4414 or placebo. Treatment allocation remained concealed from investigators and parents of participating infants throughout the study. GlaxoSmithKline Biologicals did the masking and concealment. Each dose of RIX4414 contained 10⁶ median cell-culture infective doses (CCID₅₀) of vaccine strain. Placebo contained the same constituents as the active vaccine but without the virus component; both were reconstituted with liquid calcium carbonate-based buffer before oral administration. A total of 63 225 healthy infants aged 6–13 weeks were enrolled to receive two oral doses of RIX4414 (n=31 673) or placebo (n=31 552) at about 2 and 4 months of age and were followed up for safety for up to 3 months after the first dose.12 Infants received other routine paediatric immunisations during the study period in accordance with local recommendations. Oral poliovirus vaccination was provided at an interval of at least 2 weeks before or after a dose of RIX4414 or placebo.

Cases of severe gastroenteritis of any cause, intussusception, and serious adverse events were captured through active hospital-based surveillance during follow-up, as previously described.13 Severe gastroenteritis was clinically defined as an episode of diarrhoea (the passage of three or more loose or watery stools within a 24-h period) with or without vomiting that needed overnight treatment in hospital or rehydration treatment (equivalent to WHO plan B or C),13 or both, in a medical facility, such as hospital, clinic, or supervised rural healthcare centre. Additionally, severity was calculated with the 20-point Vesikari scale.13 In accordance with this scale, an episode of gastroenteritis with a score of 11 or more was regarded as severe.

Stool samples from infants with severe gastroenteritis were tested for the presence of rotavirus by ELISA (Rotaclone, Meridian Bioscience, Cincinnati, OH, USA) at GlaxoSmithKline Biologicals’ laboratories (Rixensart, Belgium). All rotavirus-positive stool samples were tested by reverse transcriptase PCR followed by reverse hybridisation assay and sequencing (optional) at Delft Diagnostic Laboratory (Delft, Netherlands) to identify G and P types.

Statistical analysis
The primary endpoint was the assessment of efficacy from 2 weeks after dose two until 1 year of age as previously reported.12 The secondary endpoint was the assessment of efficacy during the second year and for the combined 2-year period from 2 weeks after dose two until about 24 months of age. The cohorts consisted of participants who completed the full two-dose vaccination course and for whom compliance with the protocol was complete. If the vaccine efficacy was truly 60% in the second-year efficacy follow-up and an attack rate of 1% was assumed for severe rotavirus gastroenteritis, the study had at least 90% power to note a 95% CI for the vaccine efficacy that would be above 0% with a target sample size of 5600 children per group.

We calculated the percentage of participants reporting at least one episode of severe gastroenteritis (overall and by G type) with 95% CI. We compared groups with two-sided Fisher’s exact test (α=0.05) and expressed the results as relative risk (RR) and absolute risk. We calculated vaccine efficacy with 95% CI for all three efficacy periods with the formula:

\[(1–RR)×100=(1– ARU)×100ARV\]
where ARU is the disease attack rate in the unvaccinated population (estimated from the placebo group)—ie, the number of infants reporting at least one severe gastroenteritis episode per total number in the placebo group, and ARV is the disease attack rate in the vaccinated group. 95% CIs for efficacy were derived from the exact CI for the Poisson rate ratio. When more than one G type was isolated for an episode, the child was counted in every G type category for analysis of efficacy by G type.

Exploratory vaccine efficacy against gastroenteritis leading to hospital admission, severe gastroenteritis with Vesikari scores of at least 11, at least 19, and equal to 20, and severe gastroenteritis due to any cause was also calculated.

Secondary analysis of efficacy was done for participants in the total vaccinated cohort of all infants who had received at least one dose of RIX4414 or placebo for the first-year efficacy subset. Vaccine efficacy against severe rotavirus gastroenteritis and its 95% CI from dose one until 2 years of age were estimated by the Cox proportional-hazard model. The time was censored at the last contact in the study period.

The cumulative hazard of a first episode was estimated as minus-log transformation (of log data to non-log data) of the Kaplan-Meier survival curve during the period from dose one until 2 years of age in all the infants who received at least one dose of either vaccine or placebo. The p value for the cumulative-hazard curve was calculated with the log-rank test.

Analysis of safety was done for all infants who had received at least one dose of study vaccine and had entered the second year of follow-up. The incidence of serious adverse events during the second year of the study was compared between groups with the two-sided asymptotic score test for the null hypothesis of identical

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**Figure 1: Trial profile (total cohort)**

63,225 participants randomly allocated

20,169 in efficacy cohort (first-year efficacy subset)

10,159 randomised to RIX4414 and included in intention-to-treat analysis (first-year efficacy subset)

10,010 randomised to placebo and included in intention-to-treat analysis (first-year efficacy subset)

2,490 did not meet inclusion criteria for second-year efficacy subset

1,357 from Peru did not participate in second year efficacy follow-up

1,133 no informed consent provided from parents or guardians for second-year efficacy period

2,496 did not meet inclusion criteria for second-year efficacy subset

1,350 from Peru did not participate in second year efficacy follow-up

1,146 no informed consent provided from parents or guardians for second-year efficacy period

7,649 included in total vaccinated cohort for 2-years’ efficacy subset

7,514 included in total vaccinated cohort for 2-years’ efficacy subset

33 did not enter surveillance period of second-year of efficacy period

21 did not enter surveillance period of second-year of efficacy period

7,636 included in total vaccinated cohort for safety-follow-up (2-years’ efficacy subset)

7,493 included in total vaccinated cohort for safety-follow-up (2-years’ efficacy subset)

239 withdrew

1 adverse event

6 serious adverse events

12 withdrew consent

112 lost to follow-up

107 moved from study area

1 other reason

275 withdrew

2 adverse event

7 serious adverse events

18 withdrew consent

125 lost to follow-up

122 moved from study area

1 not treated according to protocol

7,397 completed end visit of 2-years’ efficacy period

7,218 completed end visit of 2-years’ efficacy period

7669 included in total vaccinated cohort for 2-years’ efficacy subset

7514 included in total vaccinated cohort for 2-years’ efficacy subset

7493 included in total vaccinated cohort for safety-follow-up (2-years’ efficacy subset)

7,397 completed end visit of 2-years’ efficacy period

7,218 completed end visit of 2-years’ efficacy period

239 withdrew

1 adverse event

6 serious adverse events

12 withdrew consent

112 lost to follow-up

107 moved from study area

1 other reason

275 withdrew

2 adverse event

7 serious adverse events

18 withdrew consent

125 lost to follow-up

122 moved from study area

1 not treated according to protocol

7,397 completed end visit of 2-years’ efficacy period

7,218 completed end visit of 2-years’ efficacy period
incidence in both groups (α=0·05). In the 2-years’ efficacy subset, the percentage of participants reporting definite intussusception (surgical, radiological, or post-mortem evidence), based on the Brighton Collaboration Working Group guidelines, from dose one up to study end, was compared between groups with the two-sided asymptotic score tests for the null hypothesis of identical incidence in both groups (α=0·05). Two-sided asymptotic standardised 95% CIs were calculated for RR in the RIX4414 group compared with the placebo group.

Data analysis was done with SAS software (version 8.2) and Proc StatXact 5 on Windows NT (version 4.0).

This study is registered with ClinicalTrials.gov, number NCT00140673 (eTrack444563-023).

Role of funding source
The sponsor held the data and did the analyses, with continuous feedback from the authors, and was involved in all stages of the study, including study design. The report was written jointly by both the sponsor and the authors, who vouched for the accuracy and completeness of the reported data. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication.

Results
Figure 1 shows the trial profile for the total cohort. Vaccine efficacy during the first year of life was measured in 20169 infants. From this group, a subset of 15 183 children from ten participating countries in Latin America (Argentina [n=1269], Brazil [630], Chile [415], Colombia [1708], Dominican Republic [1129], Honduras [1545], Mexico [4335], Nicaragua [1727], Panama [1057], and Venezuela [1368]) were included in the follow-up for efficacy for the second year of life (figure 1). A total of 14 237 infants completed this follow-
up. 15 129 were included in the follow-up for safety during the second year of life. Demographic details for both initial cohorts have been described previously.12 RIX4414 and placebo groups were similar with respect to age, sex, and ethnic origin. Median age was 8 (IQR 6–11) weeks at the time of the first vaccine dose and 15 (13–19) weeks at the time of the second vaccine dose, 7723 (51%) of 15 183 infants were boys and the study population was predominantly Hispanic (12 725 [84%] of 15 183). Figure 2 shows the trial profile for the according-to-protocol cohorts derived from the original first-year efficacy cohort12 that met the inclusion criteria for and completed the second-year follow-up. Mean duration of follow-up was 8–3 months during the first-year efficacy period, 11–8 months during the second-year efficacy period and 20 months for the 2-years’ efficacy period. Mean age at study end was 24 (SD 1·3–4) months.

No child from the total vaccinated cohort had more than one episode of severe rotavirus gastroenteritis during the 2 years of follow-up. Incidence of severe gastroenteritis in the placebo group was higher during the second-year efficacy period than during the first year (table 1). Fewer episodes were reported in the RIX4414 group than in the placebo group during both individual efficacy periods and during the 2-years’ efficacy period. Similar vaccine efficacy results were obtained during the three efficacy periods and in the overall cohort of infants who had received at least one dose of vaccine or placebo; efficacy against severe rotavirus gastroenteritis from dose one until 2 years of age in the first-year efficacy subset was 80–3% (95% CI 72·4–85·9). The cumulative hazard of severe illness was significantly lower in the vaccine group than in the placebo group throughout the 2-years’ efficacy period (figure 3). The difference between groups led to roughly fivelfold reduction in risk of severe gastroenteritis in the vaccine group compared with the placebo group at 2 years of age.

Fewer infants in the RIX4414 group were admitted for severe rotavirus gastroenteritis than in the placebo group during the 2-years’ efficacy period (p<0·0001; table 2). Vaccine efficacy against hospital admission for rotavirus gastroenteritis was 85–4% (95% CI 67–4–94–4) during the first-year efficacy period, 81–5% (67·7–90·1) during the second-year efficacy period, and 83–0% (73·1–89·7) during the 2-years’ efficacy period.

G1P[8] wild-type was the predominant strain during the first rotavirus season (detected in 30 [52%] of 58 stools tested in the placebo group during the first-year efficacy period) followed by G9P[8] (10 [17%] of 58) (figure 4). A shift in type predominance was observed during the second virus season (figure 4), with the G9P[8] type gaining predominance (56 [54%] of 103) and with a marked increase in G4P[8] strains (16 [16%] of 103). Wild-type G1P[8] was noted in 21 (24%) of 103 stools tested in the placebo group during the second-year efficacy period. Circulation of the G2P[4] strain was low during both years of follow-up (in the placebo group, seven cases during the first-year efficacy period and only one case during the second-year efficacy period).

Fewer participants in the RIX4414 group had severe gastroenteritis episodes with a score of at least 11 on the Vesikari scale during the 2-years’ efficacy period (table 3). Vaccine efficacy was consistent with results obtained with the protocol-specified clinical case definition of severe rotavirus gastroenteritis (children given WHO plan B and C or needing hospital admission, or both). Efficacy increased with disease severity (table 3).

Table 1: Proportion of participants reporting at least one severe rotavirus gastroenteritis (RVGE) episodes (per protocol clinical definition) and vaccine efficacy against severe RVGE during three efficacy periods (according-to-protocol cohorts for the 2-years’ efficacy subset)

<table>
<thead>
<tr>
<th></th>
<th>Severe RVGE (95% CI)</th>
<th>Vaccine efficacy (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First year*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIX4414</td>
<td>10/7205 (0·1%; 0·1–0·3)</td>
<td>83·1% (66·6–92·3)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Placebo</td>
<td>58/7081 (0·8%; 0·6–1·1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second year†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIX4414</td>
<td>22/7175 (0·3%; 0·2–0·5)</td>
<td>79·0% (66·4–87·4)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Placebo</td>
<td>103/7062 (1·5%; 1·2–1·8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 years‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIX4414</td>
<td>32/7205 (0·4%; 0·3–0·6)</td>
<td>80·5% (71·3–87·1)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Placebo</td>
<td>161/7081 (2·3%; 1·9–2·6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are n/N (%), unless otherwise indicated. *Mean duration 8·3 months. †Mean duration 11·8 months. ‡Mean duration 20·0 months.

Figure 3: Cumulative hazard of a first episode of severe rotavirus gastroenteritis (total vaccinated cohort)
period (table 2). Vaccine efficacy against severe gastroenteritis from any cause was 40·6% (26·9–51·8) during the first year, 38·3% (26·4–48·4) during the second year, and 39·0% (30·1–46·9) during the 2-years' efficacy period. Fewer children in the RIX4414 group were admitted for severe gastroenteritis from any cause during any period (table 2). Vaccine efficacy against severe gastroenteritis from any cause during the 2-years' efficacy period was less than that in the placebo group (p<0·001). Total number of children in the RIX4414 group who needed treatment in hospital for severe gastroenteritis of any cause was 42·0% (27·2–53·9) during the first year, 37·8% (23·5–49·5) during the second year, and 39·3% (29·1–48·1) during the 2-years' efficacy period (table 2).

Data for the incidence of intussusception and serious adverse events during the first year of this study have been reported in detail elsewhere.

Adverse events per 10 000 infants were reported in the RIX4414 group than in the placebo group during the second year of follow-up (678 vs 787, respectively; p=0·01). All serious adverse events during the second year of follow-up were assessed as not related to vaccination by the respective investigators. The most frequently reported events per 10 000 children according to MedDRA system organ class were infections and infestations (503 vs 44; p=0·777), bronchiolitis (47 vs 44; p=0·777), bronchopneumonia (34 vs 40; p=0·544), urinary tract infections (20 vs 11; p=0·157), bronchitis (18 vs 17; p=0·886), and pharyngitis (13 vs 15; p=0·794). 13 infants withdrew from the study during the second year of follow-up because of serious adverse events (six in
RIX4414 group and seven in placebo group. Only three participants withdrew during this period because of non-serious adverse events (one in the RIX4414 group and two in the placebo group), which did not result in death or persistent or substantial disability or incapacity, were not life-threatening, did not need or extend hospital admission, and were not congenital anomalies.

No cases of intussusception were reported during the second year of follow-up. In the 2-years’ efficacy subset, the RR (RIX4414 vs placebo) for definite intussusception diagnosed during the first 2 years of life after administration of first vaccine dose was 0.36 (95% CI 0.12–1.06). Intussusception was reported in four of 7669 vaccine recipients and 11 of 7514 infants given placebo during the first year of life. No increased risk of definite intussusception was seen in the RIX4414 group versus the placebo group during the 2-years’ follow-up (p 0.065).

11 deaths occurred during the second year of follow-up (five in RIX4414 group and six in placebo group). Causes of death were respiratory disorders (n=2), septic shock (1), injury (1), and unspecified death (1) in the RIX4414 group, and pneumonia (2), bacterial meningitis (2), cardiac disorders (1), and road traffic accident (1) in the placebo group. All deaths were thought to be unrelated to vaccination.

**Discussion**

Two oral doses of RIX4414 when given in early infancy afforded sustained high protection against severe rotavirus gastroenteritis during the first 2 years of life when disease burden is highest. Vaccine efficacy did not differ in the two individual efficacy periods, showing that protective efficacy of the human rotavirus vaccine persists throughout the second rotavirus season despite the high viral attack rate.

The complete protection afforded against very severe rotavirus gastroenteritis episodes (Vesikari score ≥20) by two oral doses of RIX4414 was consistent with data showing two wild-type virus infections to be fully protective against subsequent episodes of severe disease. Similar to our findings, a previous phase IIb, dose-ranging study of 405 Mexican infants given RIX4414 showed sustained protective efficacy during two consecutive follow-up periods with high vaccine efficacy in prevention of severe rotavirus gastroenteritis. Roughly twice as many severe episodes of rotavirus gastroenteritis were reported in unvaccinated infants during the second year of this study compared with those reported during the first year. This finding is in agreement with the results of previous epidemiological studies in Latin America that showed a large proportion of children received care for rotavirus gastroenteritis during the second year of life and substantiates the need for early and sustained protection against severe rotavirus gastroenteritis for at least the first 2 years of life.

Importantly, RIX4414 afforded broad protection against a changing pattern of wild-type rotavirus strains during the 2-years’ efficacy period. Although G1P[8] is the most

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**Table 3:** Proportion of participants reporting severe rotavirus gastroenteritis (RVGE) episodes with a score of ≥11, ≥19 and ≥20 on the Vesikari scale and efficacy of vaccine during the 2-years’ efficacy period (according-to-protocol cohort for efficacy)

<table>
<thead>
<tr>
<th>Severe RVGE (95% CI)</th>
<th>Vaccine efficacy (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥11*</td>
<td>RIX4414 28/7205 (0.4%; 0.3–0.6) 82.1% (73.1–88.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Placebo 154/7081 (2.2%; 1.8–2.5)</td>
<td></td>
</tr>
<tr>
<td>≥19†</td>
<td>RIX4414 1/7205 (0; 0.0–0.1) 97.3% (83.8–99.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Placebo 36/7081 (0.5%; 0.4–0.7)</td>
<td></td>
</tr>
<tr>
<td>≥20‡</td>
<td>RIX4414 0/7205 (0; 0.0–0.1) 100.0% (60.8–100.0)</td>
<td>0.0004</td>
</tr>
<tr>
<td></td>
<td>Placebo 11/7081 (0.2%; 0.1–0.3)</td>
<td></td>
</tr>
</tbody>
</table>

Data are n/N (%), unless otherwise indicated. *Severity assessed with Vesikari scale.
common human rotavirus strain, type prevalence is known to vary within the same region with time, resulting in peaks of some strains.18-20 The second year of this study had a shift in strain predominance from G1P[8] to G9P[8], including a large increase in G4P[8]. RIX4414 provided a high degree of protection against severe rotavirus gastroenteritis caused by both G1 wild-type and other strains bearing P[8]-type specificity (G3, G4, and G9) (table 2). Protection against G2P[4] rotavirus seemed to be low; however, circulation of strains bearing these type-specificities was low during both years of the study.

Results of a European study (n=3994) showed RIX4414 to have an efficacy of 58·3% (95% CI 10·1–81·1) against rotavirus gastroenteritis of any severity and 85·5% (24·0–98·5) against severe illness due to G2P[4] strains during two consecutive rotavirus seasons,19 confirming that RIX4414 provides protection against these fully heterotypic (non-G1, non-P[8]) strains. In a study done in Aracaju, northeastern Brazil,20 investigators claimed that “vaccine does not afford complete protection against infection” by G[2]P4 strains. However, although the sample size was small, vaccine coverage was low, and predominance of G2P[4] strains was 100%, this study clearly showed evidence of reduced risk of severe rotavirus diarrhoea among vaccinated children in Aracaju. Indeed, severe rotavirus diarrhoea occurred in three (7%) of 44 vaccinated children compared with five (26%) of 19 non-vaccinated patients (p<0·05), with a calculated odds ratio of 0·20 (exact 95% CI 0·03–1·24). Furthermore, rather than a vaccine-related replacement event (which biologically and epidemiologically seems unlikely), the 100% G2 predominance in Aracaju most probably indicates a cyclical pattern of occurrence of this serotype in Brazil.21 Nevertheless, the issue of cross-protection draws attention to the need for further prospective surveillance studies to assess both vaccine effect and strain surveillance, in compliance with recent WHO recommendations.1 The fact that we could not fully assess the efficacy of the vaccine against rotavirus serotype G2 is, in our view, the main limitation of our study and is explained in part by the low circulation of G2 type during the 2-year follow-up period.

Worldwide, rotavirus is estimated to account for about 39% of all hospital admissions for childhood diarrhoea.22 With the high burden rotavirus disease places on health systems, an exploratory analysis of efficacy against gastroenteritis-related admissions was undertaken. The protection against hospital admission for severe rotavirus gastroenteritis noted during the first year of this study was maintained during a second rotavirus season, with an efficacy of 83·0% against gastroenteritis-related hospital admissions during the 2-year efficacy period. Vaccination also substantially reduced overall rates of admissions for severe gastroenteritis from any cause (table 2). Such a striking reduction in admissions for rotavirus gastroenteritis and overall gastroenteritis during the first 2 years of life would be expected to substantially reduce the burden of rotavirus disease in hospital systems during early childhood, with large reductions in associated costs.23

Analysis of safety during the second year of follow-up provided further evidence of the good safety profile of RIX4414. No cases of intussusception were reported during this period. The incidence of serious adverse events was lower during the second year of follow-up than that during the first year of the study;24 all serious adverse events reported during the second year of follow-up were thought to be unrelated to vaccination. As in the first year of the study, the overall serious adverse event profile during the second year of follow-up was in favour of RIX4414 vaccine with respect to prevention of gastroenteritis-related serious adverse events.

Results confirm the occurrence of rotavirus disease early in life and the continued high burden of gastroenteritis during the second year of life in Latin America. Two oral doses of RIX4414 given in early infancy showed good safety profile, were well tolerated, and provided sustained high protection against severe rotavirus gastroenteritis caused by a change in circulating rotavirus strains during the first 2 years of life when disease burden is highest. The importance of these results should not be underestimated because this study was done in developing countries from Latin America with challenging socioeconomic circumstances. Inclusion of this vaccine in routine paediatric immunisation schedules can be expected to greatly reduce the burden of rotavirus disease worldwide.

Contributors
All authors participated in the design or implementation, analysis, and interpretation of the study. ACL, EOB, MOR, FRV, AB, SD, PG, and BDV took part in all phases of the study. AB, EOB (second year of the study), BDV, and PG led the clinical team at GlaxoSmithKline Biologicals. SD did the data analysis. MOR was the coordinating principal investigator for the study. HA was the principal investigator for Argentina; ACL for Brazil; EN for Chile; PL for Colombia; LR for Dominican Republic; DMRM was the principal investigator for Honduras; FRV, GMRP, and NPR for Mexico; FE for Nicaragua; EOB (first year of the study) and XSL (second year of the study) for Panama; and IPS for Venezuela. BS participated in acquisition of data, and had full access to data. CAD participated in acquisition of data, analysis and interpretation of data, critical draft revision, and final approval of the version to be published. PR participated in study conception and design, and critical draft revision and final approval of the version of the report to be published.

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Conflict of interest statement
AB, PG, BDV, RR, NS, YC, PR, EOB, RC, and SACC are or were employees of GlaxoSmithKline Biologicals. BDV is now affiliated with Sanofi-Pasteur (Swiftwater, PA, USA). XSL received consulting fees in the past three years. ACL, PL, MMP, EN, RFV, and LPRR received honoraria or paid expert testimony or travel grants from GlaxoSmithKline. MOR received consulting fees in the past 3 years and honoraria or paid expert testimony or travel grants from GlaxoSmithKline. FRV, GMRP, NPR, IPS, DMRM, FE, LR, HA, MEN, VR, MLG, TDL, JS, CAD, BS, and JCT declare that they have no conflict of interest.

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References


Effect of Human Rotavirus Vaccine on Severe Diarrhea in African Infants

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ABSTRACT

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Drs. Madhi and Cunliffe contributed equally to this article.


BACKGROUND

Rotavirus is the most common cause of severe gastroenteritis among young children worldwide. Data are needed to assess the efficacy of the rotavirus vaccine in African children.

METHODS

We conducted a randomized, placebo-controlled, multicenter trial in South Africa (3166 infants; 64.1% of the total) and Malawi (1773 infants; 35.9% of the total) to evaluate the efficacy of a live, oral rotavirus vaccine in preventing severe rotavirus gastroenteritis. Healthy infants were randomly assigned in a 1:1:1 ratio to receive two doses of vaccine (in addition to one dose of placebo) or three doses of vaccine — the pooled vaccine group — or three doses of placebo at 6, 10, and 14 weeks of age. Episodes of gastroenteritis caused by wild-type rotavirus during the first year of life were assessed through active follow-up surveillance and were graded with the use of the Vesikari scale.

RESULTS

A total of 4939 infants were enrolled and randomly assigned to one of the three groups; 1647 infants received two doses of the vaccine, 1651 infants received three doses of the vaccine, and 1641 received placebo. Of the 4417 infants included in the per-protocol efficacy analysis, severe rotavirus gastroenteritis occurred in 4.9% of the infants in the placebo group and in 1.9% of those in the pooled vaccine group (vaccine efficacy, 61.2%; 95% confidence interval, 44.0 to 73.2). Vaccine efficacy was lower in Malawi than in South Africa (49.4% vs. 76.9%); however, the number of episodes of severe rotavirus gastroenteritis that were prevented was greater in Malawi than in South Africa (6.7 vs. 4.2 cases prevented per 100 infants vaccinated per year). Efficacy against all-cause severe gastroenteritis was 30.2%. At least one serious adverse event was reported in 9.7% of the infants in the pooled vaccine group and in 11.5% of the infants in the placebo group.

CONCLUSIONS

Human rotavirus vaccine significantly reduced the incidence of severe rotavirus gastroenteritis among African infants during the first year of life. (ClinicalTrials.gov number, NCT00241644.)
Rotavirus is the most important cause of severe gastroenteritis among children worldwide. The World Health Organization (WHO) estimates that globally 527,000 deaths occur each year among children as a result of rotavirus infection; more than 230,000 of the deaths occur in sub-Saharan Africa. Six of the seven countries with the highest mortality due to rotavirus diarrhea are located in Africa. Similarly, data generated from global rotavirus surveillance networks highlight the burden of hospitalizations for rotavirus; among young children hospitalized for acute diarrhea, the median detection rate for rotavirus was 40% globally and 41% in Africa. Therefore, measures to prevent rotavirus diarrhea in African children are urgently needed.

Vaccines represent the best hope for preventing the severe consequences of rotavirus infection, especially in impoverished regions where resources and access to care may be limited. Two oral, live attenuated rotavirus vaccines, Rotarix (GlaxoSmithKline Biologicals) and RotaTeq (Merck), have shown excellent protective efficacy against severe rotavirus gastroenteritis in trials conducted mainly in Latin America, Europe, and the United States. The WHO’s Strategic Advisory Group of Experts (SAGE) first reviewed data on these vaccines in 2005 and strongly recommended the inclusion of rotavirus vaccination in the national immunization programs of countries and regions in which, according to available data, severe rotavirus gastroenteritis has a substantial public health impact. But SAGE noted that live oral vaccines may not be as effective in protecting the poorest children in developing countries as they are in protecting children in industrialized countries and therefore recommended that efficacy trials be conducted in representative populations in Africa and Asia before the recommendation is extended. In response to this mandate, we conducted a clinical trial to determine whether Rotarix, an attenuated human rotavirus vaccine containing a G1P[8] strain, could protect African children against severe rotavirus gastroenteritis.

**Methods**

**Study Design and Participants**

We conducted a double-blind, randomized, placebo-controlled multicenter study in South Africa and Malawi to assess the efficacy, safety, and immunogenicity of Rotarix. A placebo-controlled design was chosen because the vaccine was not licensed or available in these countries at the time the study was initiated, and data were needed to inform policy decisions in low-resource countries. Children who were infected with human immunodeficiency virus (HIV) and children who had been exposed to HIV were included in the trial on the basis of the absence of serious immunosuppression in infants at the age at which these vaccines are first given (6 weeks), the experience with other live vaccines in HIV-infected children, and the need to inform decisions on the introduction of vaccine in settings with high prevalences of HIV. The study protocol and the informed consent form were approved by the ethics committee at the WHO and by the ethics committees at all study centers. The trial was conducted in accordance with Good Clinical Practice guidelines. The parents or legal representatives of the infants participating in the study provided written informed consent before the initiation of any study-related procedures. All the investigators shared responsibility for the design of the study and the accrual and analysis of the data. All the authors participated in the preparation of the manuscript and made the decision to submit the manuscript for publication.

In South Africa, healthy infants, 5 to 10 weeks of age, were enrolled from October 2005 through January 2006 and from November 2006 through early February 2007, before the anticipated rotavirus seasons of 2006 and 2007, respectively. Since rotavirus is known to circulate year-round in Malawi, infants in Malawi were enrolled from October 2006 through July 2007.

Infants were randomly assigned individually, in a 1:1:1 ratio, into three groups to receive two doses of the rotavirus vaccine at 10 and 14 weeks of age; three doses of the vaccine at 6, 10, and 14 weeks of age; or three doses of placebo. Infants in the two-dose vaccine group received a dose of placebo at 6 weeks of age. Vaccines that are administered routinely according to the guidelines of the Expanded Program on Immunization (EPI) were concomitantly administered with the vaccine or placebo. No restrictions were imposed on the breast-feeding of infants around the time of vaccination.

**Testing for HIV**

The parents or legal representatives of the infants were given the opportunity to have the infants...
tested for HIV at the time the first dose of vaccine or placebo was administered or 1 month after the last dose, and testing was performed when consent was given. Detailed information regarding the testing and treatment of infants is included in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Vaccine
The study vaccine, the calcium carbonate buffer, and the placebo were developed and manufactured by GlaxoSmithKline Biologicals. The composition of the vaccine was the same as the commercial formulation, and the placebo was the same formulation without the viral antigen.11

Analysis of Stool Samples during Episodes of Gastroenteritis
An episode of gastroenteritis was identified by the occurrence of diarrhea, whether or not it was accompanied by vomiting; diarrhea was defined as the passage of three or more stools that were looser than normal within a 24-hour period. Stool samples were collected during each episode of gastroenteritis that occurred between the date the first dose of vaccine or placebo was administered and the date the child reached 1 year of age. Stool samples were tested for rotavirus with the use of an enzyme-linked immunosorbent assay (ELISA) (Rotaclone, Meridian Bioscience). All stool samples that were positive for rotavirus were examined further with the use of a reverse-transcriptase–polymerase-chain-reaction (PCR) assay, followed by a reverse hybridization assay to determine the G and P types.12

Assessment of Vaccine Efficacy
The efficacy of the vaccine was assessed during the period from 2 weeks after the last dose of vaccine or placebo was administered until the child reached 1 year of age. Active surveillance for all gastroenteritis episodes was conducted by members of the study staff through weekly visits to parents or guardians to collect diary cards and through the collection of data from health clinics that served the study populations. The severity of each episode of gastroenteritis was evaluated with the use of the Vesikari scale13 (on which scores range from 1 to 20, with higher scores indicating greater severity) and was categorized as severe if the score was 11 or more.

Assessment of Safety
All serious adverse events including deaths were recorded for the period between the date the first dose of vaccine or placebo was administered and the date the child reached 1 year of age. The site investigator, who was unaware of the group assignments of the children, determined whether the serious adverse events appeared to have any causal association with vaccination.

Assessment of Immunogenicity
Blood samples were collected from approximately 10% of the infants immediately before the first dose of vaccine or placebo was administered and from all infants 1 month after the last dose to determine the serum concentrations of antirotavirus IgA antibody. The blood samples were analyzed with the use of an ELISA (GlaxoSmithKline Biologicals), with the assay cutoff point set at 20 U per milliliter.14

Statistical Analysis
The primary study analysis compared findings from the pooled vaccine group with those from the placebo group. The secondary end points were the efficacy of each vaccine dose (i.e., the two-dose vaccine and the three-dose vaccine) as compared with placebo. A supplementary analysis was performed to evaluate the efficacy, immunogenicity, and safety of the vaccine according to country.

Infants who had received the complete vaccination course and had entered the efficacy surveillance period, which began 2 weeks after the last dose, were included in the prespecified primary efficacy analysis (per-protocol efficacy cohort). Infants in the pooled vaccine and placebo groups who had at least one episode of severe rotavirus gastroenteritis caused by wild-type rotavirus strains during the period from 2 weeks after the last dose was administered until the infants reached 1 year of age were considered as having achieved the primary outcome. The efficacy analysis was also performed on data from the total cohort, which included infants who received at least one dose of vaccine or placebo. The safety analysis was performed on data from the total cohort. The immunogenicity analysis was performed on data from infants in the per-protocol efficacy cohort for whom immunogenicity data were available. The method used to calculate
the sample size and specific information about the statistical analysis are shown in the Supplementary Appendix.

RESULTS

STUDY POPULATION
A total of 4939 infants were enrolled and randomly assigned to one of three groups (Fig. 1); 1647 infants were assigned to the two-dose group, 1651 to the three-dose group (for a total of 3298 in pooled vaccine group), and 1641 to the placebo group. A total of 4417 infants were included in the primary efficacy analysis — 2974 in the pooled vaccine group and 1443 in the placebo group. The reasons for withdrawal from the study are listed in Figure 1. The demographic characteristics of the infants and the proportion of children who were infected with HIV were similar across the study groups. Almost all infants (≥99%) received oral poliovirus vaccine concomitantly with each dose of rotavirus vaccine or placebo (Table 1 in the Supplementary Appendix).

![Figure 1. Study Assignment and Follow-up.](image-url)
Efficacy

Severe gastroenteritis caused by circulating rotavirus was detected in 70 of 1443 infants in the placebo group (4.9%) as compared with 56 of 2974 infants in the pooled vaccine group (1.9%), resulting in a vaccine efficacy against the primary outcome of severe rotavirus gastroenteritis of 61.2% (95% confidence interval [CI], 44.0 to 73.2; P<0.001) (Table 1). Vaccination with the rotavirus vaccine prevented 5.0 episodes of severe rotavirus gastroenteritis per 100 infant-years (Table 2). The vaccine showed efficacy against severe rotavirus gastroenteritis both in infants who received two doses of vaccine (58.7% efficacy; 95% CI, 35.7 to 74.0) and in those who received three doses (63.7% efficacy; 95% CI, 42.4 to 77.8). In South Africa, the efficacy of the vaccine was 76.9% (95% CI, 56.0 to 88.4), and in Malawi the vaccine efficacy was 49.4% (95% CI, 19.2 to 68.3); 4.2 and 6.7 episodes of severe rotavirus gastroenteritis per 100 infant-years were prevented by vaccination in South Africa and Malawi, respectively (Tables 1 and 2). The efficacy of the rotavirus vaccine against rotavirus gastroenteritis of any severity is presented in Table 2 in the Supplementary Appendix.

The distribution of rotavirus G and P types

<table>
<thead>
<tr>
<th>Variable</th>
<th>Infants with at Least One Event</th>
<th>Vaccine Efficacy</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rotavirus Vaccine</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>no./total no.</td>
<td>% (95% CI)</td>
<td>no./total no.</td>
</tr>
<tr>
<td>Severe rotavirus gastroenteritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>56/2974 1.9 (1.4–2.4)</td>
<td>70/1443 4.9 (3.8–6.1)</td>
<td>61.2 (44.0–73.2)</td>
</tr>
<tr>
<td>Pooled</td>
<td>30/1496 2.0 (1.4–2.9)</td>
<td>—</td>
<td>58.7 (35.7–74.0)</td>
</tr>
<tr>
<td>Two-dose</td>
<td>26/1478 1.8 (1.2–2.6)</td>
<td>—</td>
<td>63.7 (42.4–77.8)</td>
</tr>
<tr>
<td>Three-dose</td>
<td>41/1030 4.0 (2.9–5.4)</td>
<td>38/483 7.9 (5.6–10.6)</td>
<td>49.4 (19.2–68.3)</td>
</tr>
<tr>
<td>Malawi</td>
<td>21/525 4.0 (2.5–6.0)</td>
<td>—</td>
<td>49.2 (11.1–71.7)</td>
</tr>
<tr>
<td>Pooled</td>
<td>20/505 4.0 (2.4–6.1)</td>
<td>—</td>
<td>49.7 (11.3–72.2)</td>
</tr>
<tr>
<td>Two-dose</td>
<td>6/973 0.6 (0.2–1.3)</td>
<td>—</td>
<td>81.5 (55.1–93.7)</td>
</tr>
<tr>
<td>Three-dose</td>
<td>15/1944 0.8 (0.4–1.3)</td>
<td>32/960 3.3 (2.3–4.7)</td>
<td>76.9 (56.0–88.4)</td>
</tr>
<tr>
<td>Malawi</td>
<td>9/971 0.9 (0.4–1.8)</td>
<td>—</td>
<td>72.2 (40.4–88.3)</td>
</tr>
<tr>
<td>Pooled</td>
<td>6/973 0.6 (0.2–1.3)</td>
<td>—</td>
<td>81.5 (55.1–93.7)</td>
</tr>
<tr>
<td>South Africa</td>
<td>11/1944 0.6 (0.3–1.0)</td>
<td>18/960 1.9 (1.1–2.9)</td>
<td>69.8 (32.5–87.1)</td>
</tr>
<tr>
<td>G1 strain</td>
<td>4/1944 0.2 (0.1–0.5)</td>
<td>14/960 1.5 (0.8–2.4)</td>
<td>85.9 (55.1–96.6)</td>
</tr>
<tr>
<td>Non-G1 strain</td>
<td>14/2974 0.5 (0.3–0.8)</td>
<td>16/1443 1.1 (0.6–1.8)</td>
<td>57.5 (7.2–80.8)</td>
</tr>
</tbody>
</table>

* A total of 4417 infants were included in the efficacy analysis — 2974 in the pooled vaccine group and 1443 in the placebo group.
† P values were calculated with the use of a two-sided Fisher’s exact test. P values of less than 0.05 were considered to indicate a statistically significant difference.
‡ Data in the rotavirus vaccine group are for the pooled vaccine cohort.
differed between South Africa and Malawi (Fig. 1 in the Supplementary Appendix). The G1P[8] strain was detected in 57.0% of the episodes among recipients of the placebo in South Africa and in 12.9% of the episodes among recipients of the placebo in Malawi. The type-specific efficacy against severe rotavirus gastroenteritis and the difference in incidence rates between the vaccine groups and the placebo group are shown in Table 1 and Table 2, respectively.

The incidence rate of severe gastroenteritis from any cause was 8.6% in the pooled vaccine group as compared with 12.3% in the placebo group, corresponding to a reduction in the rate with vaccination of 30.2% (95% CI, 15.0 to 42.6; P<0.001) (Table 3). The reductions in all-cause severe gastroenteritis were statistically significant in both countries. The efficacy of the vaccine in the total vaccinated cohort was similar to that in the per-protocol efficacy cohort (Tables 3 to 6 in the Supplementary Appendix).

SAFETY

At least one serious adverse event occurred during the study period in 319 of the 3298 infants in the pooled vaccine group (9.7%; 95% CI, 8.7 to 10.7) and in 189 of the 1641 infants in the placebo group (11.5%; 95% CI, 10.0 to 13.2) (Table 7 in the Supplementary Appendix). During the entire study period, 83 deaths occurred among infants in the pooled vaccine group (2.5%; 95% CI, 2.0 to 3.1) and 43 deaths occurred among those in the placebo group (2.6%; 95% CI, 1.9 to 3.5). A single case of intussusception occurred 11 weeks after the third dose of rotavirus vaccine in a 6-month-old child who was assigned to the three-dose vaccine group. The child underwent bowel resection and recovered fully. Three adverse

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Table 2. Risk of Severe Rotavirus Gastroenteritis in the Pooled Vaccine Group and the Placebo Group, According to Dose, Country, and Rotavirus Strain.*

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Rotavirus Vaccine</th>
<th>Placebo</th>
<th>Difference in Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. in Cohort</td>
<td>Episodes/100 Infants/Yr (95% CI)</td>
<td>No. in Cohort</td>
</tr>
<tr>
<td>Severe rotavirus gastroenteritis</td>
<td>2974</td>
<td>3.0 (2.3–3.9)</td>
<td>1443</td>
</tr>
<tr>
<td>Two-dose</td>
<td>1496</td>
<td>3.2 (2.2–4.6)</td>
<td>—</td>
</tr>
<tr>
<td>Three-dose</td>
<td>1478</td>
<td>2.8 (1.9–4.1)</td>
<td>—</td>
</tr>
<tr>
<td>Country‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malawi</td>
<td>1030</td>
<td>6.5 (4.8–8.8)</td>
<td>483</td>
</tr>
<tr>
<td>South Africa</td>
<td>1944</td>
<td>1.2 (0.7–2.0)</td>
<td>960</td>
</tr>
<tr>
<td>Rotavirus type‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cohort</td>
<td>2974</td>
<td>0.9 (0.6–1.5)</td>
<td>1443</td>
</tr>
<tr>
<td>G1 strain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1030</td>
<td>0.9 (0.4–2.1)</td>
<td>483</td>
</tr>
<tr>
<td>Non-G1 strain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1944</td>
<td>5.5 (4.0–7.7)</td>
<td>960</td>
</tr>
<tr>
<td>G1 strain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.9 (0.5–1.6)</td>
<td>3.0 (1.9–4.8)</td>
<td>2.1 (0.8–3.9)</td>
</tr>
<tr>
<td>Non-G1 strain</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The analyses are based on the efficacy cohort, which comprised 4417 infants — 2974 in the pooled vaccine group and 1443 in the placebo group.
† The difference in rate is calculated as the episodes per 100 infants per year in the placebo group minus the episodes per 100 infants per year in the rotavirus vaccine group.
‡ Data in the rotavirus vaccine group are for the pooled vaccine cohort.
events were judged by the investigators to be related to vaccination — two cases of sepsis and one of otitis media.

**Immunogenicity**

At 1 month after the last dose of vaccine was administered, the seroconversion rates for antirotavirus IgA in South Africa were 57.1% (95% CI, 44.7 to 68.9) in the two-dose group and 66.7% (95% CI, 54.0 to 77.8) in the three-dose group. The seroconversion rates in Malawi were 47.2% (95% CI, 30.4 to 64.5) in the two-dose group and 57.1% (95% CI, 42.2 to 71.2) in the three-dose group. In the placebo group, the seropositivity rates for antirotavirus IgA at 1 month after the last dose were 16.7% (95% CI, 14.2 to 19.5) in South Africa and 40.4% (95% CI, 34.9 to 46.1) in Malawi.

**Discussion**

This study shows that a live, oral rotavirus vaccine significantly reduces the episodes of severe rotavirus gastroenteritis in African children during the first year of life. The attack rate for severe rotavirus gastroenteritis was higher in these populations than has been reported in other studies of rotavirus vaccines.4,5 Because of this high incidence of severe disease, a vaccine efficacy of 61.2% resulted in a substantial vaccine-attributable reduction in severe rotavirus gastroenteritis (reduction of 5.0 cases per 100 infant-years). In addition, the rotavirus vaccine was associated with a reduction in all-cause severe gastroenteritis of 30.2%. This reduction in the incidence of the disease occurred in a trial that was designed to simulate real-world conditions of use; thus, the rotavirus vaccine is expected to deliver a considerable public health benefit when it is introduced into similar settings.

The overall efficacy of the rotavirus vaccine in preventing episodes of severe rotavirus gastroenteritis (61.2%) was lower than that observed in European studies and Latin American studies (96.4% and 84.8%, respectively), which included some low- to middle-income countries.4-6,15 This finding is consistent with findings from other studies of live oral vaccines, such as the oral poliovirus vaccine,16 the cholera vaccine,17 oral typhoid vaccines,18 and earlier rotavirus vaccines,19 none of which were as immunogenic or effective in populations in developing countries as they were in populations in industrialized countries. Several mechanisms have been proposed to explain why live oral rotavirus vaccines may not be as efficacious in populations of infants from low-income countries.20 Possible reasons include host characteristics, such as poor nutritional status and enteric coinfections; levels of antirotavirus antibodies in breast milk; and interference by maternal antibody or by coadministration of the oral poliovirus vaccine, which may reduce rotavirus antibody levels.21,22 The potential role of these and other factors will be important to elucidate, in order to further improve the performance of these vaccines in populations where they are most needed.

The efficacy of the rotavirus vaccine in Malawian infants in this study was lower than that in their South African counterparts (49.4% vs. 76.9%). In addition to potential differences mentioned above, rotavirus circulation differs in the two countries (a winter-spring peak in South Africa6,9 as compared with year-round circulation in Malawi16), and that difference was reflected in the study enrollment strategies (preceding the

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**Table 3. Efficacy of Rotavirus Vaccine against All-Cause Severe Gastroenteritis.***

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Infants with at Least One Event of All-Cause Severe Gastroenteritis</th>
<th>Vaccine Efficacy</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rotavirus Vaccine</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>no./total no.</td>
<td>% (95% CI)</td>
<td>no./total no.</td>
</tr>
<tr>
<td>Overall</td>
<td>256/2974</td>
<td>8.6 (7.6–9.7)</td>
<td>178/1443</td>
</tr>
<tr>
<td>Malawi</td>
<td>187/1030</td>
<td>18.2 (15.8–20.6)</td>
<td>117/483</td>
</tr>
<tr>
<td>South Africa</td>
<td>69/1944</td>
<td>3.5 (2.8–4.5)</td>
<td>61/960</td>
</tr>
</tbody>
</table>

* The analyses are based on the efficacy cohort, which comprised 4417 infants — 2974 in the pooled vaccine group and 1443 in the placebo group.
† P values were calculated with the use of a two-sided Fisher’s exact test. P values of less than 0.05 were considered to indicate a statistically significant difference.
rotavirus season in South Africa as compared with year-round in Malawi). The rotavirus sero-
positivity rate among placebo recipients 1 month after the last dose had been given was greater
among Malawian infants than among South African infants (40.4% vs. 16.7%), suggesting that
Malawian infants have high exposure to wild-
type rotavirus infection in the first 5 months of
life. Since infection with wild-type rotavirus con-
fers protection against the development of severe
rotavirus disease later in infancy, the greater
exposure of the infants in the placebo group in
Malawi to rotavirus infection before their entry
into the follow-up period may have lowered the
estimate of vaccine efficacy in Malawi. Despite
the lower point estimate for efficacy, the number
of severe cases of rotavirus gastroenteritis pre-
vented was greater in Malawi than in South Africa
(6.7 vs. 4.2 cases prevented per 100 infant-years),
owing to the higher incidence of severe rotavirus
gastroenteritis in Malawi.

In this study, the diversity of the circulating
strains was striking. In Malawi, only 12.9% of
the rotavirus strains were G1P[8] — the strain
on which this vaccine is based, and the most
commonly occurring strain globally. A sub-
stantial proportion of G2, G8, G9, and G12
strains were isolated during the course of this
study. Rotavirus types G2, G8, and G9 have cir-
culated for several years in both countries, where-
as rotavirus type G12 has been reported more
recently. It is unlikely, however, that these
differences in strains contributed to the lower
vaccine efficacy, since the efficacy against G1
and non-G1 severe rotavirus gastroenteritis was
similar. These data are consistent with an inte-
grated analysis of previous efficacy trials of the
rotavirus vaccine, which indicates that the rota-
virus vaccine provides protection against severe
rotavirus gastroenteritis caused by G1 and non-
G1 strains. The ability of a rotavirus vaccine to
protect against a wide panel of strains is impor-
tant in Africa, where the diversity of rotavirus
strains is substantial.

We did not detect significant differences in
vaccine immunogenicity or efficacy between the
cohort receiving two vaccine doses and the co-
hort receiving three doses, although this study
was not powered to detect such differences. There
was a slight but nonsignificant trend toward
higher seroconversion rates and vaccine efficacy
with the three-dose schedule. It should be noted
that in the two-dose schedule used in this study,
the doses of vaccine were administered at the
second and third childhood vaccine visit, when
the infants were an average of 11 and 16 weeks
of age, respectively. Outside the setting of a clin-
ical trial, a two-dose schedule in which the rota-
virus vaccine is administered at the second and
third childhood vaccination visits is not prac-
tical, since it is recommended that the first dose
of rotavirus vaccine be delivered before the infant
is 12 weeks of age, owing to lingering concerns
stemming from the age-dependent risk of intus-
susception associated with a previous rotavirus
vaccine. Since children in developing countries
frequently present late for vaccination visits, this
age restriction would deny many children the
opportunity to receive the rotavirus vaccine if it
were recommended at a later visit. Although a
two-dose schedule in which the vaccine is admin-
istered at the first and second childhood vaccina-
tion visits is a more practical option, such a
schedule was not tested in this study. Adminis-
tering rotavirus vaccines at younger ages could
clear the immunogenicity of the vaccines, be-
cause of the potential for greater interference of
maternal antibody and enhanced replication of
the oral poliovirus vaccine. It is important to
undertake studies to assess the effectiveness
of two doses of rotavirus vaccine adminis-
tered at earlier ages than those at which they
were administered in this study.

The WHO’s Global Advisory Committee on
Vaccine Safety (GACVS) has reviewed the safety
of the currently licensed rotavirus vaccines and
has concluded that in clinical trials of these vac-
cines, no association was seen between receipt of
the vaccines and an increased risk of intussus-
ception. Further, postmarketing surveillance data
show that an intussusception risk that is of a
similar magnitude to that which had been asso-
ciated with a previous rotavirus vaccine, Rota-
shield (Wyeth–Lederle), is unlikely. The single
case of intussusception in this trial was not tem-
porally related to rotavirus vaccination, and the
rate of serious adverse events did not differ be-
between infants who received the vaccine and those
who received the placebo. Continuing surveillance
of the safety of the vaccines as they are intro-
duced into more countries will be important.

On the basis of this study and other support-
ing data, SAGE recently recommended that rota-
virus vaccination of infants be included in all na-
tional immunization programs, in conjunction with other proven interventions for diarrheal disease. Appropriate financing mechanisms that will allow ministries of health in Africa to bring this potentially lifesaving vaccine to the children in greatest need are urgently needed.

The clinical trials were funded and coordinated by GlaxoSmithKline and the PATH Rotavirus Vaccine Program, a collaboration with the WHO and the Centers for Disease Control and Prevention, with support from the Global Alliance for Vaccines and Immunization (GAVI).

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IMPACT
Canadian Surveillance
SUBSTANTIAL MORBIDITY FOR HOSPITALIZED CHILDREN WITH COMMUNITY ACQUIRED ROTAVIRUS INFECTIONS

2005–2007 IMPACT SURVEILLANCE IN CANADIAN HOSPITALS

Nicole Le Saux, MD,* Julie A. Bettinger, PhD,† Scott A. Halperin, MD,‡ Wendy Vaudry, MD,§ and David W. Scheifele, MD,† for Members of the Canadian Immunization Monitoring Program, Active (IMPACT)

Abstract: We describe community-acquired rotavirus illness in 1359 children hospitalized at 12 centers in Canada between January 2005 and December 2007. The median age was 1.5 years. Almost half (48.6%) had significant dehydration, almost one-fifth (19%) had clinical sepsis and 7% had seizures at presentation. The median hospital stay was 3.4 days. Severe clinical presentations are less commonly described in surveillance programs.

Key Words: rotavirus infections, hospitalizations, children, morbidity from rotavirus infections, pediatric hospital surveillance

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METHODS

Active, metropolitan area surveillance for hospital admissions related to infection with rotavirus was conducted by the 12 centers of the Canadian Immunization Monitoring Program, Active (IMPACT). This network of pediatric centers accounts for approximately 90% of the pediatric tertiary care beds in the country, with referrals from all provinces and territories.6

The nurse monitor at each center identified all laboratory-confirmed rotavirus cases admitted to the IMPACT hospitals between January 1, 2005 and December 31, 2007 in children 0 to 16 years of age. All centers used the same case finding strategies, case definition, and report form. Identification of rotavirus gastroenteritis was based on laboratory diagnosis and clinical symptoms of acute gastrointestinal infection. Cases were identified on a prospective basis, while the chart abstraction occurred after discharge. Medical records searches were also used regularly to identify any missed cases of diarrhea or viral gastroenteritis using the following ICD10 codes: A08 (viral and other intestinal infections), A09 (diarrhea and gastroenteritis of infectious origin), K52.9 (noninfectious gastroenteritis), R11 (nausea and vomiting), and R15 (fetal incontinence). Any identified cases were then cross checked for a laboratory diagnosis of rotavirus and cases with a laboratory positive rotavirus diagnosis were included.

The following information was retrieved from the medical record: demographic data, underlying illnesses or immune compromising conditions, details concerning diagnosis, health care utilization, and outcome. The determination of dehydration or dehydration complications was based on health record notes.

All hospital acquired cases were excluded from this analysis. SAS version 9.1.3 (SAS Institute, Cary, NC) was used for all analyses. Continuous variables were tested with analysis of variance, categorical variables were tested with Fisher exact test and $\chi^2$ tests when appropriate.

RESULTS

A total of 1359 children were hospitalized with laboratory-confirmed, community-acquired rotavirus gastroenteritis at the 12 IMPACT centers over the 3-year period. Seasonal distributions of admissions by age group are shown in Figure, Supplemental Digital Content 1, http://links.lww.com/INF/A477. More than 90% of cases occurred between December and May. The majority of cases (43% [234/537]) in 2005, 42% [173/413] in 2006 and, 49% [199/409] in 2007) occurred in March and April.

Yearly totals and characteristics of the cases are shown in Table, Supplemental Digital Content 2, http://links.lww.com/INF/A478. The majority of cases (63%) occurred in children <2 years. The age distribution was as follows: 129 (9.5%) <3 months, 99 (7.3%) 4 to 6 months, 195 (14.3%) 7 to 11 months, and 431 (31.7%) 12 to 23 months of age. The mean age was 2.4 years while the median age was 1.5 years. This did not differ over the 3 years of surveillance ($P = 0.7$).

Healthy children constituted 61% of admissions, whereas an additional 7% were considered healthy, but had a concurrent acute infection. Among others, the most common underlying health conditions are shown in Table, Supplemental Digital Content 2, http://links.lww.com/INF/A478. Gastrointestinal disorders were responsible for more than 25% of underlying conditions, Crohn’s disease (n = 22), and gastroesophageal reflux disorder (n = 19) being most frequent. Older children (10–16 years) were significantly more likely to have underlying health conditions compared with younger children ($P < 0.0001$). None of the 1321 cases whose vaccination status was known had been vaccinated against rotavirus.

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Laboratory Detection. Rotavirus was most commonly detected using antigen detection enzyme immunoassays (1034 cases, 76.1%) followed by electron microscopy (245 cases, 18.0%) or both (79 cases, 5.8%). One case (0.1%) was detected by polymerase chain reaction.

Clinical Manifestations. Table 1 describes the clinical manifestations of infection. Vomiting/diarrhea, dehydration, and suspected sepsis were the most frequent presentations among admitted cases. Prior to admission, 1210 (89%) had diarrhea, 1225 (90%) had vomiting, and 923 (69%) had fever. Bloody diarrhea occurred most often in children 10 to 16 years of age (40%, 20/50) all of whom had underlying gastrointestinal conditions. Children <2 years were significantly more likely to present with a clinical picture suggestive of sepsis (22.1%) compared with children between 2 and 16 years (13.7%) (P < 0.001) with 50% of children 0 to 3 months of age presenting with sepsis-like picture, a rate significantly higher than among children 4 to 23 months of age (P < 0.001). Otherwise, there were no differences in clinical manifestations according to age.

Health Care Utilization and Outcome. Of available data for 1357 children, 191 (14%) had had at least 1 prior outpatient visit elsewhere. Including the emergency room visit that led to the current admission, 897 (68.5%) had 1 visit, 359 (26.4%) had 2, 54 (4%) had 3, and 14 children (1%) had 4 visits to the emergency department. The average length of stay in emergency was 7.9 hours (range: 0–41 hours) with a median of 7 hours. The mean duration of hospital stay was 3.4 days with a median of 3 days (Table 1). A total of 4555 hospital days were used for more than 3 years (1782, 1474, and 1299 days each year). In total, 48 children (3.5%) required intensive care for a mean duration of 2.4 days.

Among 835 children who were healthy and 97 who were healthy with concurrent infections, 49% (460/932) received antimicrobials on admission while 59% (252/427) who had underlying health conditions or who were premature (but otherwise healthy) did (P = 0.07).

There were no deaths during the study period from rotavirus infection; all children recovered from infection and were discharged. Over the 3 years of surveillance, 2% (n = 27) were readmitted to hospital within 14 days of hospital discharge and of these 48% (13/27) had an underlying illness.

**TABLE 1.** Clinical Manifestations and Course of Hospitalized Rotavirus Cases, 2005–2007

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>Year 2005</th>
<th>Year 2006</th>
<th>Year 2007</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 537</td>
<td>N = 413</td>
<td>N = 409</td>
<td>N = 1359</td>
</tr>
<tr>
<td>Vomiting/diarrhea without significant dehydration</td>
<td>293 (54.6)</td>
<td>202 (48.9)</td>
<td>146 (35.7)</td>
<td>641 (47.2)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>226 (42.1)</td>
<td>195 (47.2)</td>
<td>239 (58.4)</td>
<td>660 (48.6)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>23 (4.3)</td>
<td>19 (4.6)</td>
<td>18 (4.4)</td>
<td>60 (4.4)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>101 (18.8)</td>
<td>81 (19.6)</td>
<td>76 (18.6)</td>
<td>258 (19)</td>
</tr>
<tr>
<td>Seizure</td>
<td>32 (6)</td>
<td>24 (5.8)</td>
<td>29 (9.5)</td>
<td>95 (7)</td>
</tr>
<tr>
<td>Bloody diarrhea</td>
<td>25 (4.7)</td>
<td>18 (4.4)</td>
<td>23 (5.6)</td>
<td>66 (4.9)</td>
</tr>
<tr>
<td>Other manifestations*</td>
<td>27 (5)</td>
<td>37 (9)</td>
<td>44 (10.8)</td>
<td>108 (7.9)</td>
</tr>
<tr>
<td>Mean, median duration of diarrhea prior to admission (min, max)</td>
<td>2.3, 2 (0, 14)</td>
<td>2.5, 2 (0, 21)</td>
<td>2.3, 2 (0, 14)</td>
<td>2.4, 2 (0, 21)</td>
</tr>
<tr>
<td>Mean, median duration of vomiting prior to admission (min, max)</td>
<td>2.2, 2 (0, 14)</td>
<td>2.4, 2 (0, 21)</td>
<td>2.2, 2 (0, 12)</td>
<td>2.3, 2 (0, 21)</td>
</tr>
<tr>
<td>Mean, median duration of fever prior to admission (min, max)</td>
<td>1.4, 1 (0, 11)</td>
<td>1.5, 1 (0, 13)</td>
<td>1.5, 1 (0, 17)</td>
<td>1.5, 1 (0, 17)</td>
</tr>
<tr>
<td>ICU</td>
<td>17 (3.2%)</td>
<td>17 (4.1%)</td>
<td>14 (3.4%)</td>
<td>48 (3.5%)</td>
</tr>
<tr>
<td>Mean, median duration of stay in ICU (min, max)</td>
<td>2.3, 2 (1, 9)</td>
<td>2.5, 2 (1, 8)</td>
<td>2.3, 2 (1, 7)</td>
<td>2.4, 2 (1, 9)</td>
</tr>
<tr>
<td>ICU underlying condition</td>
<td>8 (17.1%)</td>
<td>10 (23.8%)</td>
<td>9 (23.1%)</td>
<td>29 (20.4%)</td>
</tr>
<tr>
<td>If underlying condition, mean, median duration of stay in ICU (min, max)</td>
<td>2.8, 1.5 (1, 9)</td>
<td>2.4, 2 (1, 8)</td>
<td>2.9, 2 (1, 7)</td>
<td>2.7, 2 (1, 9)</td>
</tr>
</tbody>
</table>

*Altered level of consciousness (41), hematemesis (15), rash (21), cardiac arrest (2), intestinal perforation (1), hepatitis (3), neutropenia or anemia (9), acute renal failure (13), worsening of underlying disease (4), acute hepatic failure (1), elevated lipase (1), and concomitant bacteremia (1) (4 children presented with more than one other clinically significant manifestation).**

**DISCUSSION**

This report describes the first national surveillance for pediatric rotavirus hospitalizations in Canada. The span of surveillance provides evidence of substantial burden of disease and morbidity associated with community-acquired rotavirus and provides some evidence that this infection consumes significant resources, even in tertiary care institutions. Yearly, in these institutions, 1300 to 1800 hospital days are used for treatment of admitted cases with community-acquired rotavirus infection. Consistent with other countries in the developed world, children <2 years represented the majority of children hospitalized in the 3-year period with community-acquired disease.1,2,7 Assuming at least 85% efficacy of vaccine in infants, vaccination could have prevented approximately 726 admissions and a median of 2178 hospital days over the course of the 3 years in the these 12 institutions in children under 2 years. The length of stay including the stay in the emergency department was just under 4 days per case, in keeping with prior North American and European reports.1,2,7,8

As in other northern climates, the rotavirus season over the 3-year period lasted from 20 to 26 weeks or between December and April during each year. Although previously similar in the United States, their rotavirus season has been delayed and shortened with the introduction of rotavirus vaccine.9 Compared with Switzerland, where 19% were noted to have upper airway infections at admission, 7% of healthy children in our study had concomitant infections.10 Prevention of rotavirus illness especially during respiratory viral season would not only decrease comorbidity inherent in dual infections but would favorably effect the health care system during peak respiratory viral season.

This 3-year study consistently demonstrated that about one-third of patients hospitalized had significant underlying illnesses. Other similar studies have shown that 13% to 22% of hospitalized patients had underlying conditions.8,10,11 The presence of older children in this cohort is likely due to the provision of secondary
ACKNOWLEDGMENTS

The authors thank the expert assistance provided by the Monitor Liaison (Heather Samson), the IMPACT nurse monitors and staff of the data center (Kim Marty, Shu Yu Fan, Wenli Zhang, Engy Grove and Debbe Heayn). The Canadian Immunization Monitoring Program, Active (IMPACT) is a national surveillance initiative managed by the Canadian Pediatric Society (CPS) and conducted by the IMPACT network of pediatric investigators.

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REFERENCES

PRODUCT MONOGRAPH

ROTARIX™

Human rotavirus, live, attenuated, oral vaccine

Oral suspension

Active immunizing agent

GlaxoSmithKline Inc.
7333 Mississauga Road
Mississauga, Ontario
L5N 6L4

Date of Revision:
February 17, 2010

Submission Control No.  122113

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Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION ............................................ 3
  SUMMARY PRODUCT INFORMATION ........................................................... 3
  DESCRIPTION ....................................................................................................... 3
  INDICATIONS AND CLINICAL USE ................................................................. 3
  CONTRAINDICATIONS ...................................................................................... 4
  WARNINGS AND PRECAUTIONS ................................................................. 4
  ADVERSE REACTIONS ....................................................................................... 6
  DRUG INTERACTIONS ..................................................................................... 11
  DOSAGE AND ADMINISTRATION .................................................................. 11
  OVERDOSAGE ................................................................................................... 12
  ACTION AND CLINICAL PHARMACOLOGY ............................................... 12
  STORAGE AND STABILITY ............................................................................. 14
  SPECIAL HANDLING INSTRUCTIONS .......................................................... 14
  DOSAGE FORMS, COMPOSITION AND PACKAGING ................................... 15

PART II: SCIENTIFIC INFORMATION ................................................................. 17
  PHARMACEUTICAL INFORMATION ............................................................. 17
  CLINICAL TRIALS ............................................................................................. 18
  TOXICOLOGY .................................................................................................... 23
  REFERENCES ..................................................................................................... 23

PART III: CONSUMER INFORMATION ................................................................. 27
ROTARIX™

Human rotavirus, live, attenuated, oral vaccine

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Dosage Form / Strength</th>
<th>Clinically Relevant Nonmedicinal Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Suspension/not less than $10^{6.0}$ CCID$_{50}$ of human rotavirus RIX4414 strain, per 1.5 mL dose.</td>
<td>Dulbecco’s Modified Eagle Medium (DMEM), sucrose, di-sodium adipate, sterile water.</td>
</tr>
</tbody>
</table>

For a complete listing see Dosage Forms, Composition and Packaging section.

DESCRIPTION

ROTARIX™ (human rotavirus, live, attenuated, oral vaccine) is a suspension presented in monodose oral applicators for oral administration. The vaccine includes an antacid component to protect the vaccine during passage through the stomach and prevent its inactivation due to acidic environment.

INDICATIONS AND CLINICAL USE

ROTARIX™ is indicated for active immunization of infants from the age of 6 weeks for the prevention of gastroenteritis caused by rotavirus types G1P[8], G2P[4], G3P[8], G4P[8] and G9P[8].

The results from the clinical trials suggest that the vaccine’s efficacy may vary with the type of rotavirus causing the infection (see Part II CLINICAL TRIALS section).
CONTRAINDICATIONS

ROTARIX™ should not be administered in:

- Infants who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- Infants who experienced hypersensitivity after previous administration of rotavirus vaccines.
- Infants with uncorrected congenital malformation (such as Meckel’s diverticulum) of the gastrointestinal tract that would predispose for intussusception.

WARNINGS AND PRECAUTIONS

General
It is good clinical practice that vaccination should be preceded by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination.

As with other vaccines, administration of ROTARIX™ should be postponed in infants suffering from acute severe febrile illness. However, the presence of a minor infection such as a cold should not result in the deferral of vaccination.

No safety or efficacy data are available for the administration of ROTARIX™ to:

- Individuals who have received a blood transfusion or blood products, including immunoglobulins, within 42 days.

No efficacy data are available for the administration of ROTARIX™ to:

- Immunocompromised patients such as individuals with malignancies receiving immunosuppressive therapy or who are otherwise immunocompromised.

The administration of ROTARIX™ should be postponed in infants suffering from diarrhea or vomiting.

Excretion of the vaccine virus in the stools is known to occur after vaccination with peak excretion around the 7th day. Viral antigen particles detected by ELISA were found in 50% (at day 7) of stools after the first dose and 17.4% (at day 3) and 4% (at day 7) of stools after the second dose. When these stools were tested for the presence of live vaccine strain, only 17% were positive.

Contacts of recent vaccinees should be advised to observe personal hygiene (e.g. wash their hands after changing child’s diapers).
As with any vaccine, a protective immune response may not be elicited in all vaccinees.

ROTARIX™ does not protect against gastroenteritis due to other pathogens than rotavirus.

No data are available on the use of ROTARIX™ for post-exposure prophylaxis.

UNDER NO CIRCUMSTANCES SHOULD ROTARIX™ BE INJECTED.

**Gastrointestinal**

There are no data on the safety and efficacy of ROTARIX™ in infants with gastrointestinal illnesses. Administration of ROTARIX™ may be considered with caution in such infants when, in the opinion of the physician, withholding the vaccine entails a greater risk.

**Immune**

In some clinical trials, ROTARIX™ was not administered to infants known to have immunodeficient household members. There is a theoretical risk that the live virus vaccine can be transmitted to non-vaccinate contacts. Therefore, ROTARIX™ should be administered with caution to individuals known to have immunodeficient close contacts such as:

- Individuals with malignancies or who are otherwise immunocompromised; or
- Individuals receiving immunosuppressive therapy.

However, because nearly all children are infected with naturally occurring rotavirus by the age of 5 years, vaccination of infants may decrease the risk of exposure of immunodeficient household contacts to naturally occurring rotavirus. The health care provider should assess the potential risks and benefits of administering ROTARIX™ to infants known to have immunodeficient close contacts.

Asymptomatic and mildly symptomatic HIV infections are not expected to affect the safety or efficacy of ROTARIX™. A clinical study in a limited number of asymptomatic or mildly symptomatic HIV positive infants showed no apparent safety problems (see ADVERSE REACTIONS, Safety in Infants with Human Immunodeficiency [HIV] Infection). Administration of ROTARIX™ in immunosuppressed infants, including infants on immunosuppressive therapy, should be based on careful consideration of potential benefits and risks.

**Sensitivity/Resistance**

The vaccine contains 1073 mg of sucrose as an excipient. This amount is too low to cause adverse events in patients with rare hereditary problems such as fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency.
Special Populations
Breastfeeding Infants: Evidence from some clinical trials with ROTARIX™ suggest breastfeeding does not reduce the protection against rotavirus gastroenteritis afforded by ROTARIX™. Therefore breastfeeding may be continued during the vaccination schedule.

Pregnant Women: ROTARIX™ is not intended for use in adults. Thus, human data on use during pregnancy are not available and animal reproduction studies have not been performed.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

- Clinical trials for the lyophilized formulation

In a total of eleven placebo controlled clinical trials, approximately 80,000 doses of ROTARIX™ were administered to approximately 40,200 infants.

In two clinical trials (Finland), ROTARIX™ lyophilized formulation was administered alone (administration of routine pediatric vaccines was staggered). The incidence and severity of diarrhea, vomiting, loss of appetite, fever and irritability was not different in the group receiving ROTARIX™ when compared to the group receiving placebo. No increase in the incidence or severity of these reactions was seen with the second dose.

In the remaining nine trials (Europe, Canada, USA, Latin America, Singapore, South Africa), ROTARIX™ lyophilized formulation was coadministered with routine paediatric vaccines (see DRUG INTERACTIONS). The adverse reaction profile observed in these subjects was similar to the adverse reaction profile observed in subjects receiving the same pediatric vaccines and placebo.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Intussusception

The risk of intussusception has been evaluated in a large safety trial conducted in Latin America and Finland where 63,225 subjects were enrolled. No increased risk of
intussusception in the ROTARIX™ group was observed and observed rates were comparable to the placebo group. Data are shown below in Tables 1 and 2.

**Table 1**  Rate of intussusception within 31 days after administration

<table>
<thead>
<tr>
<th>Intussusception</th>
<th>ROTARIX™</th>
<th>Placebo</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=31,673</td>
<td>N=31,552</td>
<td></td>
</tr>
<tr>
<td>First dose</td>
<td>1</td>
<td>2</td>
<td>0.50 (0.07;3.80)</td>
</tr>
<tr>
<td>Second dose</td>
<td>5</td>
<td>5</td>
<td>0.99 (0.31;3.21)</td>
</tr>
</tbody>
</table>

CI: Confidence Interval

**Table 2**  Rate of intussusception up to one year of age

<table>
<thead>
<tr>
<th>Intussusception</th>
<th>ROTARIX™</th>
<th>Placebo</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=10,159</td>
<td>N=10,010</td>
<td></td>
</tr>
<tr>
<td>First dose up to one year</td>
<td>4</td>
<td>14</td>
<td>0.28 (0.10;0.81)</td>
</tr>
</tbody>
</table>

CI: Confidence Interval

In 11 other clinical studies (N =12,220) there were 7 cases of intussusception reported, 5 IS cases in HRV vaccinees and 2 cases in placebo recipient. It is to be highlighted that none of these studies were powered to compare the incidence of intussusception in the ROTARIX™ and placebo groups.

**Solicited adverse reactions**

In study Rota-036, detailed safety information was collected by parents/guardians for 8 consecutive days following vaccination with ROTARIX™ (i.e. day of vaccination and the next 7 days). A diary card was completed to record irritability, cough/runny nose, the infant’s temperature, loss of appetite, vomiting, or diarrhea on a daily basis during the first week following each dose of ROTARIX™ or placebo. Adverse reactions among recipients of ROTARIX™ and placebo occurred at similar rates. See Table 3 below.
**Table 3** Percentage of subjects with each solicited general symptom assessed as causally related to vaccination, reported from Day 0 to Day 7 after each HRV vaccine/placebo dose – Rota-036 Pooled countries (Czech Republic, Finland, France, Germany, Italy and Spain)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>LL</th>
<th>UL</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough/Runny nose</td>
<td>914</td>
<td>58</td>
<td>6.3</td>
<td>4.9</td>
<td>8.1</td>
<td>490</td>
<td>29</td>
<td>5.9</td>
<td>4.0</td>
<td>8.4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>914</td>
<td>18</td>
<td>2.0</td>
<td>1.2</td>
<td>3.1</td>
<td>490</td>
<td>7</td>
<td>1.4</td>
<td>0.6</td>
<td>2.9</td>
</tr>
<tr>
<td>Fever</td>
<td>914</td>
<td>133</td>
<td>14.6</td>
<td>12.3</td>
<td>17.0</td>
<td>490</td>
<td>67</td>
<td>13.7</td>
<td>10.8</td>
<td>17.0</td>
</tr>
<tr>
<td>Irritability/Fussiness</td>
<td>914</td>
<td>299</td>
<td>32.7</td>
<td>29.7</td>
<td>35.9</td>
<td>490</td>
<td>171</td>
<td>34.9</td>
<td>30.7</td>
<td>39.3</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>914</td>
<td>126</td>
<td>13.8</td>
<td>11.6</td>
<td>16.2</td>
<td>490</td>
<td>71</td>
<td>14.5</td>
<td>11.5</td>
<td>17.9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>914</td>
<td>44</td>
<td>4.8</td>
<td>3.5</td>
<td>6.4</td>
<td>490</td>
<td>24</td>
<td>4.9</td>
<td>3.2</td>
<td>7.2</td>
</tr>
<tr>
<td><strong>Dose 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough/Runny nose</td>
<td>905</td>
<td>53</td>
<td>5.9</td>
<td>4.4</td>
<td>7.6</td>
<td>486</td>
<td>34</td>
<td>7.0</td>
<td>4.9</td>
<td>9.6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>905</td>
<td>6</td>
<td>0.7</td>
<td>0.2</td>
<td>1.4</td>
<td>486</td>
<td>8</td>
<td>1.6</td>
<td>0.7</td>
<td>3.2</td>
</tr>
<tr>
<td>Fever</td>
<td>905</td>
<td>164</td>
<td>18.1</td>
<td>15.7</td>
<td>20.8</td>
<td>486</td>
<td>95</td>
<td>19.5</td>
<td>16.1</td>
<td>23.4</td>
</tr>
<tr>
<td>Irritability/Fussiness</td>
<td>905</td>
<td>238</td>
<td>26.3</td>
<td>23.5</td>
<td>29.3</td>
<td>486</td>
<td>123</td>
<td>25.3</td>
<td>21.5</td>
<td>29.4</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>905</td>
<td>118</td>
<td>13.0</td>
<td>10.9</td>
<td>15.4</td>
<td>486</td>
<td>57</td>
<td>11.7</td>
<td>9.0</td>
<td>14.9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>905</td>
<td>18</td>
<td>2.0</td>
<td>1.2</td>
<td>3.1</td>
<td>486</td>
<td>23</td>
<td>4.7</td>
<td>3.0</td>
<td>7.0</td>
</tr>
</tbody>
</table>

N = number of subjects having received the considered dose of HRV vaccine/placebo  
\( n/\% \) = number/percentage of subjects with the specified symptom reported for the considered dose  
95\% CI: exact 95\% confidence interval, LL = Lower Limit, UL = Upper Limit

Statistically significant differences were not detected between groups for the comparison between ROTARIX™ and Placebo groups for the percentage of subjects with each specified solicited symptom (any, grade 3 and related) reported from Day 0 to Day 7 after any ROTARIX™/placebo doses (P-value > 0.05 for each comparison).

**Unsolicited Adverse Events (pooled analysis)**

Infants were monitored for unsolicited adverse reactions that occurred in the 31 day period following vaccination in 8 clinical studies. The following adverse reactions occurred at a statistically higher incidence (P-value < 0.05) among recipients of ROTARIX™ (N = 5,543) as compared with placebo recipients (N = 1,852): Rhinorrhea (ROTARIX™ 1.55%, placebo 3.02%), Pharyngitis (ROTARIX™ 1.86%, placebo 2.00%) and Bronchitis (ROTARIX™ 1.95%, placebo 1.03%). In another study (Rota-036: ROTARIX™ N = 2,646, placebo N = 1,348) the incidence of rhinorrhea, pharyngitis and bronchitis was similar between the ROTARIX™ and placebo groups.
Serious Adverse Events (SAEs):

Study Rota-023
Among the total vaccinated cohort of 63,225 infants in study Rota-023 (31,673 in the HRV group and 31,552 in the placebo group), a total of 1,975 subjects (948 infants in the HRV vaccine group and 1,047 infants in the placebo group) reported at least one SAE (up to 30-90 days post Dose 2). No imbalance was observed between treatment groups for SAEs assessed as related to vaccination by the investigators. The overall SAE profile was in favour of the HRV vaccine with significantly fewer SAEs/hospitalizations reported in the HRV vaccine group compared to the placebo group, especially with respect to preventing GE related SAEs.

In study Rota-023, a potential imbalance between groups was noted for Convulsions reported cases: 16 subjects in ROTARIX™ group (5.1/10,000) versus 6 subjects in the placebo group (1.9/10,000). However, no potential imbalance was noted between groups when SAEs related to "Convulsive disorders" were pooled ('Convulsions', 'Epilepsy', 'Grand mal convulsion', 'Status epilepticus' and 'Tonic convulsion'): 20 subjects in the ROTARIX™ group versus 12 in the placebo group.

Other clinical trials
Infants were monitored for serious adverse events that occurred in the 31 day period following vaccination in 8 clinical studies. In these eight trials, 608 subjects reported at least one SAE (450 in vaccinees and 158 in placebo recipients). The incidence of subjects reporting at least one SAE in the group receiving ROTARIX™ (8.12%, 95% CI: 7.41%; 8.87%) was similar to the incidence in the placebo group (8.53%, 95% CI: 7.30%; 9.90%).

Deaths:
In 8,262 infants enrolled and vaccinated in 10 completed trials, a total of 18 deaths were reported: 12 deaths in ROTARIX™ (0.19%, N=6,290) and 6 in placebo (0.30%, N=1,972). In the large safety study (Rota-023), 99 deaths occurred during the study*: 56 in ROTARIX™ group (N=31,673) and 43 in the placebo group (N=31,552). None of the cases were assessed as related to vaccination and no potential imbalance was detected for the 99 fatal cases in terms of overall mortality (P-value = 0.198).

Safety in Preterm Infants:
In a clinical study, 1009 preterm infants were administered ROTARIX™ or placebo (198 were 27-30 weeks gestational age and 801 were 31-36 weeks gestational age). The first dose was administered from 6 weeks after birth. SAEs were observed in 5.1% of recipients of ROTARIX™ as compared to 6.8% of placebo recipients. Similar rates of solicited and unsolicited symptoms were observed in ROTARIX™ and placebo recipients. No cases of intussusception were reported. For premature infants born less than 36 weeks of gestation, and who remain hospitalized at the time of recommended

---

* up to the data lock point.
administration, close monitoring for at least 48 hours after vaccination could be considered.

**Safety in Infants with Human Immunodeficiency (HIV) Infection**

In a clinical study, 100 infants with HIV infection were administered three doses of ROTARIX™ or placebo. The safety profile was similar between ROTARIX™ and placebo recipients.

**Table 4** Adverse reactions considered by the investigator as being at least possibly related to ROTARIX™ vaccination

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Event</th>
<th>System/Organ Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Common: ≥ 10%</td>
<td>irritability</td>
<td>Psychiatric Disorders</td>
</tr>
<tr>
<td></td>
<td>loss of appetite</td>
<td>Gastrointestinal disorders</td>
</tr>
<tr>
<td>Common: ≥ 1% and &lt; 10%</td>
<td>diarrhea, vomiting, flatulence, abdominal pain, regurgitation of food</td>
<td>Gastrointestinal disorders</td>
</tr>
<tr>
<td></td>
<td>fever, fatigue</td>
<td>General disorders and administration site conditions</td>
</tr>
<tr>
<td>Uncommon: ≥ 0.1% and &lt; 1%</td>
<td>crying, sleep disorder</td>
<td>Psychiatric Disorders</td>
</tr>
<tr>
<td></td>
<td>somnolence</td>
<td>Nervous system disorders</td>
</tr>
<tr>
<td></td>
<td>constipation</td>
<td>Gastrointestinal disorders</td>
</tr>
<tr>
<td>Rare: ≥ 0.01% and &lt; 0.1%</td>
<td>upper respiratory tract infection</td>
<td>Infections and infestations</td>
</tr>
<tr>
<td></td>
<td>hoarseness, rhinorrhea</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
</tr>
<tr>
<td></td>
<td>dermatitis, rash</td>
<td>Skin and subcutaneous tissue disorders</td>
</tr>
<tr>
<td></td>
<td>muscle cramp</td>
<td>Musculoskeletal and connective tissue disorders</td>
</tr>
</tbody>
</table>

- **Clinical trials for the liquid formulation**

In a total of 4 clinical trials, approximately 3800 doses of ROTARIX™ liquid formulation were administered to approximately 1930 infants. Those trials have shown that the safety and reactogenicity profile of the liquid formulation is comparable to the lyophilized formulation.

**Post-Marketing Adverse Drug Reactions**

The following events have been spontaneously reported during post-approval use of ROTARIX™. Because these events were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or to establish a causal relationship to vaccine exposure.

**Gastrointestinal disorders:** Hematochezia, Intussusception.

**Infections and Infestations:** Kawasaki disease
DRUG INTERACTIONS

Overview
Immunosuppressive therapies may reduce the immune response to vaccines. The potential interaction of these therapies with ROTARIX™ is not known.

Use With Other Vaccines
ROTARIX™ can be given concomitantly with any of the following monovalent or combination vaccines [including hexavalent vaccines (DTPa-HBV-IPV/Hib): diphtheria-tetanus-whole cell pertussis vaccine (DTPw), diphtheria-tetanus-acellular pertussis vaccine (DTPa), Haemophilus influenzae type b vaccine (Hib), inactivated polio vaccine (IPV), hepatitis B vaccine (HBV), pneumococcal conjugate vaccine and meningococcal serogroup C conjugate vaccine. Clinical studies demonstrated that the immune responses to and the safety profiles of the administered vaccines were unaffected.

Concomitant administration of ROTARIX™ and oral polio vaccine (OPV) does not affect the immune response to the polio antigens but may reduce that to ROTARIX™ vaccine. The immune response to ROTARIX™ is unaffected when OPV is administered two weeks apart from ROTARIX™.

DOSAGE AND ADMINISTRATION

Dosing Considerations
- ROTARIX™ is for oral use only.
- UNDER NO CIRCUMSTANCES SHOULD ROTARIX™ BE INJECTED.

Recommended Dose and Dosage Adjustment
The vaccination course consists of two doses. The first dose can be administered from the age of 6 weeks. There should be an interval of at least 4 weeks between doses. ROTARIX™ may be given to preterm infants following the same vaccination course. This could be incorporated into the Canadian Immunization Schedule (2 and 4 months). Other immunization schedules have also been evaluated (see CLINICAL TRIALS). The administration of the 2 doses should be completed by the age of 24 weeks.

In particular circumstances, if the vaccine is given at an earlier age, and that the second dose is given within the shortest interval of 4 weeks, a lower immune response might be induced (see CLINICAL TRIALS, Protective efficacy of ROTARIX™ liquid formulation).

It is strongly recommended that infants who receive a first dose of ROTARIX™ complete the 2 dose regimen with ROTARIX™. There are no data on safety, immunogenicity or efficacy when ROTARIX™ is administered for the first dose and another rotavirus vaccine is administered for the second dose or vice versa.
In clinical trials, spitting or regurgitation of the vaccine has rarely been observed and, under such circumstances, a replacement dose was not given. However, in the unlikely event that an infant spits out or regurgitates most of the vaccine dose, a single replacement dose may be given at the same vaccination visit.

There are no restrictions on the infant’s consumption of food or liquid, including breastmilk, either before or after vaccination.

There is no evidence available to suggest that breastfeeding would reduce the protection against rotavirus gastroenteritis afforded by ROTARIX™. Therefore, breastfeeding may be continued during the vaccination schedule.

The number of doses that would provide sufficient protection in immune compromised subjects has not been determined.

**Administration**
See SPECIAL HANDLING INSTRUCTIONS.

**OVERDOSAGE**

No case of overdose has been reported.

**ACTION AND CLINICAL PHARMACOLOGY**

Rotavirus infection is the leading cause of severe acute gastroenteritis in infants and young children throughout the world. Rotavirus is transmitted mainly by the fecal-oral route, through close person-to-person contact, and through fomites. Ingested virus particles infect the cells in the villi of the small intestine, typically leading to villous atrophy. Characteristic clinical features include diarrhea, vomiting, fever and abdominal discomfort, occasionally leading to fatal dehydrating illness. Improvements or increased efforts in hygiene and sanitation are known to be of limited efficacy.

Rotavirus infection affects 95% of children by the age of 3 to 5 years worldwide. The incidence of rotavirus infections is highest in children between 6 and 24 months of age. Primary infection after 3 months of age usually causes the most severe disease. Subsequent infections are possible but typically cause much milder symptoms.

The mortality rate associated with rotavirus is estimated to be 611,000 (range 454,000-705,000) annual deaths worldwide. Although the number of deaths due to rotavirus may be underestimated because testing for rotavirus is not routine, the mortality for Canada is proportionally compatible with estimated numbers from the US of 20 to 102 deaths per year. Rotavirus is estimated to cause 39% (range 29% to 45%) of childhood diarrhea hospitalizations.
Morbidity due to hospitalizations for diarrhea caused by rotavirus is high in industrialized countries. Nearly every child in the US is infected with rotavirus by the age of 5 years and the majority will have gastroenteritis, resulting in approximately 410,000 physician visits, 205,000-272,000 emergency department visits and 55,000-70,000 hospitalizations each year.

In Canada, rotavirus gastroenteritis during the winter and spring seasons have been estimated as representing between 37% (Greater Toronto) to 71% (Quebec) of community acquired gastroenteritis cases resulting in hospitalization, in children aged less than 5 years. In Quebec, the annual number of hospitalizations for rotavirus gastroenteritis in 0-4 year olds was estimated as 2,000-2,500, representing 40-50% of the annual number of its hospitalizations for gastroenteritis in this age range within the province. Hospital-acquired rotavirus infection among children also results in significant burden, both by prolonging the affected child’s hospital stay and act as a reservoir that can propagate additional cases of nosocomial rotavirus. Globally, the incidence rates of nosocomial rotavirus infection vary, ranging from 0.97 to 27.7 per 100 hospital admissions. A surveillance study conducted in the Halifax regional municipality over the period of 1991-1999 observed that rotavirus infection accounted for 31% of nosocomial diarrhea episodes with an identified pathogen in children <18 years of age. The incidence of circulating rotavirus strains documented in recent Canadian reports has indicated that the distribution of rotavirus strains identified is similar to other developed countries, with G1 as the predominant strain, with only sporadic isolations of other serotypes.

Worldwide, circulating strains of G serotypes 1 to 4, associated with P genotypes P[8] and P[4] (G1P[8], G2P[4], G3P[8], and G4P[8]) predominate. Based on a recent review of the global distribution of rotavirus serotypes/genotypes, these strains were responsible for 88.5% of rotavirus diarrhea among children worldwide, with G1P[8] type being the predominant strain accounting for 64.7% of rotavirus infections.

Based on the distribution of P and G combinations, G1P[8], G2P[4], G3P[8] and G4P[8] represent over 90% of the rotavirus infections in North America, Europe and Australia.

**Mechanism of Action**

ROTARIX™ contains a live, attenuated human rotavirus that replicates in the small intestine and induces immunity. ROTARIX™ vaccine is derived from the human 89-12 strain which belongs to G1 serotype and P[8] genotype. G1 is the most prevalent strain worldwide. It is known that the genotype P[8] is shared by most other circulating strains, including serotypes G3, G4 and G9.

The immunologic mechanism by which ROTARIX™ protects against rotavirus gastroenteritis is not completely understood. A relationship between antibody responses to rotavirus vaccination and protection against rotavirus gastroenteritis has not been established.
STORAGE AND STABILITY

Store in a refrigerator (2°C to 8°C). Do not freeze.

In order to protect the vaccine from light it is recommended that the vaccine is stored in the original package.

The expiry date of the vaccine is indicated on the label and packaging.

SPECIAL HANDLING INSTRUCTIONS

The vaccine is presented as a clear, colorless liquid, free of visible particles, for oral administration.

The vaccine is ready to use (no reconstitution or dilution is required).

The vaccine is to be administered orally without mixing with any other vaccines or solutions.

The vaccine should also be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, discard the vaccine. Any unused vaccine or waste material should be disposed of in accordance with local requirements.

This medicinal product must not be mixed with other medicinal products.
Administration of the vaccine

1. Remove the protective tip cap from the oral applicator.

2. This vaccine is for oral administration only. The child should be seated in a reclining position. Administer orally (i.e. into the child’s mouth towards the inner cheek) the entire content of the oral applicator.

3. Do not inject.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form

ROTARIX™ vaccine is available as an oral suspension (1.5 mL).
**Composition**

Each 1.5 mL dose is formulated to contain not less than $10^{6.0}$ CCID$_{50}$ of human rotavirus RIX4414 strain (live, attenuated), produced on Vero cells. Each dose also contains Dulbecco’s Modified Eagle Medium (DMEM), sucrose, di-sodium adipate and sterile water.

**Packaging**

**Oral Applicator**

ROTARIX™ is available in an oral applicator (Type 1, Ph. Eur.) with a plunger stopper (butyl rubber) in pack sizes of 1, 5, 10, 25, 50 or 100.
**PART II: SCIENTIFIC INFORMATION**

**PHARMACEUTICAL INFORMATION**

**Drug Substance**

Proper name: Human rotavirus, live, attenuated, oral vaccine.

**Product Characteristics**

ROTARIX™ (human rotavirus, live, attenuated, oral vaccine) is a monovalent, live, attenuated virus vaccine derived from the human 89-12 strain which belongs to G1 serotype and P[8] genotype. G1 is the most prevalent strain worldwide. It is known that the genotype P[8] is shared by most other circulating strains, including serotypes G3, G4 and G9. Natural infection with the virus is not limited to the G and P related antigens, but also is associated with the structural proteins VP2 and VP6, in addition to VP7 and VP4 as well as with the non-structural proteins such as NSP4. It has been shown that the induction of an immune response following vaccination with an attenuated G1P[8] human strain is sufficient to provide cross-protection against severe gastroenteritis linked to different G strains.
CLINICAL TRIALS

- Protective efficacy of ROTARIX™ lyophilized formulation

Clinical studies have been conducted in Europe and Latin America to evaluate the protective efficacy of ROTARIX™ against any and severe rotavirus gastroenteritis.

Table 5  Study demographics and trial design

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Trial design</th>
<th>Dosage and route of administration</th>
<th>No. of subjects</th>
<th>Mean age at administration in weeks (range)</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rota-004</td>
<td>Multi-centre, double blinded, randomized, placebo controlled study</td>
<td>Oral 2 doses of $10^{5.7}$ foci forming units (ffu) at 2 and 4 months of age</td>
<td>First efficacy follow-up: 245 Vaccine 123 Placebo</td>
<td>First dose: Vaccine: 8.3 (6-12) Placebo: 8.2 (6-12) Second efficacy follow-up: 241 Vaccine 120 Placebo</td>
<td>Vaccine: Male 53.5% Placebo: Male 50.4%</td>
</tr>
<tr>
<td>Rota-006</td>
<td>Multi-centre, multi-country, double blind, randomized, placebo controlled study</td>
<td>Oral 2 doses (of either $10^{4.7}$, $10^{5.2}$ or $10^{5.8}$ foci forming units (ffu)) at 2 and 4 months of age</td>
<td>First efficacy follow-up: 1,392 Vaccine 454 Placebo</td>
<td>First dose: Vaccine*: 8.3 (6-12) Placebo: 8.3 (6-12) Second efficacy follow-up: 332 Vaccine 109 Placebo</td>
<td>Vaccine &amp; Placebo Male 52%</td>
</tr>
<tr>
<td>Rota-023</td>
<td>Multi-centre, multi-country, double blinded, randomized, placebo controlled study</td>
<td>Oral 2 doses of $10^{6.5}$ CCID$_{50}$ at 2 and 3 to 4 months of age$^1$</td>
<td>First efficacy follow-up: 9,009 Vaccine 8,858 Placebo</td>
<td>First dose: Vaccine: 8.4 (5-13) Placebo: 8.4 (2-13) Second efficacy follow-up: 7,175 Vaccine 7,062 Placebo</td>
<td>Vaccine: Male 50.1% Placebo: Male 52.0%</td>
</tr>
<tr>
<td>Rota-036</td>
<td>Multi-centre, multi-country, double blinded, randomized, placebo controlled study</td>
<td>Oral 2 doses of $10^{6.5}$ CCID$_{50}$ at a 2, 3 months, 2, 4 months, 3, 4 months or 3, 5 months schedule$^1$</td>
<td>First efficacy follow-up: 2,572 Vaccine 1,302 Placebo</td>
<td>First dose: Vaccine: 11.5 (5-18) Placebo: 11.5 (6-16) Second efficacy follow-up: 2,554 Vaccine 1,294 Placebo</td>
<td>Vaccine: Male 53.6% Placebo: Male 50.9%</td>
</tr>
</tbody>
</table>

Note: The administration schedule depends on the countries in which the studies were conducted.
* This is applicable to the $10^{5.8}$ ffu titre vaccine

Clinical studies on protective efficacy were undertaken with ROTARIX™ lyophilized formulation, on which ROTARIX™ approval was based. Subsequently, clinical studies were undertaken with the liquid formulation to assess the elicited immune response compared to the lyophilized formulation, including a non-inferiority study (see Protective efficacy of ROTARIX™ liquid formulation).
Results

A clinical study performed in Europe (Rota-036) evaluated ROTARIX™ given according to different European schedules (2, 3 months; 2, 4 months; 3, 4 months; 3, 5 months) in more than 3,800 subjects. Severity of gastroenteritis was defined according to the Vesikari 20-point scale which evaluates the full clinical picture of rotavirus gastroenteritis by taking into account the severity and duration of diarrhea and vomiting, the severity of fever and dehydration as well as the need for treatment.

Safety

For safety information refer to the Adverse Reactions section, Part 1

Efficacy

Table 6 Efficacy following two doses of ROTARIX™ persisting through the first and second rotavirus seasons

<table>
<thead>
<tr>
<th></th>
<th>1st Rotavirus Season</th>
<th>2nd Rotavirus Season</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Efficacy (%)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Any rotavirus gastroenteritis</td>
<td>87.1*</td>
<td>79.6;92.1</td>
</tr>
<tr>
<td>Severe rotavirus gastroenteritis (Vesikari score ≥11)</td>
<td>95.8*</td>
<td>89.6;98.7</td>
</tr>
<tr>
<td>Rotavirus gastroenteritis requiring medical attention</td>
<td>91.8*</td>
<td>84.9;96.3</td>
</tr>
<tr>
<td>Hospitalization due to rotavirus gastroenteritis</td>
<td>100*</td>
<td>81.8;100</td>
</tr>
</tbody>
</table>

* Statistically significant (p< 0.05)

Vaccine efficacy during the first year of life progressively increased with increasing disease severity, reaching 100% (95% CI: 84.7;100) for Vesikari scores ≥17.
A clinical study performed in Latin America (Rota-023) evaluated ROTARIX™ in more than 17,500 subjects. Severity of gastroenteritis was defined according to WHO criteria. The protective vaccine efficacy against severe rotavirus gastroenteritis requiring hospitalization and/or rehydration therapy in a medical facility and the type specific vaccine efficacy after 2 doses of ROTARIX™ are presented in the Table 8A below:

Due to the rareness of the G2P[4] serotype, a meta analysis was performed. A pooled analysis of four efficacy studies, listed in Table 5, showed a 71.4% (95% CI:20.1:91.1) efficacy against severe rotavirus gastroenteritis (Vesikari score ≥11) caused by rotavirus G2P[4] type during the first year of life. Please see Table 8B below:
### Table 8A  Type specific vaccine efficacy following 2 doses of ROTARIX™ (Rota-023)

<table>
<thead>
<tr>
<th>Type</th>
<th>Severe rotavirus gastroenteritis (1st year of life)</th>
<th></th>
<th>Severe rotavirus gastroenteritis (2nd year of life)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ROTARIX™ N=8,858; Placebo N=9,009</td>
<td></td>
<td>ROTARIX™ N=7,175; Placebo N=7,062</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Efficacy (%)</td>
<td>95% CI</td>
<td>Efficacy (%)</td>
<td>95% CI</td>
</tr>
<tr>
<td>All rotavirus gastroenteritis</td>
<td>84.7*</td>
<td>71.7;92.4</td>
<td>79.0*</td>
<td>66.4;87.4</td>
</tr>
<tr>
<td>G1P[8]</td>
<td>91.8*</td>
<td>74.1;98.4</td>
<td>72.4*</td>
<td>34.5;89.9</td>
</tr>
<tr>
<td>G2P[4]</td>
<td>41.0</td>
<td>-79.2; 82.4</td>
<td>1.6</td>
<td>-7.626.1;98.6</td>
</tr>
<tr>
<td>G3P[8]</td>
<td>87.7*</td>
<td>8.3;99.7</td>
<td>71.9</td>
<td>-47.7;97.1</td>
</tr>
<tr>
<td>G4P[8]</td>
<td>50.8*</td>
<td>-844;99.2</td>
<td>63.1*</td>
<td>0.7;88.2</td>
</tr>
<tr>
<td>G9P[8]</td>
<td>90.6*</td>
<td>61.7;98.9</td>
<td>87.7*</td>
<td>72.9;95.3</td>
</tr>
<tr>
<td>Strains with P[8] genotype</td>
<td>90.9*</td>
<td>79.2;96.8</td>
<td>79.5*</td>
<td>67.0;87.9</td>
</tr>
</tbody>
</table>

N=ATP cohort for efficacy

*statistically significant (p<0.05)

" The numbers of cases on which the estimates of efficacy against G4P[8] were based were very small (1 case in the ROTARIX™ group and 2 cases in the placebo).

### Table 8B  Pooled analysis of sever RV GE (score greater than or equal to 11 on Vesikari scale) due to G2P[4] type and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first year follow-up (studies Rota-004, Rota-006, Rota-023, and Rota-036, ATP cohort for efficacy)

<table>
<thead>
<tr>
<th>Study</th>
<th>HRV</th>
<th></th>
<th>Placebo</th>
<th></th>
<th>VE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n</td>
<td>%</td>
<td>N</td>
<td>n</td>
</tr>
<tr>
<td>Rota-004</td>
<td>245</td>
<td>0</td>
<td>0.0</td>
<td>123</td>
<td>1</td>
</tr>
<tr>
<td>Rota-006</td>
<td>1,392</td>
<td>0</td>
<td>0.0</td>
<td>454</td>
<td>3</td>
</tr>
<tr>
<td>Rota-023</td>
<td>9,009</td>
<td>5</td>
<td>0.1</td>
<td>8,858</td>
<td>9</td>
</tr>
<tr>
<td>Rota-036</td>
<td>2,572</td>
<td>1</td>
<td>0.0</td>
<td>1,302</td>
<td>2</td>
</tr>
<tr>
<td>All*</td>
<td>1,3218</td>
<td>6</td>
<td>0.0</td>
<td>10,737</td>
<td>15</td>
</tr>
</tbody>
</table>

Results from the first efficacy follow-up period on the ATP cohort for efficacy

*VE defined as 1-stratified Poisson rate ratio
**Immune response**

The immunologic mechanism by which ROTARIX™ protects against rotavirus gastroenteritis is not completely understood. A relationship between antibody responses to rotavirus vaccination and protection against rotavirus gastroenteritis has not been established. The following table shows the percentage of infants with serum anti-rotavirus IgA antibody titres ≥ 20 U/ml (by ELISA) one to two months after the second dose of vaccine or placebo as observed in different studies.

**Table 9  Percent of infants with serum anti-rotavirus IgA antibody titres ≥ 20 U/mL 1 to 2 months after the second dose**

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Vaccine conducted in</th>
<th>N</th>
<th>% ≥20U/mL</th>
<th>95% CI</th>
<th>Placebo conducted in</th>
<th>N</th>
<th>% ≥20U/mL</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2, 3 months</td>
<td>France, Germany</td>
<td>239</td>
<td>82.8</td>
<td>77.5;87.4</td>
<td>127</td>
<td>8.7</td>
<td>4.4;15.0</td>
<td></td>
</tr>
<tr>
<td>2, 4 months</td>
<td>Spain</td>
<td>186</td>
<td>85.5</td>
<td>79.6;90.2</td>
<td>89</td>
<td>12.4</td>
<td>6.3;21.0</td>
<td></td>
</tr>
<tr>
<td>3, 5 months</td>
<td>Finland, Italy</td>
<td>180</td>
<td>94.4</td>
<td>90.097.3</td>
<td>114</td>
<td>3.5</td>
<td>1.0;8.7</td>
<td></td>
</tr>
<tr>
<td>3, 4 months</td>
<td>Czech Republic</td>
<td>182</td>
<td>84.6</td>
<td>78.5;89.5</td>
<td>90</td>
<td>2.2</td>
<td>0.3;7.8</td>
<td></td>
</tr>
<tr>
<td>2, 3 to 4 months</td>
<td>Latin America; 11 countries</td>
<td>393</td>
<td>77.9</td>
<td>73.8;81.6</td>
<td>341</td>
<td>15.1</td>
<td>11.7;19.0</td>
<td></td>
</tr>
</tbody>
</table>

**Immune Response in Preterm Infants**

In a clinical study conducted in preterm infants, ROTARIX™ was immunogenic; 85.7% of subjects achieved serum anti-rotavirus IgA antibody titres ≥20 U/mL (by ELISA) one month after the second dose of the vaccine.

- **Protective efficacy of ROTARIX™ liquid formulation**

Four controlled studies were undertaken with ROTARIX™ liquid formulation to assess elicited immune response. Three of these were comparative studies in which healthy infants were enrolled to receive two doses of ROTARIX™ liquid or lyophilized formulations, given at the age of 2 and 3 months (Rota-048), 2 and 4 months (Rota-057), or 3 and 4 months (Rota-061). The immune response elicited by ROTARIX™ liquid formulation was comparable to that elicited by the lyophilized formulation (Table 10).

**Table 10  Percent of infants with serum anti-rotavirus IgA antibody titres ≥ 20U/mL 1 month after the second dose**

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Studies conducted in</th>
<th>Liquid Formulation</th>
<th>Lyophilized Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>% ≥20U/mL</td>
</tr>
<tr>
<td>2, 3 months</td>
<td>Finland</td>
<td>80</td>
<td>90.0</td>
</tr>
<tr>
<td>2, 4 months</td>
<td>Panama</td>
<td>449</td>
<td>80.8</td>
</tr>
<tr>
<td>3, 4 months</td>
<td>Finland</td>
<td>746</td>
<td>88.6</td>
</tr>
</tbody>
</table>
In a study conducted in Vietnam (Rota-051), the immune response in terms of seroconversion rates and GMCs in the group that received two doses of ROTARIX™ liquid vaccine with the first and second dose given at 8 and 12 weeks of age (4 weeks apart) was lower than the response in the group that received two doses of ROTARIX™ liquid vaccine with the first and second dose given at 8 and 16 weeks of age (8 weeks apart).

Serum anti-RV IgA antibodies are generally accepted as a valid surrogate marker of protection, and published data suggests that the ROTARIX™-induced serum anti-RV IgA antibodies might be a good correlate of vaccine induced protection, despite the absence of an established immune correlate of protection. The immune response observed after two doses of ROTARIX™ liquid formulation was comparable to the immune response observed after 2 doses of ROTARIX™ lyophilized formulation, the vaccine efficacy for the liquid formulation is assumed to be similar to that observed with the lyophilized formulation.

**TOXICOLOGY**

Preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity.

**REFERENCES**


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PART III: CONSUMER INFORMATION

ROTARIX™
Human rotavirus, live, attenuated oral vaccine

This leaflet is part III of a three-part "Product Monograph" published when ROTARIX™ (human rotavirus, live, attenuated oral vaccine) was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about ROTARIX™. Contact your doctor or pharmacist if you have any questions about the vaccine.

ABOUT THIS VACCINE

What the vaccine is used for:
ROTARIX™ is a viral vaccine, containing live, attenuated human rotavirus, that helps to protect your child against gastroenteritis (diarrhea and vomiting) caused by rotavirus infection.

Rotavirus infection is the most common cause of severe diarrhea in infants and young children. Rotavirus is easily spread from hand-to-mouth due to contact with stools from an infected person. Most children with rotavirus diarrhea recover on their own. However, some children become very ill with severe vomiting, diarrhea and life-threatening loss of fluids that requires hospitalization. Rotavirus infections are responsible for hundreds of thousands of deaths worldwide every year especially in developing countries, where nutrition and health care are not optimal.

When a person is given the vaccine, the immune system (the body’s natural defences) will make antibodies against the most commonly occurring types of rotavirus. These antibodies protect against disease caused by these types of rotavirus.

As with all vaccines, ROTARIX™ may not completely protect all people who are vaccinated against the rotavirus infections. It is intended to prevent.

What it does:
When your child receives this vaccine, his/her immune system (the body’s natural defence) will make antibodies that will recognize the most commonly occurring types of rotavirus. These antibodies protect against disease caused by these types of rotavirus and will protect your child from infection.

When it should not be used:
Please see WARNINGS AND PRECAUTIONS section.

Take special care with ROTARIX™:
Excretion of the live vaccine virus in the stools of vaccinated children is known to occur after vaccination, especially around the 7th day. Persons in contact with recent vaccinated children should wash their hands after changing the child’s diapers.

ROTARIX™ should be given with caution to children in close contact with individuals having any disease or receiving any medicine which may reduce his/her resistance to infection.

What the medicinal ingredient is:
ROTARIX™ consists of live, attenuated human rotavirus.

What the important nonmedicinal ingredients are:
The important nonmedicinal ingredients are Dulbecco’s Modified Eagle Medium (DMEM), sucrose, di-sodium adipate, and sterile water.

What dosage forms it comes in:
The ROTARIX™ vaccine is a suspension for oral administration.

ROTARIX™ is supplied as a suspension in a single dose oral applicator.

WARNINGS AND PRECAUTIONS
BEFORE you use ROTARIX™ talk to your doctor or pharmacist if your child:

- has previously had any allergic reaction to rotavirus vaccines or any component contained in ROTARIX™ (the active substances and other ingredients in ROTARIX™; see What the medicinal ingredient is and What the important nonmedicinal ingredients are sections). Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.
- has an intolerance to some sugars (See What the important nonmedicinal ingredients are).
- was born with a malformation of the gastrointestinal system that would predispose for intussusception.
- has any disease or is taking any medicine which reduces his/her resistance to infection.
- has a severe infection with a high temperature. It might be necessary to postpone the vaccination until recovery. A minor infection such as a cold should not be a problem, but talk to your doctor first.
- has diarrhea or is vomiting. It might be necessary to postpone the vaccination until recovery.
INTERACTIONS WITH THIS VACCINE

Please tell your doctor if your child is taking or has recently taken any other medicines, including medicines obtained without a prescription, or has recently received any other vaccine.

ROTARIX™ may be given at the same time your child receives other normally recommended vaccinations, such as diphtheria, tetanus, pertussis (whooping cough), *Haemophilus influenzae* type b, inactivated polio, hepatitis B, pneumococcal vaccines as well as meningococcal serogroup C conjugate vaccine.

PROPER USE OF THIS VACCINE

**Usual dose:**
The Health Care provider will administer the recommended dose of ROTARIX™ to your child. The vaccine (1.5 mL liquid) will be given orally. Under no circumstance should this vaccine be administered by injection.

Your child will receive two doses of the vaccine. Each dose will be given on a separate occasion with an interval of at least 4 weeks between the two doses. The first dose may be given from the age of 6 weeks. The two doses of the vaccine must have been given by the age of 24 weeks, although they should preferably have been given before 16 weeks of age.

ROTARIX™ may be given to infants who were born prematurely following the same vaccination course.

Your doctor may suggest giving the ROTARIX™ vaccine during the 2 and 4 month visits when getting some of the other vaccines.

In case your child spits out or regurgitates most of the vaccine dose, a single replacement dose may be given at the same vaccination visit.

There are no restrictions on the infant’s consumption of food or liquid, including breastmilk, either before or after the vaccination.

When ROTARIX™ is given to your child for the first dose, it is recommended that your child also receives ROTARIX™ (and not another rotavirus vaccine) for the second dose.

**Missed Dose:**
It is important that you follow the instructions of your Health Care Provider regarding return visits. If you forget to go back to your doctor at the scheduled time, ask your doctor for advice.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, ROTARIX™ can cause side effects, although not everybody gets them. Side effects that occurred during clinical trials with ROTARIX™ were as follows:

Very common (side effects which may occur in more than 10% of doses):
- loss of appetite
- irritability

Common (side effects which may occur between 1% and 10% of doses):
- fever, fatigue
- diarrhea, vomiting, or regurgitation of food, flatulence and abdominal pain.

Uncommon (side effects which may occur between 0.1% and 1% of doses):
- sleep disorder, sleepiness
- constipation

Rare (side effects which may occur between 0.01% and 0.1% of doses):
- upper respiratory tract infections, hoarseness, runny nose
- dermatitis, rash
- muscle cramp

This is not a complete list of side effects. For any unexpected effects while taking ROTARIX™, contact your doctor or pharmacist.

HOW TO STORE IT

- Keep out of reach and sight of children.
- Store in a refrigerator (2°C to 8°C).
- Do not freeze.
- Store in original package to protect from light.
REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects information on serious and unexpected adverse events following vaccination. If you suspect you have had a serious or unexpected event following receipt of a vaccine you may notify the Public Health Agency of Canada:

By toll-free telephone: 1-866-844-0018  
By toll-free fax: 1-866-844-5931  

By regular mail:  
Vaccine Safety  
130 Colonnade Road  
Ottawa, Ontario  
K1A 0K9 Address Locator 6502A

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:  
http://www.gsk.ca  
or by contacting the sponsor, GlaxoSmithKline Inc.  
7333 Mississauga Road  
Mississauga, Ontario  
L5N 6L4  
1-800-387-7374

This leaflet was prepared by GlaxoSmithKline Inc.

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NACI Statement
An Advisory Committee Statement (ACS)

National Advisory Committee on Immunization (NACI)†

Updated Statement on the use of Rotavirus Vaccines

Preamble

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

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Liaison Representatives: Dr. B. Bell (Center for Disease Control and Prevention), Ms. K. Pielak (Canadian Nursing Coalition for Immunization), Dr. S. Rechner (College of Family Physicians of Canada), Dr. M. Salvadori (Canadian Paediatric Society), S. Pelletier (Community Hospital Infection Control Association), Dr. N. Sicard (Canadian Public Health Association), Dr. V. Senikas (Society of Obstetricians and Gynaecologists of Canada), Dr. P. Plourde (Committee to Advise on Tropical Medicine and Travel), Dr. P. Van Buyneder (Council of Chief Medical Officers of Health), Dr. P. Orr (Association of Medical Microbiology and Infectious Disease Canada)

Ex-Officio Representatives: Ms. M. FarhangMehta (Centre for Immunization and Respiratory Infectious Diseases), Dr. S. Desai (Centre for Immunization and Respiratory Infectious Diseases), LCol (Dr.) James Anderson (Department of National Defence), Dr. Ezzat Farzad (First Nations and Inuit Health Branch – Office of Community Medicine), Dr. F. Hindieh (Biologics and Genetic Therapies Directorate), Dr. D. Elliott (Centre for Immunization and Respiratory Infectious Diseases), Dr. P. Varughese (Centre for Immunization and Respiratory Infectious Diseases)

Déclaration d’un comité consultatif (DCC)

Comité consultatif national de l’immunisation (CCNI)†

Mise à jour de la déclaration sur l’utilisation des vaccins antirotavirus

Preamble

Le Comité consultatif national de l’immunisation (CCNI) donne à l’Agence de la santé publique du Canada des conseils constants et à jour liés à l’immunisation dans les domaines de la médecine, des sciences et de la santé publique. L’Agence de la santé publique du Canada reçoit que les conseils et les recommandations figurant dans la présente déclaration reposent sur les connaissances scientifiques les plus récentes et diffusent le document à des fins d’information. Les personnes qui administreront le vaccin doivent également connaître le contenu des monographies de produit pertinentes. Les recommandations d’utilisation et les autres renseignements qui figurent dans le présent document peuvent différer du contenu des monographies de produit des fabricants du vaccin au Canada. Les fabricants ont fait approuver leur vaccin et démontré son innocuité et son efficacité uniquement lorsqu’il est utilisé conformément à la monographie de produit. Les membres du CCNI et les agents de liaison doivent se conformer à la politique

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Représentants de liaison : D’r B. Bell (Center for Disease Control and Prevention des États-Unis), Mme K. Pielak (Coalition canadienne des infirmières et infirmiers pour l’immunisation), D’r S. Rechner (Collège des médecins de famille du Canada), D’r M. Salvadori (Société canadienne de pédieatrie), S. Pelletier (Association pour la prévention des infections à l’hôpital et dans la communauté), D’r N. Sicard (Association canadienne de santé publique), D’r V. Senikas (Société des obstétriciens et gynécologues du Canada), D’r P. Plourde (Comité consultatif de la médecine tropicale et de la médecine des voyages), D’r PVan Buyneder (Conseil des médecins hygiénistes en chef), D’r P. Orr (l’Association pour la microbiologie médicale et l’infectiologie Canada)

Représentants d’office : Mme M. FarhangMehta (Centre de l’immunisation et des maladies respiratoires infectieuses), D’r S. Desai (Centre de l’immunisation et des maladies respiratoires infectieuses), D’r B. Law (Centre de l’immunisation et des maladies respiratoires infectieuses), LCol (Dr.) James Anderson (ministère de la Défense nationale), D’r Ezzat Farzad (Direction générale de la santé des Premières nations et des Inuits – Bureau de la médecine communautaire), D’r F. Hindieh (Direction des produits biologiques et des thérapies génétiques), D’r D. Elliott (Centre de l’immunisation et des maladies respiratoires infectieuses), D’r P. Varughese (Centre de l’immunisation et des maladies respiratoires infectieuses)
monographs. NACI members and liaison members conduct themselves within the context of the Public Health Agency of Canada's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

Introduction

Since the publication of the Statement on the Recommended Use of Pentavalent Human-Bovine Reassortant Rotavirus Vaccine in CCDR in January 2008(1) a new rotavirus vaccine (Rotarix™, GlaxoSmithKline Inc.) has been authorized for use. Additional epidemiologic, safety and effectiveness information relevant to the use of rotavirus vaccines has also become available. While the two authorized vaccines (RotaTeq®, Merck Canada, Inc. and Rotarix™) both protect against rotavirus gastroenteritis, they differ in their composition and scheduled usage. This statement provides an update on the recommendations for use of pentavalent human-bovine reassortant rotavirus vaccine (RotaTeq®) and provides information on the safety, efficacy, and recommended use of live, attenuated monovalent human rotavirus vaccine (Rotarix™).

NACI Recommendations:

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). The vaccination series should be completed by 8 months (8 months plus 0 days). (Recommendation – Grade A – good evidence to recommend immunization)

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 first dose should be given between 6 weeks (6 weeks and 0 days) and up to 15 weeks (14 weeks plus 6 days). The vaccination series should be completed by 8 months (8 months plus 0 days) (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)

Recommandations du CCNI :

1. Nourrissons en santé : Les vaccins antirotavirus sont recommandés pour les nourrissons âgés de 6 semaines (6 semaines et 0 jour) à 15 semaines (14 semaines et 6 jours). La série vaccinale devrait se terminer à 8 mois (8 mois et 0 jour). (Recommandation – Catégorie A – données probantes suffisantes pour recommander l’immunisation)

2. Nourrissons prématurés : Les nourrissons qui sont âgés entre 6 semaines (6 semaines plus 0 jour) et 8 mois (8 mois plus 0 jour) d’âge chronologique et qui sont en santé et non hospitalisés peuvent recevoir RotaTeq® ou Rotarix™. La première dose devrait être administrée entre l’âge de 6 semaines (6 semaines et 0 jour) et de 15 semaines (14 semaines et 6 jours). La série vaccinale devrait se terminer à 8 mois (8 mois et 0 jour). (Recommandation – Catégorie A – données probantes suffisantes pour recommander l’immunisation)

3. Nourrissons immunodéprimés : D’après le risque théorique associé aux vaccins à virus vivant attesté chez les nourrissons immunodéprimés et compte tenu du peu de données relatives à cette population, le CCNI recommande que les nourrissons atteints ou soupçonnés d’être atteints d’un déficit immunitaire ne reçoivent pas RotaTeq® ni Rotarix™ sans consultation préalable auprès d’un médecin spécialiste ou d’un expert dans ces troubles. (Recommandation – Catégorie E – données probantes suffisantes pour déconseiller l’immunisation)

4. Nourrissons ayant des antécédents d’intussusception : En s’appuyant sur des données récentes, le CCNI recommande que les nourrissons ayant des antécédents d’intussusception ne reçoivent pas de vaccins antirotavirus. (Recommandation – Catégorie E – données probantes suffisantes pour déconseiller l’immunisation)
NACI reviewed such considerations as the burden of illness of the disease to be prevented and the target population(s), safety, immunogenicity, efficacy, effectiveness of the vaccine(s), vaccine schedules, and other aspects of the overall immunization strategy. Following critical appraisal of individual studies, summary tables with ratings of the quality of the evidence using NACI’s methodological hierarchy (Tables 7 and 8) were prepared, and proposed recommendations for vaccine use developed. The Working Group chair and a PHAC medical specialist presented the evidence and proposed recommendations to NACI. Following thorough review of the evidence and consultation at NACI meetings, the committee voted on specific recommendations. The description of relevant considerations, rationale for specific decisions, and knowledge gaps are described in the text. The full knowledge synthesis is maintained by the PHAC at the following url: http://www.phac-aspc.gc.ca/naci-ccni/index-eng.php#lr. PHAC maintains documentation of these processes throughout knowledge synthesis and recommendation development.

A literature review was conducted for the previous rotavirus statement(1) using the Medline database, from 1966 to 2007, with the following MeSH headings: Rotavirus infection, rotavirus disease, rotavirus vaccine. In follow up to this, another literature review was done to review relevant publications from 2007 to 2009. The same MeSH headings were used to collect new publications. A brief description from the previous review is presented below, along with new data.

### Methods


Une recension des écrits a été effectuée pour la déclaration antérieure sur le vaccin antirotavirus(1) au moyen d’une recherche dans la base de données Medline, pour la période 1966-2007, avec les mots clés MeSH suivants : rotavirus infection, rotavirus disease, rotavirus vaccine. Par la suite, une autre recension des écrits a été réalisée pour retracer des études pertinentes publiées de 2007 à 2009. Les mêmes mots clés MeSH ont été utilisés pour la compilation des nouvelles publications. Une brève description de la recension antérieure est présentée ci dessous, de même que des données nouvelles.

### Summary of Epidemiology and Burden of Disease

Rotavirus is a double-stranded RNA virus composed of an inner core, an internal capsid and an outer capsid. The viral serotype is defined by 2 structural viral proteins (VP) in the outer capsid: VP7, the glycoprotein (G protein) and VP4, the protease-cleaved protein (P protein)(2). These outer capsid proteins elicit neutralizing antibodies believed to be important for protection. Eleven VP7 (G) serotypes and twelve VP4 (P) serotypes are known to cause disease in humans(3). Because the two gene segments that encode these proteins can segregate independently, there is the potential for many VP7/VP4 combinations and a typing system consisting of both G and P types has been developed(2-3).

In the US and, based upon limited data in Canada, six rotavirus serotypes (P1A[8]G1, P1B[4]G2, P1A[8]G3, P1A[8]G4, P1A[8]G9, and P2A[6]G9) cause the majority of disease. These strains are generally designated by their G serotype specificity (serotypes G1-4 and G9). Approximately 55-65% of all RV gastroenteritis in 2 Canadian studies(4,5) were caused by G1 serotype. However, although non-G1 serotypes are generally less common, the Canadian studies(4,5) were caused by G1 serotype. However, although non-G1 serotypes are generally less common, the potential for many VP7/VP4 combinations and a typing system consisting of both G and P types has been developed(2-3).

### Résumé de l’épidémiologie et du fardeau de la maladie

Le rotavirus est un virus à ARN double brin formé d’un noyau central, d’une capsule interne et d’une capsule externe. Le sérotype viral est défini par deux protéines virales (VP) de structure, situées dans la capsule externe : VP7, la glycoprotéine (protéine G), et VP4, la protéine clivée par une protéase (protéine P)(2). Ces protéines de la capsule externe provoquent la formation d’anticorps neutralisants qui joueraient, semble-t-il, un rôle de protection important. Onze sérotypes VP7 (G) et douze sérotypes VP4 (P) sont connus comme étant pathogènes pour les humains(3). Comme une ségrégation indépendante de ces deux segments de gène qui codent ces protéines est possible, de nombreuses combinaisons VP7/VP4 peuvent exister et un système de typage, fondé sur les types G et P, a été mis au point(2,3).

prevalence of individual serotypes varies year to year and geographically. Each of the other G serotypes can predominate in a given year\(^6\).

Rotavirus is a common cause of gastroenteritis in children accounting overall for 10% to 40% of all childhood gastroenteritis\(^7-10\). Canadian epidemiologic data has been reviewed previously\(^1\). Based upon available Canadian data it is estimated that rotavirus gastroenteritis is associated with considerable healthcare utilization with approximately 36% of children with rotavirus seeing a physician, 15% visiting an emergency department, and 7% requiring hospitalization\(^11\). Rotavirus causes the majority of childhood gastroenteritis requiring hospitalization; overall, between one in 62\(^11\) and one in 312\(^12\) children <5 years of age will require hospitalization for rotavirus. Parents of children with rotavirus gastroenteritis are more likely than parents of children with non-rotavirus gastroenteritis to miss work (54% versus 37%\(^9\)). Household transmission is common, with at least one other family member experiencing diarrhea in 47% of rotavirus cases\(^5,13\).

A recent retrospective study on the burden of rotavirus infections in British Columbia\(^14\) further addresses the issue of the Canadian burden of rotavirus disease. This study included data from administrative databases between 2000 and 2007 in one region in Canada. It found that the incidence of rotavirus disease among children 0-4 years of age was 50.9 per 100 000 population; the hospitalization rate was 20 per 100 000 population. These data have a few important limitations, including a retrospective study design, a limited geographic area investigated, and the use of administrative data.

Prospective surveillance data from the Canadian Immunization Monitoring Program, Active (IMPACT) has recently become available. Between January 2005 and December 2007, 1,359 children were hospitalized\(^15,16\) with lab-confirmed, community-acquired rotavirus gastroenteritis at the 12 IMPACT hospitals. None of the 1,321 cases in which vaccination status was known had received rotavirus vaccine. 63% of cases occurred in infants ≤2 years; mean age of cases was 2.4 years. Underlying co-morbidities were present in 32% of children; gastrointestinal disorders accounted for more than 25% of underlying conditions with Crohn’s disease and gastroesophageal reflux disease being most common. Overall, 48.6% of admitted children had dehydration and the mean duration of diarrhea and vomiting prior to admission was 2.3 days and 2.4 days, respectively. Healthcare utilization associated with rotavirus infection was considerable; including the emergency room visit that led to the hospital admission, 68.5% of children had 1 visit, 26.4% had 2 visits, 4% had three visits, and 1% had four visits to the Emergency Department. Children spent an average of 7.9 hours in the Emergency Department prior to admission and were hospitalized for an average of 3.4 days. In total, 48 children (3.5%) required intensive healthcare utilization associated with rotavirus infection.

Le rotavirus est une cause fréquente de gastroentérite chez les enfants, étant responsable en général de 10% à 40% de toutes les gastroentérites infantiles\(^7-10\). Les données épidémiologiques canadiennes ont déjà été passées en revue\(^1\). Selon les données disponibles au Canada, on estime que la gastroentérite à rotavirus est associée à une utilisation considérable des soins de santé : environ 36% des enfants infectés par un rotavirus consultent un médecin, 15% se rendent dans un service des urgences et 7% doivent être hospitalisés\(^11\). Le rotavirus cause la majorité des gastroentérites infantiles qui nécessitent une hospitalisation ; dans l’ensemble, quelque part entre un enfant sur 62\(^11\) et un enfant sur 312\(^12\) de <5 ans devra être hospitalisé pour une infection à rotavirus. Les parents d’enfants atteints d’une gastroentérite à rotavirus sont plus nombreux que les parents d’enfants souffrant d’une gastroentérite non à rotavirus à s’absenter du travail (54% contre 37%\(^9\)). La transmission familiale est fréquente ; au moins un autre membre de la famille de 47% des cas d’infection à rotavirus souffrant de diarrhée\(^5,13\).

Une étude rétrospective récente du fardeau des infections à rotavirus en Colombie Britannique\(^14\) a approfondi la question du fardeau des maladies à rotavirus au Canada. Cette étude s’est basée sur des données tirées de bases de données administratives pour la période 2000-2007 dans une région du Canada. Elle a montré que l’incidence des maladies à rotavirus chez les enfants de 0 à 4 ans s’établissait à 50,9 pour 100 000 habitants et le taux d’hospitalisation s’élevait à 20 pour 100 000 habitants. Ces données comportent certaines limites importantes, notamment le fait qu’il s’agisse d’une étude rétrospective, de l’examen d’une région géographique limitée et de l’utilisation de données administratives.

Le Programme canadien de surveillance active de l’immunisation (IMPACT) a récemment publié des données provenant d’une étude de surveillance prospective. Entre janvier 2005 et décembre 2007, 1 359 enfants ont été hospitalisés\(^15,16\) dans les 12 hôpitaux du réseau d’IMPACT en raison d’une gastroentérite à rotavirus d’origine communautaire, laquelle a été confirmée en laboratoire. Aucun des 1 321 cas dont le statut vaccinal était connu n’avait reçu de vaccin antirotavirus. Soixante trois pour cent des cas concernaient des nourrissons de 2 ans et moins ; l’âge moyen des cas était de 2,4 ans. Une co-morbidité sous-jacente était présente chez 32% des enfants ; les troubles gastro intestinaux représentaient plus de 25% des affections sous-jacentes, la maladie de Crohn et le reflux gastro oesophagien étant les plus fréquents. Dans l’ensemble, 48,6% des enfants hospitalisés étaient déshydratés, et la durée moyenne des épisodes de diarrhée et de vomissements précédant l’hospitalisation était de 2,3 jours et de 2,4 jours, respectivement. En raison de l’infection à rotavirus, on a considérablement eu recours aux soins de santé, notamment la consultation aux urgences qui a mené à une hospitalisation (1 consultation chez 68,5% des enfants, 2 consultations chez 26,4% des enfants, 3 consultations chez 4% des enfants et 4 consultations chez 1% des enfants). Les enfants ont séjourné en moyenne 7,9 heures en salle d’urgence avant leur hospitalisation et ont été admis pour une durée moyenne de 3,4 jours. Au total,
care for a mean duration of 2.4 days; no children with community-acquired infection died. A total of 497 children were hospitalized in IMPACT hospitals with laboratory-confirmed, hospital-acquired rotavirus gastroenteritis during the same 3 year surveillance period. Thus, hospital acquired infection represented 27% (497/1856) of all admissions for rotavirus gastroenteritis. Children less than 1 year of age were disproportionately affected by hospital-acquired rotavirus (59% vs 31% of community-acquired cases). None of the children with hospital-acquired rotavirus infection had received rotavirus vaccine. Two children less than 1 year of age with underlying health conditions and hospital-acquired infections died but neither of these deaths were directly attributable to rotavirus infection.

In summary, available published data demonstrate a considerable burden of illness due to rotavirus among Canadian children under the age of five years.

**Update on RotaTeq®**

RotaTeq® is a live, oral pentavalent human-bovine reassortant vaccine that contains 5 live reassortant rotaviruses. RotaTeq® has been authorized for use in Canada for the prevention of rotavirus gastroenteritis in infants 6 to 32 weeks of age since August of 2006. It has been recommended for routine use in infants by the Advisory Committee on Immunization Practices (ACIP) in the United States since August 2006. In January of 2008, NACI recommended that RotaTeq® be offered to infants aged 6 to 32 weeks of age whose parents/guardians wish to reduce the risk of rotavirus gastroenteritis(1).

**Update on the safety of RotaTeq®**

In Phase III studies of RotaTeq® involving almost 72,000 healthy infants, no increased risk of intussusception or other serious adverse events was observed(17,18). In the United States, postmarketing safety of RotaTeq® is being monitored by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) through evaluation of reports to two systems: the passive surveillance system Vaccine Adverse Events Reporting System (VAERS) and the Vaccine Safety Datalink (VSD), an active surveillance system.19(19)

Between February 2006 and March 2008, approximately 14 million doses of RotaTeq® were distributed in the United States; the number of doses administered is not known.20-22(20) Available data do not indicate that RotaTeq® is associated with intussusception.20-21(20) Assessment of a potential association between RotaTeq® and intussusception was performed by comparing the number of cases of intussusception reported to VAERS following receipt of RotaTeq® to the number of cases expected to occur by chance alone. Background rates of intussusception in infants 6 to 14 weeks of age, 15 to 23

48 enfants (3.5 %) ont eu besoin de soins intensifs pendant une période moyenne de 2,4 jours; aucun enfant ayant une infection d’origine communautaire n’est décédé. En tout, dans les hôpitaux du réseau d’IMPACT, 497 enfants ont été hospitalisés avec une gastro entérite à rotavirus nosocomiale confirmée en laboratoire pendant la même période de surveillance de 3 ans. Ainsi, l’infection nosocomiale était responsable de 27 % (497/1 856) des admissions attribuables à une gastro entérite à rotavirus. Le nombre d’enfants de moins de 1 an ayant contracté l’infection à rotavirus nosocomiale était disproportionné (59 % vs 31 % des cas d’origine communautaire). Aucun des enfants atteints d’une infection à rotavirus nosocomiale n’avait reçu de vaccin antirotavirus. Deux enfants de moins d’un an ayant des affections sous jacentes et une infection nosocomiale sont décédés, mais aucun des décès n’était directement attribuable à une infection à rotavirus.

En résumé, les données publiées disponibles indiquent que le fardeau de la maladie associé au rotavirus chez les enfants canadiens de moins de cinq ans est considérable.

**Mise à jour sur RotaTeq®**

RotaTeq® est un vaccin pentavalent oral à souches réassorties de virus vivant humain bovin qui contient 5 souches réassorties de rotavirus. L’usage de RotaTeq® a été autorisé au Canada en août 2006 pour la prévention de la gastro entérite à rotavirus chez les nourrissons âgés de 6 à 32 semaines. Son administration systématique chez les nourrissons a été recommandée par l’Advisory Committee on Immunization Practices (ACIP) des États Unis en août 2006. En janvier 2008, le CCNI a recommandé que RotaTeq® soit offert aux nourrissons âgés de 6 à 32 semaines dont les parents ou tuteurs souhaitent réduire le risque de gastro entérite à rotavirus(1).

**Mise à jour sur l’innocuité de RotaTeq®**

Dans des études de phase III de RotaTeq® portant sur près de 72 000 nourrissons en santé, aucune augmentation du risque d’intussusception ou d’autres événements indésirables graves n’a été observée(17,18). Aux États Unis, l’innocuité post commercialisation de RotaTeq® est surveillée par les Centers for Disease Control and Prevention (CDC) et la Food and Drug Administration (FDA), qui évaluent les rapports produits par deux systèmes : le système de surveillance passive Vaccine Adverse Events Reporting System (VAERS) et le système de surveillance active Vaccine Safety Datalink (VSD) (19).

Entre février 2006 et mars 2008, environ 14 millions de doses de RotaTeq® ont été distribuées aux États Unis; le nombre de doses administrées n’est cependant pas connu(20-22). Les données disponibles ne démontrent pas que RotaTeq® est associé à l’intussusception(20,21). L’association potentielle entre RotaTeq® et l’intussusception a été évaluée par comparaison du nombre de cas d’intussusception signalés au VAERS, après l’administration de RotaTeq® avec le nombre de cas attendus du seul fait du hasard. Les taux de base de l’intussusception chez les nourrissons de 6 à 14 semaines, de 15 à 23 semaines et de 24 à 35 semaines ont été établis d’après les diagnostics lors du congé de l’hôpital dans
weeks of age, and 24 to 35 weeks of age were determined from hospital discharge diagnoses at the VSD study sites for the period 2000-2004, prior to the introduction of RotaTeq®.

From February 1, 2006 to March 31, 2008, VAERS received reports of 267 cases of intussusception that met the Brighton Collaboration case definition 22) 91 of these (34%) occurred within 1-21 days of vaccination, 48/91 (53%) occurred within 1-7 days of vaccination. The number of cases of intussusception reported to VAERS during either the 1-21 day period or the 1-7 day period following any dose of RotaTeq® did not exceed the number of cases expected to occur by chance alone. Although an apparent clustering of intussusception cases during the 7 day period following the first dose of RotaTeq® was observed, it is not possible using VAERS data alone to determine whether this observed increase is due to enhanced reporting of intussusception cases following the first vaccine dose or to a slightly increased risk of intussusception in the 7 day period following the first dose 20-22).

Further evaluation of the post-marketing safety of RotaTeq® is available from the Vaccine Safety Datalink (VSD), an active surveillance network of eight managed care organizations distributed across the US and encompassing 2.9% of the US population. The VSD is able to test hypotheses generated by VAERS or pre-marketing clinical studies. Following administration of over 200,000 doses in the VSD, no increased risk of intussusception has been demonstrated in the 30 day period following any dose of RotaTeq® 23). With more than 160,000 first doses administered in the VSD and pre-licensure trials, no cases of intussusception were identified in the 7 day period following vaccination 23).

Post-marketing safety surveillance through VAERS and the VSD have also not demonstrated an increased risk of other serious adverse events following vaccination with RotaTeq® including hematochezia, meningitis, encephalitis, seizures, Kawasaki disease, myocarditis, or Gram-negative sepsis 22,24). The Global Advisory Committee on Vaccine Safety (GACVS) recently reviewed all available data from the US (where RotaTeq® has been introduced) and the European Union (where Rotarix™ was being used), on the potential association between Kawasaki disease and rotavirus vaccines and concluded there was no evidence for a causal association between rotavirus vaccines and Kawasaki disease 25).

In summary, postmarketing surveillance following distribution of more than 14 million doses of RotaTeq® in the US, do not demonstrate or suggest an increased risk of intussusception or other serious adverse events among infants following RotaTeq® vaccine.

les sites d’étude du VSD pour la période 2000-2004, avant l’introduction de RotaTeq®.

Entre le 1er février 2006 et le 31 mars 2008, le VAERS a reçu 267 rapports de cas d’intussusception qui correspondaient à la définition de cas de la Brighton Collaboration 22); 91 d’entre eux (34 %) sont survenus dans les 21 premiers jours suivant la vaccination, 48/91 (53 %) dans les 7 premiers jours. Le nombre de cas d’intussusception signalés au VAERS soit durant la période de 21 jours ou de 7 jours suivant l’administration de n’importe quelle dose de RotaTeq® ne dépassait pas le nombre de cas attendus du seul fait du hasard. Bien qu’on ait observé une agrégation apparente des cas d’intussusception durant la période de 7 jours suivant l’administration de la première dose de RotaTeq®, il n’est pas possible, à partir des données du VAERS seulement, de déterminer si cette augmentation est due à une meilleure déclaration des cas d’intussusception après la première dose du vaccin ou à une légère hausse du risque d’intussusception dans les 7 jours suivant l’administration de la première dose 20-22.

Une évaluation plus approfondie de l’innocuité après la commercialisation de RotaTeq® peut être obtenue du Vaccine Safety Datalink (VSD), un réseau de surveillance active regroupant huit organisations de soins intégrés disséminées dans tous les É. U. et englobant 2.9 % de la population américaine. Le VSD est capable de vérifier les hypothèses produites par le VAERS ou les études cliniques de pré commercialisation. À la suite de l’administration de plus de 200 000 doses, le VSD n’a relevé aucune augmentation du risque d’intussusception dans les 30 jours suivant la réception de toute dose de RotaTeq® 23). Plus de 160 000 premières doses ont été administrées dans le cadre des essais du VSD et des essais préalables à l’homologation, et aucun cas d’intussusception n’a été détecté dans les 7 jours suivant la vaccination 23).

D’après les données de surveillance de l’innocuité après la commercialisation obtenues par le VAERS et le VSD, la vaccination par RotaTeq® n’est suivie d’aucune augmentation du risque d’autres événements indésirables graves, notamment la présence de selles sanglantes, de la méningite, de l’encéphalite, de crises convulsives, de la maladie de Kawasaki, de la myocardite ou septicième à Gram négatif 22,24). Le Comité consultatif mondial de la sécurité vaccinale (GACVS) a passé en revue récemment toutes les données disponibles en provenance des É. U. (où le vaccin RotaTeq® a été introduit) et de l’Union européenne (où le vaccin Rotarix™ est utilisé) portant sur l’association potentielle entre la maladie de Kawasaki et les vaccins antirotavirus et a conclu qu’aucune preuve n’indiquait l’existence d’une association causale entre les vaccins antirotavirus et la maladie de Kawasaki 23).

En résumé, les données de surveillance post commercialisation après la distribution de plus de 14 millions de doses de RotaTeq® aux É. U. ne démontrent pas ni ne laissent entrevoir une augmentation du risque d’intussusception ou d’autres événements indésirables graves chez les nourrissons suivant l’administration du vaccin RotaTeq®.
The CDC and the FDA will continue to monitor adverse events reported following vaccination with RotaTeq® in the US.

On May 7, 2010 Health Canada issued an advisory indicating ongoing review of information regarding the presence of porcine circovirus. We are currently reviewing new information regarding the presence of porcine circovirus (PCV-1 and PCV-2) DNA in rotavirus vaccine. While porcine circovirus is considered a contaminant in these vaccines, it is not known to cause illness in humans. Health Canada stated that there is no evidence that the presence of PCV-1 or PCV2 in rotavirus vaccines poses a safety risk to patients and highlighted the fact that rotavirus vaccines have a strong safety record both in clinical trials and in clinical experience with millions of patients.(26)

Update on the effectiveness of RotaTeq®

In Phase III trials leading to the licensure of RotaTeq®, overall vaccine efficacy of 3 doses of RotaTeq® against severe rotavirus gastroenteritis caused by G serotypes contained in the vaccine (G1, G2, G3, G4) was 98.2% (95% CI 89.6-100%) and against rotavirus gastroenteritis of any severity was 73.8% (95% CI 67.2-79.3%) during the first full rotavirus season after completion of vaccination. Among 144 infants in Phase III trials who received at least one dose of RotaTeq® >10 weeks after a previous dose, similar efficacy against G1-G4 rotavirus gastroenteritis of any severity was observed when compared to infants who received doses on schedule <10 weeks following a previous dose (74%; 95%CI 67-79% vs. 63%; 95% CI, <0-94%)(27). In the Finnish Extension Study, 21,000 of the approximately 70,000 infants involved in the pivotal Rotavirus Efficacy and Safety Trial (REST) were followed until 3.5 years of age(18;28). Reduction of overall rotavirus gastroenteritis-associated hospitalizations and emergency department visits up to 3.1 years post-dose 3 was 94% (95% CI 91 - 96%); efficacy against rotavirus gastroenteritis of any severity was 63% (95% CI 44 – 75%)(28). During the same follow up period, evaluation of the serotype-specific prevention of rotavirus gastroenteritis-associated hospitalizations and emergency department visits among infants who had received 3 doses of vaccine revealed sustained reduction in rates of gastroenteritis caused by G1-G4 and G9 rotavirus of 82-95%(29).

The REST trial was not designed to evaluate the efficacy of less than 3 doses of RotaTeq®. However, post-hoc analysis of hospitalizations and emergency room visits from this study population demonstrated high rates of protection following the first and second dose of vaccine. Between 14 days after dose one and receipt of dose 2, a rate reduction of 100% (95% CI 72-100%) for rotavirus types G1-G4 and of 82% (95% CI 39-97%) for rotavirus due to any serotype was observed; between 2 weeks after dose two and receipt of dose 3, a rate reduction of 91% (95% CI 63-99%) for rotavirus types G1-G4 and of 84% - 96%); efficacy against rotavirus gastroenteritis of any severity was 63% (95% CI 44 – 75%)(28). During the same follow up period, evaluation of the serotype-specific prevention of rotavirus gastroenteritis-associated hospitalizations and emergency department visits among infants who had received 3 doses of vaccine revealed sustained reduction in rates of gastroenteritis caused by G1-G4 and G9 rotavirus of 82-95%(29).

Les CDC et la FDA continueront de surveiller les événements indésirables signalés après la vaccination par RotaTeq® aux É. U.

Le 7 mai 2010, Santé Canada a émis un avis sur une évaluation en cours de réalisation des données concernant la présence de circovirus porcin. Nous sommes présentement à examiner de nouvelles données concernant la présence d’ADN de circovirus porcin (PCV 1 et PCV 2) dans les vaccins antirotavirus. Bien que l’on considère que ces vaccins sont contaminés par le circovirus porcin, il ne semble pas que ce dernier cause une maladie chez l’humain. Selon Santé Canada, rien n’indique que la présence de PCV 1 ou de PCV 2 dans les vaccins antirotavirus pose un risque pour la sécurité des patients et souligne que le profil d’innocuité des vaccins antirotavirus était excellent lors des essais cliniques et l’est demeuré après une utilisation clinique auprès de millions de patients.(26)

Mise à jour sur l’efficacité de RotaTeq®

Dans les essais de phase III qui ont mené à l’homologation de RotaTeq®, l’efficacité globale de trois doses de RotaTeq® contre la gastro entérite à rotavirus grave causée par des sérotypes G contenus dans le vaccin (G1, G2, G3, G4) atteignait 98,2 % (IC à 95 % 89,6 100) et s’élevait à 73,8 % (IC à 95 % 67,2 79,3 %) contre la gastro entérite à rotavirus de toute gravité durant la première saison entière d’infection à rotavirus une fois la vaccination terminée. Chez 144 nourrissons inscrits aux essais de phase III qui ont reçu au moins une dose de RotaTeq® plus de 10 semaines après une dose antérieure, l’efficacité du vaccin contre la gastroentérite à rotavirus G1 G4 de toute gravité était similaire à celle observée chez les nourrissons qui avaient reçu des doses selon le calendrier moins de 10 semaines après une dose antérieure (74%; IC à 95 % 67 79 % c. 63 %; IC à 95 %, <0 94 %)(27). Dans l’étude d’extension de l’essai central REST (Rotavirus Efficacy and Safety Trial) menée en Finlande, 21 000 des quelque 70 000 nourrissons originaux ont été suivis jusqu’à l’âge de 3,5 ans(18;28). Le nombre total d’hospitalisations et de consultations aux urgences associées à la gastroentérite à rotavirus jusqu’à 3,1 ans après la 3e dose a diminué de 94 % (IC à 95 % 91 96 %); l’efficacité du vaccin contre la gastroentérite à rotavirus de toute intensité atteignait 63 % (IC à 95 % 44 75 %)(28). Durant la même période de suivi, une évaluation par sérotype du degré de prévention des hospitalisations et des consultations aux urgences associées à la gastroentérite à rotavirus chez les nourrissons qui avaient reçu 3 doses du vaccin a mis en évidence une baisse soutenue de 82 % à 95 % des taux de gastroentérite causée par les rotavirus G1 G4 et G9(29).

L’essai REST ne visait pas à évaluer l’efficacité d’un nombre de doses de RotaTeq® inférieur à 3. Toutefois, l’analyse après coup des hospitalisations et des consultations aux urgences dans cette population a révélé des taux élevés de protection après l’administration de la première et de la deuxième dose du vaccin(30). Entre le 14e jour suivant la première dose et l’administration de la 2e dose, le taux d’infection par les sérotypes G1 G4 a diminué de 100 % (IC à 95 % 72 100 %) et le taux d’infection par tout sérotype de 82 % (IC à 95 % 39 97 %); entre le 14e jour suivant la 2e dose et l’administration de la 3e dose, une réduction du taux de 91 % (IC à 95 % 63 99 %) a été observée pour les sérotypes G1 G4 et de 84 %
(95% CI 54-96%) for rotavirus due to any serotype was observed. Boom et al. evaluated the effectiveness of complete (3-doses) or partial (1 or 2 doses) immunization with RotaTeq® in an urban emergency room in the US. Vaccine effectiveness against rotavirus hospitalization and emergency room visits was 69% (95% CI: 71-100%) following 1 dose, 81% (95% CI: 13-96%) following 2 doses and 88% (95% CI: 68-96%) following 3 doses using a case control design comparing children with lab-confirmed rotavirus gastroenteritis to a group of controls with either rotavirus-negative gastroenteritis or acute respiratory illness. These data suggest that infants vaccinated during the rotavirus season may derive substantial early protection against severe rotavirus disease despite not having completed a full series of immunization.

The impact of routine immunization of US infants with RotaTeq® was recently evaluated by the CDC using data from the National Respiratory and Enteric Virus Surveillance System (NREVSS) and the New Vaccine Surveillance Network (NVSN) using several outcomes: timing of the onset of the season, number of cases, frequency of tests and proportion of tests positive.

When compared to the 6 previous seasons (2000-2006), rotavirus activity during the 2007-2008 season was delayed by 15 weeks. During 2000-2006, median onset of rotavirus disease occurred in mid-December. In 2008, onset of rotavirus activity occurred in late February reflecting an eight week delay. This analysis also showed a dramatic decrease in the overall number of cases reported. In viewing the 2007-2008 season as a whole, a decrease in magnitude of rotavirus illness greater than 50% was observed. While some year-to-year variability in the number of cases can occur, both the total number of tests performed and the number of tests positive for rotavirus were substantially lower during the 2007-2008 rotavirus season than during any of the seasons from 2000 to 2006. In comparing the total number of rotavirus tests performed in the 2007-2008 season, 11% more tests were performed but there was a 67% decrease in the number of positive specimens detected. The delayed season and atypically low percentage of rotavirus-positive tests was observed in all regions studied. Among children enrolled in the NVSN during January 1 – April 30 in 2006, 2007, and 2008, the overall percentage of stool specimens positive for rotavirus was 50%, 45%, and 6%, respectively. This dramatic reduction in the proportion of stools testing positive for rotavirus was observed in children tested in the inpatient settings.

Since the publication of the CDC surveillance results described above, several other studies done in different clinical settings and geographic regions throughout the US have been reported. Each of these studies has demonstrated considerable reductions in the number of cases of rotavirus gastroenteritis, hospitalizations due to rotavirus gastroenteritis, and proportion of rotavirus hospitalizations due to any serotype was observed. Boom et coll. evaluated the effectiveness of complete (3 doses) or partial (1 or 2 doses) of RotaTeq® in relation with the consultations aux urgences dans un milieu urbain aux États Unis. Dans une étude cas/témoins comparant les enfants atteints d’une gastroentérite à rotavirus confirmée en laboratoire à un groupe témoin de sujets ayant une gastroentérite non causée par un rotavirus ou atteints d’une maladie respiratoire aiguë, l’efficacité de la protection conférée par le vaccin antirotavirus empêchant une hospitalisation ou une consultation aux urgences était de 69% (IC à 95% = 71% à 100%) après 1 dose, 81% (IC à 95% = 13% à 96%) après 2 doses et de 88% (IC à 95% = 68% à 96%) après 3 doses. Ces données semblent indiquer que la vaccination des nourrissons durant la saison d’infection à rotavirus peut conférer une protection précoce importante contre les maladies graves à rotavirus même si la série vaccinale n’est pas complète.

L’impact de la vaccination systématique des nourrissons américains au moyen de RotaTeq® a été évalué récemment par les CDC, qui se sont servis des données du National Respiratory and Enteric Virus Surveillance System (NREVSS) et du New Vaccine Surveillance Network (NVSN) en mesurant plusieurs paramètres soit la date du début de la saison, le nombre de cas, la fréquence des tests et la proportion des tests positifs. Comparativement aux 6 saisons précédentes (2000-2006), la période d’activité du rotavirus durant la saison 2007-2008 a été retardée de 15 semaines. Entre 2000 et 2006, la date médiane d’apparition des maladies à rotavirus a été la mi-décembre. En 2008, l’activité du rotavirus a débuté à la fin février, soit avec un retard de huit semaines. Cette analyse a également fait ressortir une baisse spectaculaire du nombre global de cas signalés. Lorsqu’on examine la saison 2007-2008 dans son ensemble, l’ampleur des maladies à rotavirus a diminué de plus de 50%. Bien que le nombre de cas puisse varier d’une année à l’autre, tant le nombre total de tests effectués que le nombre de tests positifs pour le rotavirus étaient beaucoup plus faibles durant la saison 2007-2008 que pendant les sept saisons précédentes (2000-2006). Si l’on considère le nombre total de tests de détection du rotavirus effectués durant la saison 2007-2008, on constate que 11% plus de tests ont été réalisés, mais que le nombre d’échantillons positifs détectés a baissé de 67%. Dans toutes les régions étudiées, la saison a été retardée et le pourcentage de tests positifs pour le rotavirus était anormalement faible. Chez les enfants inscrits dans le NVSN, entre le 1er janvier et le 30 avril 2006, 2007 et 2008, le pourcentage total d’échantillons de selles positifs pour le rotavirus était de 50%, 45% et 6%, respectivement. Cette réduction considérable du nombre d’échantillons de selles positifs pour le rotavirus a été observée chez les enfants hospitalisés.

Depuis la publication des résultats de surveillance des CDC décrits ci-dessus, plusieurs autres études menées dans différents milieux cliniques et régions géographiques aux quatre coins des É. U. ont été publiées. Chacune de ces études a constaté des réductions considérables du nombre de cas de gastroentérite à rotavirus, du nombre d’hospitalisations associées à une gastroentérite à rotavirus et de la proportion de tests positifs pour le rotavirus.
tests positive since the initiation of routine rotavirus immunization (with RotaTeq®) among US infants in 2006.

While these results must be viewed with some caution given that the data from the 2007-2008 rotavirus season represent only one season of data, the consistency of the trends observed between the NREVSS, the NVSN and other studies across geographic regions suggest that there has been a dramatic reduction in the burden of disease caused by rotavirus in the US during the 2007-2008 season. This reduction in rotavirus activity coincides with increased use of RotaTeq® following the recommendation of the Advisory Committee on Immunization Practices for universal immunization of US infants in February 2006(42). While nationally representative vaccine coverage data is not available, information from population-based sentinel immunization information sites in the US indicates an increase in mean coverage with one dose of RotaTeq® among infants aged 3 months from 49.1% in May 2007 to 56.0% in March 2008 (43); mean 3-dose coverage among children aged 13 months increased from 3.4% in May 2007 to 33.7% in March 2008. Most children over the age of 2 years at the start of the 2007-2008 rotavirus season would not have received rotavirus vaccine because they were above the upper age limit to receive RotaTeq® when it was licensed in 2006. The observed reduction in rotavirus activity during the 2007-2008 rotavirus season is greater than can be attributed to direct protective effects in vaccine recipients, suggesting that immunization of a proportion of the population might offer indirect benefits to unvaccinated persons by reducing transmission of rotavirus in the community (i.e. herd immunity).

Ongoing disease surveillance and epidemiological studies in Canada and the US are needed to confirm the impact of rotavirus vaccine on rotavirus disease in 2007-2008 and in future rotavirus seasons. Prospective surveillance data from the Canadian Immunization Monitoring Program, Active (IMPACT) will soon be available to provide better epidemiologic data regarding rotavirus burden of illness and vaccine effectiveness in Canada.

**Monovalent human rotavirus vaccine: Rotarix™**

This section contains information on a second vaccine product available in Canada against rotavirus infections. This vaccine has been recommended for use in the routine infant schedule by the ACIP since June 2008 (43).

**Vaccine composition** (44;45)

Rotarix™ is a live, attenuated monovalent G1[P8] human rotavirus vaccine derived from a naturally circulating G1[P8] rotavirus strain 89-12 that was isolated from the stool of a 15-month old child with mild rotavirus diarrhea in December 1988. The parent virus was then passaged in African Green Monkey kidney cells, cloned, and further passaged in Vero cells. The vaccine is supplied as a liquid rotavirus vaccine since the introduction of the vaccination systematic against the rotavirus (par Rota Teq®) chez des nourrissons américains en 2006.

Même si ces résultats doivent être interprétés avec une certaine circonspection vu que les données pour 2007-2008 ne représentent qu’une seule saison, la constance des tendances observées par le NREVSS, le NVSN et d’autres études dans différentes régions géographiques donne à penser que le fardeau de la maladie causée par le rotavirus aux É. U. a connu une baisse spectaculaire durant la saison 2007-2008. Cette baisse de l’activité du rotavirus coïncide avec l’usage accru de RotaTeq® après que l’Advisory Committee on Immunization Practices eut recommandé la vaccination universelle des nourrissons aux É. U. en février 2006 (42). On ne dispose pas de données représentatives à l’échelle nationale sur la couverture vaccinale, mais les renseignements fournis par des sites sentinelles d’information sur l’immunisation basés dans une population aux É. U. indiquent une augmentation du taux moyen de couverture par une dose de RotaTeq® chez les nourrissons âgés de 3 mois, qui est passé de 49,1 % en mai 2007 à 56,0 % en mars 2008 (43); la couverture moyenne par 3 doses chez les enfants âgés de 13 mois est passée de 3,4 % en mai 2007 à 33,7 % en mars 2008. La plupart des enfants de plus de 2 ans au début de la saison 2007 n’auraient pas reçu le vaccin antirotavirus, car ils avaient passé l’âge limite pour recevoir RotaTeq® lorsqu’il a été homologué en 2006. La réduction de l’activité du rotavirus observée durant la saison 2007-2008 est supérieure à ce qu’on pourrait attribuer aux effets protecteurs directs chez les vaccinés, ce qui donne à penser que la vaccination d’une proportion de la population peut conférer des avantages indirects aux personnes non vaccinées en réduisant la transmission du rotavirus dans la collectivité (immunité collective).


**Vaccin monovalent à rotavirus humain : RotarixMC**

La présente section fournit de l’information sur un deuxième vaccin contre les infections à rotavirus offert au Canada. Depuis juin 2008, l’ACIP recommande d’inclure ce vaccin dans le calendrier de vaccination systématique des nourrissons (42).

**Composition du vaccin** (44;45)

RotarixMC est un vaccin vivant monovalent à rotavirus humain de sérotype G1[P8] fabriqué à partir de la souche 89-12 du rotavirus de sérotype G1[P8] qui circule dans la nature et qui a été isolé dans les selles d’un enfant de 15 mois atteint de diarrhée bénigne à rotavirus en décembre 1998. Le virus parent a été cultivé dans des cellules rénales de singe africain, cloné puis cultivé sur des cellules Vero. Le vaccin est vendu sous forme d’une suspension
suspension in single-dose oral applicators for oral administration.

Each 1.5 ml dose of vaccine contains not less than 10^{6.0} CCID_{50} (cell culture infectious dose 50\%) of the parent strain of human rotavirus. The vaccine also contains sucrose, di-sodium adipate, Dulbecco’s Modified Eagle Medium, and sterile water. The current Rotarix™ oral applicator product does contain latex, but non-latex products may also be available in 2010. To inquire about non-latex containing product availability or to check lot numbers on existing or future supplies, please contact the manufacturer GlaxoSmithKline Inc.’s Medical Information Line at 1-800-387-7374.

**Storage and Handling**

Rotarix™ should be kept refrigerated at 2°C to 8°C and protected from light.

**Immunogenicity**

The immune correlates of protection from rotavirus infection and disease are not fully understood. Correlation between antibody responses and protection from disease has not been established and therefore clinical trials for rotavirus vaccine approval have been based on efficacy rather than immunologic correlates of efficacy.

Evaluation of the immune response to Rotarix™ has been assessed in clinical trials in 6 European countries\(^{(44)}\) and 11 Latin American countries\(^{(45)}\) that included 1180 immunized infants. In these trials a 2-dose vaccine course resulted in IgA seroconversion rates, defined as serum anti-rotavirus ELISA IgA ≥ 20 U/ml, which ranged from 77.9% to 94.4% (95% CI 73.8% - 97.3\%) one to two months following the second dose of vaccine. One North American randomized controlled trial\(^{(46)}\) was done that included 421 immunized infants. Infants received either 10^{5.2} ffu or 10^{6.4} ffu viral concentration of vaccine or placebo. Using the same measure of immunity, IgA ELISA > 20U/ml, 67.4%, 78.5% and 6.3\% infants respectively, developed antibodies. Seroconversion after one dose was reported for a small subset of infants. Of those who received 105.2 ffu viral concentration of vaccine, 64\% of infants developed serum IgA to rotavirus. Among those who received 106.4 ffu viral concentration, 56\% developed serum IgA to rotavirus. Also in this study, 20 immunized infants were seronegative after their first dose of vaccine; these infants seroconverted after their second dose. All of the above randomized controlled trials suggest that the majority of infants develop antibodies to the vaccine after completing a two dose series.

The safety and immunogenicity of 2-doses of Rotarix™ was evaluated in 1009 preterm infants\(^{(47)}\). Among a subset of 147 infants born after at least 27 weeks of gestational age, seroconversion (defined as serum anti-rotavirus ELISA ≥ 20 U/ml IgA at the ELISA), defined by des titres sériques ≥ 20 U/ml d’IgA contre le rotavirus à un dosage ELISA, qui varient entre 77,9 % et 94,4 % (IC à 95 % 73,8 % - 97,3 %) un à deux mois après la deuxième dose du vaccin. Un essai comparatif randomisé a été effectué en Amérique du Nord\(^{(48)}\) chez 421 nourrissons vaccinés. Ces derniers ont reçu soit une concentration virale de 105,2 UFF ou 106,4 UFF du vaccin ou un placebo. Utilisant la même mesure de l’immunité (> 20 U/ml IgA à l’ELISA), les auteurs ont constaté que 67,4 %, 78,5 % et 6,3 %, respectivement, des nourrissons ont produit des anticorps. La séroconversion après une dose a été signalée pour un petit sous ensemble de nourrissons. Parmi ceux qui ont reçu 105,2 UFF du vaccin, 64 % ont produit des IgA sériques contre le rotavirus. Quant à ceux qui ont reçu 106,4 UFF de concentration virale, 56 % ont produit des IgA sériques contre le rotavirus. Dans cette même étude, 20 nourrissons vaccinés étaient séronégatifs après leur première dose du vaccin; une séroconversion est apparue après la deuxième dose. Tous les essais comparatifs randomisés mentionnés ci dessus semblent indiquer que la majorité des nourrissons ont produit des anticorps contre le vaccin après avoir terminé une série vaccinale de deux doses.

**Entreposage et manipulation**

RotarixMC doit être conservé au réfrigérateur entre 2 et 8 °C et à l’abri de la lumière.

**Immunogénicité**

Les corrélats immunologiques de la protection contre l’infection et la maladie à rotavirus n’ont pas encore été parfaitement élucidés. La corrélation entre les réponses immunitaires et la protection contre la maladie n’a pas été établie; ainsi, les essais cliniques pour l’approbation du vaccin antirotavirus se sont fondés sur l’efficacité plutôt que sur les corrélats immunologiques de l’efficacité.

La réponse immunitaire à RotarixMC a été évaluée dans des essais cliniques effectués dans 6 pays européens\(^{(44)}\) et 11 pays d’Amérique latine\(^{(45)}\) portant sur 1 180 nourrissons immunisés. Dans ces essais, l’administration de 2 doses a entraîné des taux de séroconversion (IgA), définie par des titres sériques ≥ 20 U/ml d’IgA contre le rotavirus à un dosage ELISA, qui varient entre 77,9 % et 94,4 % (IC à 95 % 73,8 % - 97,3 %) un à deux mois après la deuxième dose du vaccin. Un essai comparatif randomisé a été effectué en Amérique du Nord\(^{(46)}\) chez 421 nourrissons vaccinés. Ces derniers ont reçu soit une concentration virale de 105,2 UFF ou 106,4 UFF du vaccin ou un placebo. Utilisant la même mesure de l’immunité (> 20 U/ml IgA à l’ELISA), les auteurs ont constaté que 67,4 %, 78,5 % et 6,3 %, respectivement, des nourrissons ont produit des anticorps. La séroconversion après une dose a été signalée pour un petit sous ensemble de nourrissons. Parmi ceux qui ont reçu 105,2 UFF du vaccin, 64 % ont produit des IgA sériques contre le rotavirus. Quant à ceux qui ont reçu 106,4 UFF de concentration virale, 56 % ont produit des IgA sériques contre le rotavirus. Dans cette même étude, 20 nourrissons vaccinés étaient séronégatifs après leur première dose du vaccin; une séroconversion est apparue après la deuxième dose. Tous les essais comparatifs randomisés mentionnés ci dessus semblent indiquer que la majorité des nourrissons ont produit des anticorps contre le vaccin après avoir terminé une série vaccinale de deux doses.

L’innocuité et l’immunogénicité de 2 doses de RotarixMC ont été évaluées chez 1 009 nourrissons prématurés\(^{(47)}\). Dans un sous groupe de 147 nourrissons nés après au moins 27 semaines d’âge gestationnel, on a observé une séroconversion (définie comme étant
IgA ≥ 20 U/ml) was observed in 85.7% (95%CI: 79.0-90.9) of infants one month after the second vaccine dose. The safety and immunogenicity of 3-doses of Rotarix™ was evaluated in 50 South African children with HIV(49). Among 21 children with mean CD4 counts of 2145 μL (SD 746) in whom data was available, seroconversion was observed in 57.1% (95%CI: 36-61) of infants 2 months following the third dose. Data on seroconversion rates after 2 doses is not available.

**Efficacy**

The efficacy of the authorized formulation of Rotarix™ has been evaluated in 2 Phase III clinical trials(49;50) conducted in Latin America(49) and in Europe(50) in which a total of 21,741 infants have been studied (11,581 who received Rotarix™ and 10,160 who received placebo.) These are summarized in evidence Tables 1, 2 and 9. Efficacy during the second season following immunization was evaluated in the European trial and in a subset of infants enrolled in Latin America (7,175 who received Rotarix™ and 7,062 who received placebo)(51). These trials enrolled healthy infants aged 6 to 13 weeks (14 weeks minus 1 day). Two doses of Rotarix™ were given orally beginning at 6-14 weeks of age with a minimum interval of 4 weeks between doses without restriction due to breastfeeding or administration of other licensed childhood vaccines. All doses were administered by 24 weeks of age.

Overall, the efficacy of 2 doses of Rotarix™ against severe rotavirus gastroenteritis in Phase III trials was high in the first rotavirus epidemic season following immunization, ranging from 85%(49) to 96%(50). Protection persisted during the second epidemic rotavirus season, with vaccine efficacy ranging from 79%(51) to 86%(50) (Table 1).

While formal studies of the efficacy of a single dose of Rotarix™ have not been performed, efficacy data are available for the period between Dose 1 to Dose 2 of Rotarix™ in the European Phase III trial(50). During the period from Dose 1 to before Dose 2 (mean duration: 61 days in each study group), significantly fewer subjects in Rotarix™ group reported any wild-type rotavirus gastroenteritis compared to the placebo group (P-value = 0.019). Vaccine efficacy against any rotavirus gastroenteritis during this interval was 89.8% (95% CI 8.9-99.8%).

Rotarix™ is a monovalent vaccine designed to protect against G1P[8] rotavirus infection. However, the genotype P[8] is shared by most other circulating strains. Protection induced by natural infection with RV is not limited to G and P antigens, but is also associated with structural proteins VP2 and VP6 (in addition to VP4 and VP7), and to non-structural proteins. Therefore, cross-protection.

One concentration d’IgA sériques anti-rotavirus ≥ 20 U/ml dosés par ELISA) chez 85.7 % (IC à 95 % = 79,0 à 90,9) des nourrissons, un mois après la deuxième dose de vaccin.

On a évalué l’innocuité et l’immunogénicité de 3 doses de RotarixMC chez 50 enfants sud africains infectés par le VIH(48). Chez 21 enfants présentant une numération moyenne de lymphocytes CD4 de 2 145/μL (écart type = 746) dont on pouvait étudier les données, on a constaté une séroconversion chez 57,1 % (IC à 95 % = 36-61) des nourrissons, 2 mois après la troisième dose. Les données sur le taux de séroconversion après l’administration de 2 doses n’étaient pas disponibles.

**Efficacité**

L’efficacité de la préparation autorisée de RotarixMC a été évaluée dans 2 essais cliniques de phase III(49;50) menés en Amérique latine(49) et en Europe(50) sur 21 741 nourrissons (11 581 qui ont reçu RotarixMC et 10 160 qui ont reçu un placebo). Ces données sont résumées dans les Tableaux 1, 2 et 9. L’efficacité durant la deuxième saison suivant la vaccination a été évaluée dans l’essai européen et dans un sous ensemble de nourrissons en Amérique latine (7 175 qui ont reçu RotarixMC et 7 062 qui ont reçu un placebo)(51). Pour ces essais, on a recruté des nourrissons en santé âgés de 6 à 13 semaines (14 semaines moins 1 jour). Deux doses de RotarixMC ont été administrées par voie orale à partir de l’âge de 6 à 14 semaines, avec un intervalle minimum de 4 semaines entre les doses, et aucune restriction n’a été imposée en ce qui concerne l’allaitement ou l’administration d’autres vaccins homologués pour les enfants. À l’âge de 24 semaines, toutes les doses avaient été administrées.

Dans l’ensemble, l’administration de 2 doses de RotarixMC était très efficace contre la gastro entérite à rotavirus grave dans les essais de phase III durant la première saison épidémique d’infection à rotavirus suivant l’immunisation, le degré d’efficacité variant entre 85 % (49) et 96 % (50). L’effet protecteur a persisté durant la deuxième saison épidémique, l’efficacité du vaccin variant entre 79 % (51) et 86 % (50) (Tableau 1).

Bien que des études structurées de l’efficacité d’une dose unique de RotarixMC n’aient pas été effectuées, des données sur l’efficacité ont été recueillies pour la période entre la dose 1 et la dose 2 de RotarixMC dans l’essai européen de phase III(50). Durant l’intervalle entre la dose 1 et la dose 2 (durée moyenne : 61 jours dans chaque groupe étudié), un nombre beaucoup plus faible de sujets dans le groupe RotarixMC que de sujets dans le groupe placebo ont signalé une gastro entérite causée par un rotavirus de type sauvage (valeur p = 0.019). L’efficacité du vaccin contre toute forme de gastro entérite à rotavirus durant cet intervalle s’élevait à 89,8 % (IC à 95 % 8.9 99,8 %).

RotarixMC est un vaccin monovalent qui vise à protéger contre l’infection par le rotavirus de sérotype G1P[8]. Toutefois, le génotype P[8] est présent dans la plupart des autres souches en circulation. La protection conférée par l’infection naturelle à RV n’est pas limitée aux antigènes G et P, mais est aussi associée aux protéines structurales VP2 et VP6 (en plus de VP4 et de VP7) et à des protéines non structurales. Une protection croisée contre.
against infection due to non-G1 serotypes was expected and was evaluated in the Phase III clinical trials (Table 2). Although for some strains only a small number of cases were detected, some degree of cross-protection was demonstrated. The efficacy against non-G1 strains ranged from 41%-92% with pooled efficacy against severe RV diarrhea caused by non-G1 types of 88% through two rotavirus seasons(49). Vaccine efficacy against non-G1 serotypes was statistically higher than in the placebo group for G3P[8], G4P[8], and G9P[8] serotypes but not for G2P[4] serotype. This result could be expected as G2P[4] serotype does not share the P[8] genotype. However, for the second rotavirus season and for the combined first and second seasons, statistically significant efficacy against severe disease due to G2P[4] was observed (85.5%; 95%CI 24.0-98.5). Observed cross-protection against the other serotypes persisted through the second season.

Vaccine efficacy did not decrease in breastfeeding infants. Vaccine efficacy against any RV GE and severe RV GE in the group who were breastfed up to dose one was 86% and in those infants breast-fed up to dose two was 96% as compared to 91% and 96% respectively, in the group who was not breast-fed at any of the doses.

Efficacy in pre-term infants and immunocompromised infants has not been evaluated although limited available immunogenicity data suggest that neither pre-term delivery nor asymptomatic or mildly symptomatic HIV infections are likely to affect the efficacy of Rotarix™(47;48). It should be noted that immunogenicity of Rotarix™ in HIV positive infants has only been assessed following 3 doses of vaccine.

Table 1: Summary of efficacy studies of Rotarix™(49;51)

<table>
<thead>
<tr>
<th></th>
<th>1st Rotavirus Season</th>
<th></th>
<th>2nd Rotavirus Season</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Efficacy** (%)</td>
<td>95% CI</td>
<td>Efficacy*** (%)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Any rotavirus gastroenteritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latin America(49;51)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe(50)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>87.1*</td>
<td>76.9 - 92.1</td>
<td>71.9*</td>
<td>61.2 - 79.8</td>
</tr>
<tr>
<td>Severe Rotavirus gastroenteritis (Vesikari score &gt; 11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latin America(49;51)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe(50)</td>
<td>84.7*</td>
<td>71.7 - 92.4</td>
<td>79.0*</td>
<td>66.6 - 87.4</td>
</tr>
<tr>
<td></td>
<td>95.8*</td>
<td>89.6 - 98.7</td>
<td>85.6*</td>
<td>75.8 - 91.9</td>
</tr>
<tr>
<td>Hospitalization due to rotavirus gastroenteritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latin America(49)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe(50)</td>
<td>85*</td>
<td>69.6 - 93.5</td>
<td>83.0*</td>
<td>73.1 - 89.7</td>
</tr>
<tr>
<td></td>
<td>100*</td>
<td>81.8 - 100</td>
<td>92.2*</td>
<td>65.6 - 99.1</td>
</tr>
</tbody>
</table>

** = not available
- Efficacy reported for the according-to-protocol cohort, defined as participants who completed the full 2-dose vaccination course and adhered to the protocol; reported efficacy is against any G serotype
* = Statistically significant (p<0.05)
†† = Number of infants included in efficacy analysis = 3,874 (2,572 Rotarix™ vs 1,302 placebo)
Tableau 1 : Résumé des études d’efficacité de RotarixMC(49-51)

<table>
<thead>
<tr>
<th>Toute gastro-entérite à rotavirus</th>
<th>1re saison d’infection à RV</th>
<th>2e saison d’infection à RV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amérique latine(49)</td>
<td>Efficacité** (%)</td>
<td>IC à 95 %</td>
</tr>
<tr>
<td>Europe(50)</td>
<td>n.d.</td>
<td>87,1*</td>
</tr>
<tr>
<td></td>
<td>61,2 - 79,8</td>
<td></td>
</tr>
<tr>
<td>Gastro-entérite à rotavirus grave (Score de Vesikari &gt; 11)</td>
<td>84,7*</td>
<td>71,7 - 92,4</td>
</tr>
<tr>
<td>Amérique latine(49,51)</td>
<td>95,8*</td>
<td>89,6 - 98,7</td>
</tr>
<tr>
<td>Europe(50)</td>
<td>89,6 - 98,7</td>
<td></td>
</tr>
<tr>
<td>Hospitalisation attribuable à une gastro-entérite à rotavirus</td>
<td>85*</td>
<td>69,6 - 93,5</td>
</tr>
<tr>
<td>Amérique latine(49)</td>
<td>100*</td>
<td>81,8 - 100</td>
</tr>
</tbody>
</table>

n.d. = non disponible
- Efficacité indiquée pour la cohorte selon le protocole, définie comme le groupe de participants qui ont terminé la série vaccinale complète de 2 doses et ont respecté le protocole;
efficacité signalée s’applique à tout sérotype G
* Statistiquement significatif (p < 0,05)
** La 1ère période d’efficacité a été définie comme la période de 2 semaines suivant la dose 1 jusqu’à la fin de la première saison d’épidémie d’infection à rotavirus
*** La 2e période d’efficacité a été définie comme la période s’étendant entre la consultation à la fin de la première période épidémique d’infection à rotavirus et la fin de la deuxième période épidémique d’infection à rotavirus
† Nombre de nourrissons inclus dans l’analyse d’efficacité = 17 867 (9 009 ayant reçu RotarixMC c. 8 858 ayant un reçu un placebo)
†† Nombre de nourrissons inclus dans l’analyse d’efficacité = 3 874 (2 572 ayant reçu RotarixMC c. 1 302 ayant reçu un placebo)

Table 2: Summary of efficacy of Rotarix™ against G1 and non-G1 serotype rotavirus infection evaluated through two seasons of rotavirus(45;49-51)

<table>
<thead>
<tr>
<th>Type</th>
<th>Through One Rotavirus Season</th>
<th>Through Two Rotavirus Seasons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rotavirus gastroenteritis of any severity</td>
<td>Severe rotavirus gastroenteritis</td>
</tr>
<tr>
<td>G1[P8] Latin America</td>
<td>91.8*</td>
<td>74.1 - 98.4</td>
</tr>
<tr>
<td>Europe</td>
<td>95.6*</td>
<td>87.9 - 98.8</td>
</tr>
<tr>
<td>G2[P4] Latin America</td>
<td>41.0</td>
<td>-79.2 - 82.4</td>
</tr>
<tr>
<td>Europe</td>
<td>62.0</td>
<td>&lt;0 - 94.4</td>
</tr>
<tr>
<td>G3[P8] Latin America</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Europe</td>
<td>89.9*</td>
<td>9.5 - 99.8</td>
</tr>
<tr>
<td>G4[P8] Latin America</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Europe</td>
<td>88.3*</td>
<td>57.5 - 97.9</td>
</tr>
<tr>
<td>G9[P8] Latin America</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Europe</td>
<td>75.6*</td>
<td>51.1 - 88.5</td>
</tr>
</tbody>
</table>
### Tableau 2 : Résumé de l'efficacité de RotarixMC contre l'infection à rotavirus des sérotypes G1 et non G1 évaluée au cours de deux saisons d'infection à rotavirus

<table>
<thead>
<tr>
<th>Type</th>
<th>Gastro entérite à rotavirus de toute gravité</th>
<th>Gastro entérite à rotavirus grave</th>
<th>Gastro entérite à rotavirus de toute gravité</th>
<th>Gastro entérite à rotavirus grave</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1[8]</td>
<td>Amérique latine 91,8* Europe 95,6*</td>
<td>74,1 - 98,4 87,9 - 98,8</td>
<td>90,8* 96,4*</td>
<td>70,5 - 98,2 85,7 - 99,6</td>
</tr>
<tr>
<td>G1[8]</td>
<td>Amérique latine 91,8* Europe 95,6*</td>
<td>74,1 - 98,4 87,9 - 98,8</td>
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</tr>
</tbody>
</table>

* Statiquement significatif (p < 0,05)

n.d. = non disponible
**Effectiveness**
Post-marketing studies examining the impact of introduction of Rotarix™ into routine infant immunization programs have demonstrated considerable reductions in overall burden of illness following implementation of a Rotarix™ immunization program. In Australia, among children under 15 months, the annualized rate of gastroenteritis related emergency room visits was lower in the year following introduction of a publicly funded infant rotavirus immunization program than in any of the previous 7 years(53) (75 per 1000 vs 80.6-131.0 per 1000). In Mexico, deaths due to acute diarrhea among children less than 5 years of age dropped 42% when compared to the pre-vaccination period(53). In Belgium, the proportion of stools collected from children aged ≤ 5 years suffering from diarrhea that were positive for rotavirus fell by more than half in the year following introduction of funding for childhood vaccination with Rotarix™(54).

**Vaccine safety and adverse events**
The safety of Rotarix™ has been evaluated in 12 clinical trials(44) involving 76,918 infants (41,479 received Rotarix™, 35,439 received placebo).

**Intussusception**
The risk of intussusception following Rotarix™ was evaluated in a large-scale safety and efficacy trial conducted in Latin America and Finland (n = 63,225; 31,673 received Rotarix™ and 31,552 received placebo)(45). No increased risk of intussusception following receipt of Rotarix™ was observed compared to the placebo group. Thirteen cases of intussusception occurred within 31 days of either dose of vaccine (6 in the Rotarix™ group and 7 in the placebo group; RR: 0.85; 95% CI 0.30-2.42). No clustering of intussusception cases was observed within 7 or 14 days following immunization.

In all 11 other clinical trials with Rotarix™ (n= 12,220), a total of 7 cases of intussusception were reported (5 in the Rotarix™ group and 2 in the placebo group)(45). Across all clinical trials the reported frequency of intussusception was 0.047% for Rotarix™ recipients and 0.05% for placebo recipients.

Following distribution of approximately 23 million doses of Rotarix™ worldwide, in post-marketing surveillance until Jan. 11, 2008, a total of 190 cases of intussusception (0.81/100,000 doses distributed) have been reported to GlaxoSmithKline(55).

**Hematochezia**
Hematochezia, defined as the occurrence of bloody stools, was not prospectively solicited in any of the Rotarix™ studies but would be expected to have been captured as an unsolicited event. Hence, a review of unsolicited reports was done in order to assess the occurrence of

**Efficacité**
Les études post commercialisation permettant d’examiner l’incidence du recours à RotarixMC dans les programmes de vaccination systématique chez les nourrisson indiquent que le fardeau global de la maladie diminue considérablement après la mise en œuvre d’un programme de vaccination par RotarixMC. En Australie, chez les enfants de moins de 15 mois, le taux de gastro entérite annualisé nécessitant une consultation aux urgences était plus faible dans l’année suivant la mise en place d’un programme de vaccination antirotavirus subventionné par l’État chez les nourrissons que dans les 7 années précédentes, peu importe l’année(53) (75 pour 1000 vs 80.6-131.0 pour 1 000). Au Mexique, les décès causés par une diarrhée aiguë chez les enfants de moins de 5 ans ont chuté de 42 % par rapport à la période précédant la vaccination(53). En Belgique la proportion de selles d’enfants âgés de 5 ans ou moins atteints de diarrhée ayant un résultat positif pour le rotavirus a diminué de plus de la moitié dans l’année suivant le financement d’une vaccination des enfants par RotarixMC(54).

**Innocuité du vaccin et événements indésirables**
L’innocuité de RotarixMC a été évaluée dans 12 essais cliniques(44) portant au total sur 76 918 nourrissons (41 479 ayant reçu RotarixMC, 35 439 ayant reçu un placebo).

**Intussusception**
Le risque d’intussusception après l’administration de RotarixMC a été évalué dans un essai de grande envergure sur l’innocuité et l’efficacité qui a été effectué en Amérique latine et en Finlande (n = 63 225; 31 673 ayant reçu RotarixMC et 31 552 ayant reçu un placebo)(45). Aucune augmentation du risque d’intussusception après la réception de RotarixMC n’a été observée par rapport au groupe placebo. Treize cas d’intussusception ont été enregistrés dans les 31 jours suivant l’une ou l’autre dose du vaccin (6 dans le groupe RotarixMC et 7 dans le groupe placebo; RR : 0,85; IC à 95 % 0,30 2,42). Aucune agrégation des cas d’intussusception n’a été relevée dans les 7 ou 14 jours suivant la vaccination.

Dans les 11 autres essais cliniques de RotarixMC (n = 12 220), 7 cas d’intussusception ont été signalés au total (5 dans le groupe RotarixMC et 2 dans le groupe placebo)(45). Dans l’ensemble des essais cliniques, la fréquence signalée de l’intussusception était de 0,047 % pour les sujets qui avaient reçu RotarixMC et de 0,05 % pour les sujets placebo.

Suite à la distribution mondiale d’environ 23 millions de doses de RotarixMC, un total de 190 cas d’intussusception (0,81/100 000 doses distribuées) avait été signalé à GlaxoSmithKline dans le cadre de la surveillance post commercialisation en date du 11 janvier 2008(55).

**Présence de selles sanglantes**
Les cas de présence de selles sanglantes n’ont pas été recherchés de façon prospective dans aucune des études sur RotarixMC, mais on s’attendrait à ce que ce trouble soit consigné comme un événement non sollicité. Un examen des rapports non sollicités a donc été effectué pour évaluer la survenue d’un tel problème.
hematochezia. Various terms were used for reporting adverse events related to blood in stools across studies. Using the Medical Dictionary for Regulatory Activities (MedDRA) High Level Term (HLT) “gastrointestinal hemorrhages” data is provided below on the occurrence of this adverse event. In the Core Integrated Safety Summary, which is an internal GSK database aggregating all clinical trials of Rotarix™ and includes 36,755 Rotarix™ recipients and 34,454 placebo recipients, at least one adverse event within the MedDRA HLT “gastrointestinal hemorrhages” was reported by 19 (0.05%) vaccine recipients and 9 (0.03%) placebo recipients regardless of time-to-onset from vaccination(45). No statistically significant difference was noted between the Rotarix™ and the placebo groups for each of the considered MedDRA HLT Preferred Terms included under “gastrointestinal hemorrhages (95% CI for relative risk included 1.0). Hematochezia, specifically, was reported in 15 (0.04%) of Rotarix™ recipients and 7 (0.02%) of placebo recipients (RR 1.13; 0.43-3.28). Of the 28 adverse events coded under the MedDRA HLT “gastrointestinal hemorrhages”, 24 cases [17 (0.046%) in vaccine recipients and 7 (0.020%) in placebo recipients] had symptom onset within the 31-day post-vaccination period. The events resolved in all cases. None of these 28 subjects were reported to have intussusception(45).

Other Serious Adverse Events Following Immunization

Serious adverse events were evaluated in 31,673 Rotarix™ recipients compared to 31,552 placebo recipients in a large Phase III trial conducted in Latin America.(49) In this trial, a total of 928 (291/10,000) serious adverse events were reported among Rotarix™ recipients and 1047 (332/10,000) serious adverse events were reported in the placebo group (RR 0.88, 95%CI 0.81-0.96; p=0.005). The Rotarix™ rate of hospitalization was 280/10,000 in the Rotarix™ group versus 318/10,000 in the placebo group (RR 0.88; 95%CI 0.88, 95% CI 0.81-0.96; p=0.005).

In the Core Integrated Safety Summary, 36,755 Rotarix™ recipients and 34,454 placebo recipients, at least 1 serious adverse event was reported in 1.7% of Rotarix™ recipients and 1.9% of placebo recipients (RR 0.9; 95% CI 0.81-1.01). The relative risks of serious adverse events due to diarrhea, gastroenteritis, and dehydration were lower among Rotarix™ recipients than placebo recipients (Table 3). Overall mortality did not differ significantly between Rotarix™ recipients and placebo recipients. During the course of the studies regardless of time-to-onset, there were 68 (0.19%) deaths following administration of Rotarix™ and 50 (0.15%) deaths following placebo administration with a relative risk of 1.31 [95% CI: 0.89; 1.93]. All reported deaths were assessed by the investigators as not related to vaccination. No statistically significant difference was noted for deaths reported to occur within the 31-day period following vaccination.

Autres événements indésirables graves suivant l'immunisation

La survenue d'événements indésirables graves a été comparée chez 31 673 personnes ayant reçu RotarixMC et 31 552 sujets placebo dans un vaste essai de phase III mené en Amérique latine(49). Dans cet essai, 928 (291/10 000) événements indésirables graves ont été recensés chez les vaccinés et 1 047 (332/10 000) dans le groupe placebo (RR 0,88, IC à 95 % 0,81 0,96; p = 0,005). Le taux d’hospitalisation s’élevait à 280/10 000 dans le groupe RotarixMC contre 318/10 000 dans le groupe placebo (RR 0,88; IC à 95 % 0,88, IC à 95 % 0,81 0,96; p = 0,005).

Chez les 36 755 sujets ayant reçu RotarixMC et les 34 454 sujets placebo inclus dans le Core Integrated Safety Summary, au moins 1,7 % des vaccinés et 1,9 % des sujets placebo avaient présenté au moins 1 événement indésirable grave (RR 0,9; IC à 95 % 0,81 1,01). Les risques relatifs d’événements indésirables graves associés à la diarrhée, à la gastroentérite et à la déshydratation étaient plus faibles chez les vaccinés que chez les sujets placebo (Tableau 3). Globalement, il n’y avait pas de différence significative de la mortalité entre les vaccinés et les sujets placebo. Si l’on fait abstraction du moment d’apparition, au cours de ces études on a recensé 68 (0,19 %) décès après l’administration de RotarixMC et 50 (0,15 %) décès après l’administration d’un placebo, soit un risque relatif de 1,31 [IC à 95 % : 0,89; 1,93]. Tous les décès signalés ont été évalués par les chercheurs comme n’étant pas liés à la vaccination. Aucune différence statistiquement significative n’a été constatée dans le cas des décès enregistrés dans les 31 jours...
post-vaccination period and for deaths reported to occur during the entire course of studies regardless of time-to-onset.

In order to assess seizures as an adverse unsolicited event, three time periods were assessed: from dose 1 to visit 3, within 31 days after any dose, and 43 days after any dose. Using the Latin American trial, statistically significantly more events coded with the preferred term “convulsions” were reported among Rotarix™ recipients than placebo recipients between dose 1 and 30-90 days following dose 2 (16 [0.05%] versus 6 [0.02%]; p=0.03)\(^{(45)}\). However, no statistically significant difference in these events was observed between Rotarix™ recipients and placebo recipients in any time frame following vaccination if preferred terms encompassing all convolution-like events were combined\(^{(45)}\). In the European trial, no statistically significant difference was observed between convolution-related serious adverse events in participants who received Rotarix™ compared with the placebo group within 31 or 43 days after any dose\(^{(56)}\).

Selected other neurologic serious adverse events are shown in Table 3.

### Table 3: Summary of Serious Adverse Events (SAE) occurring 0-30 days following any dose\(^{(44,58)}\)

<table>
<thead>
<tr>
<th><strong>Adverse Event</strong></th>
<th><strong>Rotarix™ n=36,755 n (%)</strong></th>
<th><strong>Placebo n=34,454 n (%)</strong></th>
<th><strong>Relative Risk (95% CI)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 SAE</td>
<td>627 (1.7)</td>
<td>659 (1.9)</td>
<td>0.9 (0.81 - 1.01)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (0.02)</td>
<td>25 (0.07)</td>
<td>0.35 (0.14 - 0.78)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>72 (0.2)</td>
<td>111 (0.32)</td>
<td>0.62 (0.45 - 0.84)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>9 (0.02)</td>
<td>21 (0.06)</td>
<td>0.43 (0.17 - 0.97)</td>
</tr>
<tr>
<td>Death</td>
<td>33 (0.09)</td>
<td>20 (0.06)</td>
<td>1.64 (0.92 - 3.02)</td>
</tr>
<tr>
<td>Intussusception</td>
<td>9 (0.02)</td>
<td>7 (0.02)</td>
<td>1.23 (0.41 - 3.9)</td>
</tr>
<tr>
<td>Bronchiolitis</td>
<td>127 (0.35)</td>
<td>137 (0.4)</td>
<td>0.88 (0.68 - 1.13)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>122 (0.33)</td>
<td>122 (0.35)</td>
<td>0.99 (0.76 - 1.28)</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Select other: convulsion febrile seizure encephalitis epilepsy</td>
<td>17 (0.05)</td>
<td>24 (0.07)</td>
<td>0.65 (0.33 - 1.27)</td>
</tr>
<tr>
<td></td>
<td>11 (0.03)</td>
<td>7 (0.02)</td>
<td>1.18 (0.41 - 3.67)</td>
</tr>
<tr>
<td></td>
<td>3 (0.01)</td>
<td>6 (0.02)</td>
<td>0.3 (0.04 - 1.55)</td>
</tr>
<tr>
<td></td>
<td>3 (0.01)</td>
<td>0</td>
<td>2.99 (0.24 - 156.9)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>4 (0.01)</td>
<td>0.19 (0.0 - 2.07)</td>
</tr>
</tbody>
</table>
Kawasaki Disease
No increased risk of Kawasaki disease was observed following administration of Rotarix™ in clinical trials. Overall, Kawasaki disease was reported in 17 (0.03 %) of Rotarix™ recipients and 9 (0.02 %) of placebo recipients (RR 1.7; 95% CI 0.7-4.4). No clustering of cases was observed in the 31 day period following a dose of vaccine and time between vaccine and onset of disease was highly variable (range 3 days to 9 months).

Solicited Adverse Events Following Immunization
The incidence of solicited adverse events of any severity including fever, cough, diarrhea, vomiting, irritability, and loss of appetite within 7 days of immunization was evaluated in the European trial using diary cards completed by parents/guardians. Reported solicited adverse events did not differ between the infants who received Rotarix® and those who received placebo following the first or second vaccine dose (Table 4a and Table 4b).

Maladie de Kawasaki
Dans les essais cliniques, le risque de maladie de Kawasaki n’a pas augmenté après l’administration de RotarixMC. Dans l’ensemble, la maladie de Kawasaki a été signalée chez 17 (0.03 %) des vaccinés et 9 (0.02 %) des sujets placebo (RR 1.7; IC à 95 % 0.7-4.4). Aucune agrégation des cas n’a été observée durant la période de 31 jours suivant l’administration d’une dose du vaccin, et l’intervalle entre la vaccination et l’apparition de la maladie variait grandement (de 3 jours à 9 mois).

Événements indésirables après la vaccination sollicités
L’incidence des événements indésirables sollicités de toute gravité, incluant la fièvre, la toux, la diarrhée, les vomissements, l’irritabilité et la perte d’appétit, dans les 7 jours suivant l’immunisation, a été évaluée dans l’essai européen à l’aide de relevés quotidiens tenus par les parents/tuteurs. Les événements indésirables sollicités qui ont été signalés ne différaient pas chez les nourrissons qui avaient reçu RotarixMC et ceux qui avaient reçu un placebo après la première ou la deuxième dose (tableau 4a et tableau 4b).
**Table 4a.** Percentage of subjects with solicited general symptoms assessed as causally related to immunization, data from day 0 to day 7 post first dose Rotarix™ or Placebo(45).

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Rotarix™ (N = 914)</th>
<th>Placebo (N = 490)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
<td>2.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>44</td>
<td>4.8</td>
</tr>
<tr>
<td>Fever</td>
<td>133</td>
<td>14.6</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>126</td>
<td>13.8</td>
</tr>
<tr>
<td>Irritability, fussiness</td>
<td>299</td>
<td>32.7</td>
</tr>
<tr>
<td>Cough/runny nose</td>
<td>58</td>
<td>6.3</td>
</tr>
</tbody>
</table>

**Table 4b.** Percentage of subjects with solicited symptoms assessed as causally related to immunization, data from day 0 to day 7 post second dose Rotarix™ or Placebo(45).

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Rotarix™ (N = 905)</th>
<th>Placebo (N = 486)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6</td>
<td>0.7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18</td>
<td>2.0</td>
</tr>
<tr>
<td>Fever</td>
<td>164</td>
<td>18.1</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>118</td>
<td>13.0</td>
</tr>
<tr>
<td>Irritability, fussiness</td>
<td>238</td>
<td>26.3</td>
</tr>
<tr>
<td>Cough/runny nose</td>
<td>53</td>
<td>5.9</td>
</tr>
</tbody>
</table>
Innocuité chez les nourrissons prématurés
L’innocuité de RotarixMC a été évaluée chez 1 009 nourrissons prématurés (198 avaient un âge gestationnel de 27-30 semaines et 801 avaient un âge gestationnel de 31-36 semaines)(47). On n’a relevé aucune différence dans les taux d’événements indésirables graves entre les nourrissons ayant reçu RotarixMC et ceux ayant reçu le placebo (5,1 % vs 6,8 %). Les taux de symptômes sollicités et non sollicités étaient comparables entre les deux groupes. Aucun cas d’intussusception n’a été signalé.

Innocuité chez les nourrissons infectés par le VIH
On a examiné l’innocuité de RotarixMC chez 100 nourrissons sud africains (50 avaient reçu RotarixMC et 50, le placebo)(48). Incidence des événements indésirables graves et des événements indésirables sollicités et non sollicités n’a pas différé entre les groupes.

Le 7 mai 2010, Santé Canada a émis un avis sur une évaluation en cours de réalisation des données concernant la présence de circovirus porcin. Nous sommes présentement à examiner de nouvelles données concernant la présence d’ADN de circovirus porcin (PCV 1 et PCV 2) dans les vaccins antirotavirus. Bien que l’on considère que ces vaccins sont contaminés par le circovirus porcin, il ne semble pas que ce dernier cause une maladie chez l’humain. Selon Santé Canada, rien n’indique que la présence de PCV-1 ou de PCV-2 dans les vaccins antirotavirus pose un risque pour la sécurité des patients et souligne que le profil d’innocuité des vaccins antirotavirus était excellent lors des essais cliniques et l’est demeuré après une utilisation clinique auprès de millions de patients(26).

Viral shedding and transmission
Following administration of Rotarix™, viral antigen shedding in the stool was detected by ELISA in 50% - 80% of infants on day 7 following the first vaccine dose, and 4% - 18% of infants on day 7 following the second dose(56). When ELISA-positive stools were tested for the presence of live vaccine virus, 17% of vaccinees had live rotavirus detectable in stool at day 7 following the first dose. All observed shedding in vaccinees was asymptomatic.

Safety in Preterm Infants
The safety of Rotarix™ was evaluated in 1009 preterm infants (198 were 27-30 weeks gestational age and 801 were 31-36 weeks gestational age)(47). No difference in the rates of serious adverse events was observed between infants who received Rotarix™ and those who received placebo (5.1 % vs 6.8%). Rates of solicited and unsolicited symptoms were comparable between the two groups. No cases of intussusception were reported.

Safety in HIV Infected Infants
The safety of Rotarix™ was evaluated in 100 South African infants (50 received Rotarix™ and 50 received placebo)(48). Incidence of serious adverse events and solicited and unsolicited adverse events did not differ between the groups.

On May 7, 2010 Health Canada issued an advisory indicating ongoing review of information regarding the presence of porcine circovirus. We are currently reviewing new information regarding the presence of porcine circovirus (PCV-1 and PCV-2) DNA in rotavirus vaccine. While porcine circovirus is considered a contaminant in these vaccines, it is not known to cause illness in humans. Health Canada stated that there is no evidence that the presence of PCV-1 or PCV2 in rotavirus vaccines poses a safety risk to patients and highlighted the fact that rotavirus vaccines have a strong safety record both in clinical trials and in clinical experience with millions of patients(26).

Excrétion et transmission du virus
Après l’administration de RotarixMC, de 50 % à 80 % des nourrissons ont excrété des antigènes viraux dans leurs selles (détecté par la méthode ELISA) le 7e jour suivant la première dose du vaccin, et de 4 % à 18 % des nourrissons le 7e jour suivant la deuxième dose(56). Lorsque la présence du virus vaccinal vivant a été recherchée dans les selles positives à l’ELISA, le rotavirus vivant était détectable dans les selles de 17 % des vaccinés le 7e jour suivant la première dose. L’excrétion du virus chez les vaccinés était dans tous les cas asymptomatique.
Trials evaluating the potential for transmission of vaccine virus from vaccines to their contacts are currently underway.

**Concomitant administration of other childhood vaccines**

Rotarix™ may be administered concomitantly with all routinely recommended infant vaccines. The impact of concomitant administration of Rotarix™ with DTPa-HBV-IPV/Hib, DTPa, DTaP-IPV, Hib, DTPw-HBV, HBV, pneumococcal conjugate vaccine, meningococcal serogroup C conjugate vaccine, and IPV have been evaluated and the immune responses and safety profile have been shown to be unaffected by concomitant administration. Concomitant administration of Rotarix™ and OPV may result in reduced immune response to Rotarix™. Thus, OPV should be given at least 2 weeks apart from Rotarix™.

**Interchangeability**

There are no data on safety, immunogenicity, or efficacy when Rotarix™ is administered as the first dose and RotaTeq® vaccine is used as the second dose or vice versa. Whenever possible, the rotavirus vaccine series should be completed with the same product. However, in the event that the product used for a previous dose(s) is not known, the series should be completed with the available product. If any dose in the series was RotaTeq®, a total of 3 doses of vaccine should be administered.

**Dosage and Schedule**

Rotarix™ is given as 2 separate 1.5 ml oral doses. Rotarix™ should never be injected.

The first dose of Rotarix™ should be given between 6 weeks (6 weeks plus 0 days) and 15 weeks (14 weeks plus 6 days of age). There should be an interval of at least 4 weeks between the first and second dose. All doses should be completed by the age of 32 weeks (8 months plus 0 days).

In the absence of data regarding administration of Rotarix™ in the home setting and given concerns about maintenance of the cold chain, the committee recommends that all doses be given in a clinic/office setting under the direction of a healthcare provider.

**Interrupted Schedules**

If for any reason an incomplete dose is administered (e.g., infant spits or regurgitates the vaccine), no replacement dose should be administered.

For infants in whom the first dose of Rotarix™ vaccine is inadvertently administered off label at age >15 weeks, the rest of the Rotarix™ vaccination series should be completed with a minimum of 4 weeks between each dose.

Des essais évaluant le risque de transmission du virus vaccinal des vaccinés à leurs contacts sont présentement en cours.

**Administration simultanée d’autres vaccins destinés aux enfants**

RotarixMC peut être administré en même temps que tous les vaccins généralement recommandés pour les nourrissons. Après évaluation de l’impact de l’administration de RotarixMC au même moment que le DCaT-VHB-VPI/Hib, le DCaT, le DCaT VPI, le Hib, le DCT VHB, le VHB, le vaccin antipneumococcique conjugué, le vaccin conjugué contre le méningocoque du sérogroupe C et le VPI, il a été établi que la réponse immunitaire et le profil d’innocuité ne variaient pas avec l’administration simultanée d’autres vaccins. L’administration de RotarixMC au même moment que le vaccin antipoliomyélite oral peut entraîner une réponse immunitaire plus faible envers RotarixMC. Par conséquent, le vaccin antipoliomyélite devrait être administré à au moins 2 semaines d’intervalle.

**Interchangeabilité**

On ne dispose d’aucune donnée sur l’innocuité, l’immunogénicité ou l’efficacité de RotarixMC lorsqu’il est utilisé pour la première dose et RotaTeq® pour la seconde dose ou vice versa. Dans la mesure du possible, on devrait avoir recours au même produit pour toute la série vaccinale contre le rotavirus. Si on ignore l’identité du produit utilisé pour une dose précédente, on devrait compléter la série en utilisant le produit disponible. Si la série comprend au moins une dose de RotaTeq®, 3 doses en tout du vaccin devraient être administrées.

**Posologie et calendrier**

RotarixMC est administré en 2 doses orales séparées de 1.5 ml. Ce vaccin ne devrait jamais être injecté.

La première dose de RotarixMC devrait être administrée entre l’âge de 6 semaines (6 semaines et 0 jour) et de 15 semaines (14 semaines et 6 jours). Il devrait y avoir un intervalle d’au moins 4 semaines entre la première et la seconde dose. Toutes les doses devraient déjà avoir été reçues à l’âge de 32 semaines (8 mois plus 0 jour).

En l’absence de données concernant l’administration de RotarixMC dans un milieu familial et compte tenu des problèmes concernant le maintien de la chaîne du froid, le Comité recommande que toutes les doses soient administrées dans une clinique/cabinet sous la direction d’un dispensateur de soins.

**Interruption du calendrier vaccinal**

Si pour une raison ou une autre, une dose incomplète est donnée (p. ex. le nourrisson crache ou régurgite le vaccin), l’administration d’une dose de remplacement n’est pas recommandée.

Si un nourrisson devait par mégarde recevoir la première dose de RotarixMC à un âge de > 15 semaines, contrairement aux directives figurant sur l’étiquette, les doses subséquentes du vaccin devraient être données à un intervalle minimum de 4 semaines entre chaque
All doses should be administered by 8 months plus 0 days of age.

**Previous RV infection**
Infants who have had rotavirus gastroenteritis before receiving the full course of vaccinations should still initiate or complete the 2-dose schedule because the initial infection frequently provides only partial immunity\(^\text{59}\).  

**Breastfeeding**
The efficacy of RotarixTM is similar among infants who are breastfed and those who are not\(^\text{59}\), therefore, infants who are being breastfed can receive RotarixTM.

**Intercurrent illness**
Like other vaccines, RotarixTM can be administered to infants with transient mild illnesses, and to those with or without fever\(^\text{59}\). See “Precautions” below for guidance on vaccine administration to infants with acute gastroenteritis.

**Premature infants (< 37 weeks gestation)**
Available data in 1009 preterm infants demonstrates that Rotarix\textsuperscript{TM} is safe and induces similar immune response to that achieved in full term infants\(^\text{47}\). Because premature infants have lower levels of maternal antibodies against rotavirus, they may theoretically be at increased risk of both severe naturally occurring rotavirus gastroenteritis and of adverse reactions to the rotavirus vaccine. A Washington State study found that premature infants have an increased risk for hospitalization from gastroenteritis, including viral gastroenteritis\(^\text{60}\). In a Toronto study, a history of prematurity was found in 13% of children admitted with RV in the first year of life which was higher than the regional rate of prematurity of 7%, suggesting the possibility of more severe disease in this group\(^\text{61}\).

Based upon available data, and because of the susceptibility of this population, NACI feels the potential benefit of vaccination of premature infants outweighs the potential risk. Infants who are between 6 weeks and 8 months plus 0 days of chronological age, are healthy and are not hospitalized can receive Rotarix\textsuperscript{TM}.

**Exposure of immunocompromised persons or pregnant women to vaccinated infants**
Following administration of Rotarix\textsuperscript{TM}, viral antigen shedding in the stool may be detected in up to 80% of vaccinees with peak shedding observed at 7 days post dose 1. Live rotavirus vaccine is detectable in the stool of 17% of vaccines at day 7 following the first dose.

**Infection à RV antérieure**
Dans le cas des nourrissons qui ont souffert d’une gastro entérine à rotavirus avant d’avoir reçu toute la série vaccinale, il faut tout entreprendre ou compléter la série de 2 doses, car l’infection initiale ne confère souvent qu’une immunité partielle\(^\text{59}\).

**Allaitement**
L’efficacité de Rotarix\textsuperscript{MC} est similaire chez les nourrissons qui sont allaités et ceux qui ne le sont pas\(^\text{59}\); les nourrissons allaités peuvent donc recevoir Rotarix\textsuperscript{MC}.

**Maladies intercurrentes**
Comme d’autres vaccins, Rotarix\textsuperscript{MC} peut être administré aux nourrissons atteints d’une affection transitoire bénigne, de même qu’à ceux qui présentent une fièvre ou non\(^\text{59}\). Consulter la section « Précautions » ci dessous afin de connaître les directives concernant la vaccination des nourrissons qui présentent une gastro entérine aiguë.

**Nourrissons prématurés (âge gestationnel de < 37 semaines)**
Les données dont on dispose sur 1 009 nourrissons prématurés montrent que Rotarix\textsuperscript{MC} est sûr et induit une réponse immunitaire semblable à celle des nourrissons nés à terme\(^\text{47}\). Comme les bébés prématurés possèdent des titres plus faibles d’anticorps maternels contre le rotavirus, ils peuvent théoriquement courir un plus grand risque de gastro entérine grave due à un rotavirus naturel et de présenter des réactions indésirables au vaccin antirotavirus. Une étude effectuée dans l’État de Washington a indiqué que les nourrissons prématurés courent un plus grand risque d’être hospitalisés pour une gastro entérine, y compris pour une gastro entérine virale\(^\text{60}\). Dans une étude menée à Toronto, des antécédents de prématurité ont été relevés chez 13 % des enfants admis pour une infection à RV au cours de leur première année de vie, soit un taux plus élevé que le taux régional de prématurité de 7 %, ce qui évoque la possibilité que la maladie soit plus grave dans ce groupe\(^\text{61}\).

D’après les données disponibles et à cause de la susceptibilité de cette population, le CCNI estime que l’avantage potentiel de la vaccination des bébés prématurés l’emporte sur le risque potentiel. Les nourrissons âgés de 6 semaines à 8 mois plus 0 jour (âge chronologique) qui sont en bonne santé et ne sont pas hospitalisés peuvent recevoir Rotarix\textsuperscript{MC}.

**Exposition des personnes immunodéprimées ou des femmes enceintes à des nourrissons vaccinés**
Jusqu’à 80 % des vaccinés peuvent excréter des antigènes viraux dans leurs selles après l’administration de Rotarix\textsuperscript{MC}, l’excrétion étant maximale 7 jours après la première dose. Le vaccin à rotavirus vivant peut être détecté dans les selles de 17 % des vaccinés 7 jours après la première dose.
Data on the potential for horizontal transmission of vaccine virus has not been published. A study on 100 twin pairs has been completed, but has yet to be published. However, the benefit of protecting immunocompromised household contacts from naturally occurring RV by immunizing infants is believed, by many experts, to outweigh the theoretical risk of transmitting vaccine virus. Thus, infants living in households with persons who have or are suspected to have immunosuppressive conditions or who are receiving immunosuppressive medications can be vaccinated. To minimize the risk of transmission of vaccine virus, careful handwashing should be used after contact with the vaccinated infant, especially after handling feces (i.e., after changing a diaper), and before food preparation and direct contact with the immunocompromised person.

Infants living in households with pregnant women can be vaccinated. Because most women of childbearing age have pre-existing immunity to rotavirus through natural exposure, the risk of infection and disease from vaccine virus is low. Additionally, rotavirus infection during pregnancy is not known to pose a risk to the fetus.

**Contraindications**

Infants who have a history of anaphylactic reaction to any component of the vaccine or its container should not be vaccinated. Should an infant develop an anaphylactic reaction after receiving one dose of vaccine, further doses should not be given and the child should be referred to an allergist. The Rotarix™ oral applicator contains latex rubber therefore infants with anaphylactic allergy to latex should not receive Rotarix™.

**History of intussusception:** No association between Rotarix™ and intussusception has been demonstrated in large-scale safety trials or in post-marketing surveillance. However, because of the previously documented association of Rotashield™ (Wyeth-Lederle) with increased rates of intussusception, incomplete understanding of the pathogenic mechanisms underlying this increased risk, and the possibility that infants with a history of intussusception are at increased risk of subsequent episodes, infants with a history of intussusception should not be given Rotarix™. This recommendation may change as further safety data becomes available.

**Immunocompromised Infants:** While available data of 50 South African children with asymptomatic or minimally symptomatic HIV infection who received 3 doses of Rotarix™ suggest that Rotarix™ is safe and immunogenic in this population, data in other immunocompromised populations is not available. Based on the theoretical risk of live attenuated viral vaccines in immunocompromised infants, and very minimal data in this population, infants with suspected or known immunocompromising conditions should

Aucune donnée sur le risque de transmission horizontale du virus vaccinal n’a été publiée. Une étude portant sur 100 paires de jumeaux a été effectuée, mais n’a pas encore été publiée. Toutefois, de nombreux experts sont d’avis que les avantages découlant de la protection des contacts familiaux immunodéprimés contre une infection à rotavirus naturelle au moyen de la vaccination des nourrissons l’emportent sur le risque théorique de transmission du virus vaccinal. Les nourrissons vivant avec des personnes qui sont ou que l’on soupçonne d’être immunodéprimées ou qui prennent des médicaments immunosuppresseurs peuvent donc être vaccinés. Afin de réduire au minimum le risque de transmission du virus vaccinal, il faut se laver soigneusement les mains après un contact avec le nourrisson vacciné, en particulier après un contact avec ses selles (p. ex. après avoir changé une couche) ainsi qu’avant la préparation d’aliments et avant tout contact direct avec la personne immunodéprimée.

Les nourrissons vivant avec une femme enceinte peuvent être vaccinés. En tenant compte que la plupart des femmes en âge de procréer sont déjà immunisées contre le rotavirus à la suite d’une exposition naturelle antérieure, le risque d’infection et de maladies associées au virus vaccinal est faible. En outre, l’infection à rotavirus pendant la grossesse ne présente aucun risque connu pour le fœtus.

**Contre indications**

Les nourrissons qui ont des antécédents de réaction anaphylactique à un des composants du vaccin ou à son contenant ne devraient pas être immunisés. Si un nourrisson présente une réaction anaphylactique après avoir reçu une dose du vaccin, les doses subséquentes ne devraient pas être administrées et l’enfant devrait être adressé à un allergologue. Comme l’applicateur oral de RotarixMC contient du caoutchouc latex, les nourrissons qui sont allergiques au latex ne devraient pas recevoir ce vaccin.

**Antécédents d’intussusception :** Aucune association entre RotarixMC et l’intussusception n’a été démontrée dans le cadre d’essais d’innocuité à grande échelle ou de la surveillance post-commercialisation. Cependant, puisqu’une association a été observée précédemment entre RotashieldMD et des taux accrus d’intussusception, puisqu’on comprend mal les mécanismes pathogènes à la base de cette augmentation du risque et qu’il est possible que les nourrissons ayant des antécédents d’intussusception courent un plus grand risque d’épisodes subséquents, les nourrissons présentant des antécédents d’intussusception ne devraient pas recevoir RotarixMC. Cette recommandation pourra être modifiée lorsqu’on disposera de plus de données sur l’innocuité.

**Sujets immunodéprimés :** Les données recueillies auprès de 50 enfants sud africains présentant une infection à VIH asymptomatique ou légèrement symptomatique ayant reçu 3 doses de RotarixMC indiquent que RotarixMC est sûr et immunogène dans cette population; cependant, on ne dispose pas de données sur d’autres populations immunodéprimées. Compte tenu du risque théorique posé par l’administration d’un vaccin antiviral vivant atténué à des nourrissons immunodéprimés et de la très faible quantité de données disponibles chez cette population, les nourrissons ayant une affection souffrante ou connue entraînant
not receive RotaTeq® or Rotarix™ without consultation with a physician specialist or expert in these conditions.

Precautions

Acute gastroenteritis: The immunogenicity and efficacy of Rotarix™ has not been studied in infants with concurrent gastroenteritis. However, in these infants, as is the case with oral polio vaccine, immunogenicity and effectiveness of the vaccine may theoretically be reduced(63). Therefore, in infants with moderate-to-severe gastroenteritis, rotavirus vaccine should be deferred until the condition improves unless deferral will result in scheduling of the first dose > 14 weeks plus 6 days of age. Infants with mild gastroenteritis can be vaccinated.

Pre-existing chronic gastrointestinal conditions: The safety and efficacy of Rotarix™ has not been established in children with pre-existing chronic gastrointestinal conditions. However, infants with chronic gastrointestinal disease who are not receiving immunosuppressive therapy are likely to benefit from rotavirus vaccination and therefore can be vaccinated.

Recommendations for use of rotavirus vaccines

These recommendations replace the recommendations in the November 2008 statement(1). NACI recommends the use of the rotavirus vaccines RotaTeq® or Rotarix™ for:

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). (Recommendation – Grade A – good evidence to recommend immunization)

   Vaccination may be provided with either pentavalent human-bovine reassortant vaccine (RotaTeq®) or with monovalent human rotavirus vaccine (Rotarix™). Vaccination should not be initiated in infants aged 15 weeks and 0 days or older as the safety of providing the first dose of rotavirus vaccine in older infants is not known. The minimum interval between doses of rotavirus vaccine is 4 weeks. All doses of rotavirus vaccine should be administered by age 8 months, 0 days. (Table 5)

   Canadian epidemiology suggests that there is a high prevalence of rotavirus gastroenteritis among children less than 5 years of age. Many of these children require visits to their primary care provider and some require hospitalization. Death in Canada due to rotavirus gastroenteritis is fortunately a rare event. Neither currently authorized product has been associated with an increased risk of intussusception, although ongoing monitoring will continue to play an essential role in our immunization programs.

Usage recommandé des vaccins antirotavirus

Les présentes recommandations remplacent celles publiées dans la déclaration de novembre 2008(1). Le CCNI recommande l’administration des vaccins antirotavirus RotaTeq® ou RotarixMC aux sujets suivants :

1. Nourrissons en santé : Le vaccin antirotavirus est recommandé pour les nourrissons âgés de 6 semaines (6 semaines et 0 jour) à 15 semaines (14 semaines et 6 jours). (Recommendation – Catégorie A – données probantes suffisantes pour recomander l’immunisation)

   On peut utiliser soit le vaccin pentaavalent à souches réassorties de virus humain-bovin (RotaTeq®) ou le vaccin monovalent à rotavirus humain (RotarixMC). On ne devrait pas commencer la vaccination chez les nourrissons âgés de 15 semaines et 0 jour ou plus, car on ne sait pas s’il est sûr d’administrer la première dose du vaccin antirotavirus chez les nourrissons plus vieux. L’intervalle minimal entre les doses est de 4 semaines. Toutes les doses du vaccin antirotavirus devraient avoir été administrées avant l’âge de 8 mois, 0 jour (Tableau 5).

   L’épidémiologie de la gastro entérite à rotavirus au Canada donne à penser que les taux de prévalence sont élevés chez les enfants de moins de 5 ans. Bon nombre de ces enfants doivent consulter leur dispensateur de soins primaires et certains d’entre eux doivent être hospitalisés. Heureusement, il est rare au Canada qu’une gastro entérite à rotavirus ne se solde par un décès. Même si aucun des deux produits actuellement autorisés n’a été associé à une augmentation du risque d’intussusception, la surveillance continue demeurerait un élément essentiel de nos programmes d’immunisation.
Insufficient data about strain distribution of RV in Canada and geographical and seasonal trends in distribution make prediction of the absolute impact of a universal RV vaccine program difficult. Preliminary effectiveness data in the US after the introduction of RotaTeq® suggest that vaccine effectiveness in vaccinated infants is similar to vaccine efficacy reported in clinical trials and that, in addition, a significant indirect protection of unimmunized persons may be observed even with relatively low coverage rates. Prospective surveillance data from IMPACT will soon be available to provide better RV epidemiologic data regarding burden of illness and rotavirus strain distribution in Canada.

The decision to include rotavirus vaccine(s) in universal, publicly-funded Provincial and Territorial programs will depend upon multiple factors such as detailed cost-benefit evaluation and assessment of other elements of the Erikson and DeWals analytic framework for immunization programs in Canada(64).

Based on World Health Organization review of the evidence, Strategic Advisory Group of Experts on Immunization (SAGE) recommends the inclusion of rotavirus vaccination of infants into all national immunization programs. In countries where diarrheal deaths account for >10% of mortality among children aged <5 years, the introduction of the vaccine is strongly recommended(65).

2. Preterm infants: Infants who are between 6 weeks and 8 months plus 0 days of chronological age who are healthy and not hospitalized, can receive RotaTeq® or Rotarix™. The first dose should be given between 6 weeks and 14 weeks plus 6 days. (Recommendation – Grade A – good evidence to recommend immunization)

Available data in 1009 preterm infants demonstrates that Rotarix™ is safe and induces similar immune response to that achieved in full term infants(47). A study of RotaTeq® indicated that the live attenuated vaccine was safe and effective in children of this gestational age(48). Based upon available, data, NACI feels the potential benefit of vaccination of premature infants outweighs the potential risk. Infants who are between 6 weeks and 14 weeks plus 6 days of chronological age who are healthy and not hospitalized, can begin a series of either RotaTeq® or Rotarix™. The minimum interval between doses of rotavirus vaccine is 4 weeks. All doses of rotavirus vaccine should be administered by age 8 months, 0 days based on chronological age (Recommendation – Grade A – good evidence to recommend immunization)

En raison du manque de données sur la distribution des souches de RV au Canada et des tendances géographiques et saisonnières, il est difficile de prédire l’impact absolu d’un programme universel de vaccination contre le RV. Selon des données préliminaires recueillies aux É. U. après l’introduction de Rota Teq®, l’efficacité du vaccin chez les nourrissons immunisés est similaire à celle signalée dans les essais cliniques, et une protection indirecte notable peut être observée chez les personnes non immunisées même lorsque les taux de couverture vaccinale sont relativement faibles. Nous disposerons bientôt des données de surveillance prospective du programme IMPACT, qui brosseront un tableau épidémiologique plus complet du fardeau de la maladie et de la distribution des souches de rotavirus au Canada.

La décision d’inclure un ou des vaccins antirotavirus dans les programmes provinciaux et territoriaux de vaccination universelle subventionnés par l’État dépendra de plusieurs facteurs, notamment des résultats de l’évaluation détaillée coûts avantages et de l’évaluation d’autres éléments du cadre analytique d’Erikson et DeWals pour les programmes d’immunisation au Canada(64).

Fondé sur le survol de données effectué par l’Organisation mondiale de la Santé, le Groupe consultatif stratégique d’experts de la vaccination (SAGE) recommande l’inclusion de la vaccination des nourrissons contre le rotavirus dans tous les programmes nationaux de vaccination. Dans les pays où > 10 % des décès chez les enfants de < 5 ans sont causés par la diarrhée, l’introduction du vaccin est fortement recommandée(65).

2. Nourrissons prématûrés : Les nourrissons qui sont âgés entre 6 semaines et 8 mois plus 0 jour d’âge chronologique et qui sont en santé et non hospitalisés peuvent recevoir RotaTeq® ou Rotarix™. La première dose devrait être administrée entre 6 semaines et 14 semaines et 6 jours. (Recommendation – Catégorie A – données probantes suffisantes pour recommander l’immunisation)

Des données recueillies chez 1 009 nourrissons prématûrés démontrent que Rotarix™ est sûr chez les prématurés et induit une réponse immunitaire semblable à celle des nourrissons nés à terme(48). Une étude portant sur RotaTeq® a révélé que le vaccin à virus vivant atténué était sûr et efficace chez les enfants de cet âge gestationnel(49). Selon les données disponibles, le CCNI estime que l’avantage potentiel de la vaccination des nourrissons prématurés l’emporte sur le risque potentiel. Les nourrissons âgés de 6 semaines à 14 semaines et 6 jours (âge chronologique) qui sont en santé et ne sont pas hospitalisés peuvent entreprendre la série soit de RotaTeq® ou de Rotarix™. L’intervalle minimal entre les doses du vaccin antirotavirus est de 4 semaines. Toutes les doses du vaccin devraient être administrées avant l’âge de 8 mois, 0 jour (âge chronologique) (Recommandation de catégorie A – données probantes suffisantes pour recommander l’immunisation)
3. Nourrissons immunodéprimés : D’après le risque théorique associé aux vaccins à virus vivant atténué chez les nourrissons immunodéprimés et compte tenu du peu de données relatives à cette population, le CCNI recommande que les nourrissons atteints ou soupçonnés d’être atteints d’un déficit immunitaire ne reçoivent pas RotaTeq® ni Rotarix™ sans consultation préalable d’un médecin spécialiste ou d’un expert dans ces troubles. (Recommandation – Catégorie E – données probantes suffisantes pour déconseiller l’immunisation)

4. Nourrissons ayant des antécédents d’intussusception : En s’appuyant sur des données récentes, le CCNI recommande que les nourrissons ayant des antécédents d’intussusception ne reçoivent pas de vaccins antirotavirus. (Recommandation – Catégorie E – good evidence to recommend against immunization).

À aucune association entre Rotarix™ ou RotaTeq® et l’intussusception n’a été démontrée dans des essais à grande échelle sur l’innocuité ni dans le cadre de la surveillance post commercialisation. Les enfants ayant des antécédents d’intussusception ont été exclus des essais sur l’immunogénicité et l’efficacité. La présente recommandation se fonde sur l’association précédemment établie entre Rotashield™ et l’augmentation des taux d’intussusception, sur le manque de connaissances relatives aux mécanismes pathogènes à l’origine de cette augmentation de risque, sur l’absence de données dans cette population et sur la possibilité que les nourrissons ayant des antécédents d’intussusception courent un plus grand risque d’épisodes subséquents.

Table 5: Summary of vaccine characteristics and recommended uses of the two currently authorized rotavirus vaccines, RotaTeq® and Rotarix™

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RotaTeq®</th>
<th>Rotarix™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent rotavirus strain</td>
<td>Human - bovine strain WC3</td>
<td>Human strain 89-12 (Type G1P1A[8])</td>
</tr>
<tr>
<td>Vaccine composition</td>
<td>Reassortant strains: G1xWC3; G2xWC3; G3xWC3; G4xWC3; P1A[8]xWC3</td>
<td>Human strain 89-12 (Type G1P1A[8])</td>
</tr>
<tr>
<td>Formulation</td>
<td>Liquid (no reconstitution required)</td>
<td>Liquid (no reconstitution required)</td>
</tr>
<tr>
<td>Applicator</td>
<td>Latex-free dosing tube</td>
<td>Glass oral applicator with latex rubber in plunger and cap</td>
</tr>
<tr>
<td>Volume per dose</td>
<td>2 ml</td>
<td>1.5 ml(45)</td>
</tr>
<tr>
<td># doses in series</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Minimum age at dose 1</td>
<td>6 weeks</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Maximum age at dose 1</td>
<td>14 weeks + 6 days</td>
<td>14 weeks + 6 days</td>
</tr>
<tr>
<td>Minimal intervals between doses</td>
<td>4 weeks</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Maximum age for last dose</td>
<td>8 months + 0 days</td>
<td>8 months + 0 days</td>
</tr>
<tr>
<td>Caractéristique</td>
<td>RotaTeq®</td>
<td>Rotarix&lt;sup&gt;MC&lt;/sup&gt;</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>----------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Souche mère du rotavirus</td>
<td>Humain – souche bovine WC3</td>
<td>Souche humaine 89 12 (Type G1P1A[8])</td>
</tr>
<tr>
<td>Composition vaccinale</td>
<td>Souches réassorties : G1xWC3; G2x-WC3; G3xWC3; G4xWC3; P1A[8]xWC3</td>
<td>Souche humaine 89 12 (Type G1P1A[8])</td>
</tr>
<tr>
<td>Formulation</td>
<td>Liquide (aucune reconstitution requise)</td>
<td>Liquide (aucune reconstitution nécessaire)</td>
</tr>
<tr>
<td>Applicateur</td>
<td>Tube doseur sans latex</td>
<td>Applicateur oral de verre avec caoutchouc naturel (latex) dans le piston et le capuchon</td>
</tr>
<tr>
<td>Volume par dose</td>
<td>2 ml</td>
<td>1.5 ml&lt;sup&gt;(45)&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nbre de doses dans une série</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Âge minimal lors de la 1&lt;sup&gt;re&lt;/sup&gt; dose</td>
<td>6 semaines</td>
<td>6 semaines</td>
</tr>
<tr>
<td>Âge maximal lors de la 1&lt;sup&gt;re&lt;/sup&gt; dose</td>
<td>14 semaines + 6 jours</td>
<td>14 semaines + 6 jours</td>
</tr>
<tr>
<td>Intervalles minimaux entre les doses</td>
<td>4 semaines</td>
<td>4 semaines</td>
</tr>
<tr>
<td>Âge maximal pour la dernière dose</td>
<td>8 mois + 0 jour</td>
<td>8 mois + 0 jour</td>
</tr>
</tbody>
</table>

**Table 6. Levels of evidence based on research design**

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence from randomized controlled trial(s)</td>
</tr>
<tr>
<td>II-1</td>
<td>Evidence from controlled trial(s) without randomization</td>
</tr>
<tr>
<td>II-2</td>
<td>Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group using clinical outcome measures of vaccine efficacy</td>
</tr>
<tr>
<td>II-3</td>
<td>Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.</td>
</tr>
<tr>
<td>III</td>
<td>Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.</td>
</tr>
</tbody>
</table>

**Tableau 6. Niveaux de preuve fondés sur la méthodologie de la recherche**

<table>
<thead>
<tr>
<th>Niveau</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Données probantes provenant d’un ou de plusieurs essais cliniques comparatifs randomisés.</td>
</tr>
<tr>
<td>II-1</td>
<td>Données probantes provenant d’un ou de plusieurs essais cliniques comparatifs sans randomisation.</td>
</tr>
<tr>
<td>II-2</td>
<td>Données probantes provenant d’études analytiques de cohortes ou cas/témoins, de préférence de plus d’un centre ou groupe de recherche utilisant des indicateurs cliniques de résultats de l’efficacité d’un vaccin.</td>
</tr>
<tr>
<td>II-3</td>
<td>Données probantes provenant d’études de plusieurs séries chronologiques avec ou sans intervention. Les résultats spectaculaires obtenus dans un contexte non contrôlé (comme les résultats de l’introduction de la pénicilline dans les années 1940) pourraient aussi être considérés comme faisant partie de ce type de données probantes.</td>
</tr>
<tr>
<td>III</td>
<td>Opinions d’experts respectés se basant sur des expériences cliniques, des études descriptives et des études de cas ou des rapports de comités d’experts.</td>
</tr>
</tbody>
</table>
Table 7. Quality (internal validity) rating

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>A study (including meta-analyses or systematic reviews) that meets all design-specific criteria* well.</td>
</tr>
<tr>
<td>Fair</td>
<td>A study (including meta-analyses or systematic reviews) that does not meet (or it is not clear that it meets) at least one design-specific criterion* but has no known “fatal flaw”.</td>
</tr>
<tr>
<td>Poor</td>
<td>A study (including meta-analyses or systematic reviews) that has at least one design-specific* “fatal flaw”, or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations.</td>
</tr>
</tbody>
</table>

* General design specific criteria are outlined in Harris et al. (66)

Tableau 7. Cote de qualité (validité interne)

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonne</td>
<td>Étude (notamment les méta-analyses ou les recensions systématiques) répondant bien à tous les critères propres à la méthodologie*.</td>
</tr>
<tr>
<td>Passable</td>
<td>Étude (notamment les méta-analyses ou les recensions systématiques) ne répondant pas (ou du moins pas clairement) à au moins un critère propre à la méthodologie* mais n'ayant pas de « lacune majeure » connue.</td>
</tr>
<tr>
<td>Mauvaise</td>
<td>Étude (notamment les méta-analyses ou les recensions systématiques) ayant au moins une « lacune majeure » propre à la méthodologie* ou une accumulation de lacunes moins importantes ne permettant pas de formuler des recommandations à partir des résultats de l’étude.</td>
</tr>
</tbody>
</table>

* Les critères généraux propres à la méthodologie sont décrits dans Harris et coll. (66)

Table 8. NACI Recommendations for Immunization

<table>
<thead>
<tr>
<th>Letter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>NACI concludes that there is <strong>good</strong> evidence to recommend immunization.</td>
</tr>
<tr>
<td>B</td>
<td>NACI concludes that there is <strong>fair</strong> evidence to recommend immunization.</td>
</tr>
<tr>
<td>C</td>
<td>NACI concludes that the existing evidence is <strong>conflicting</strong> and does not allow making a recommendation for or against immunization, however other factors may influence decision-making.</td>
</tr>
<tr>
<td>D</td>
<td>NACI concludes that there is <strong>fair</strong> evidence to recommend against immunization.</td>
</tr>
<tr>
<td>E</td>
<td>NACI concludes that there is <strong>good</strong> evidence to recommend against immunization.</td>
</tr>
<tr>
<td>I</td>
<td>NACI concludes that there is <strong>insufficient</strong> evidence (in either quantity and/or quality) to make a recommendation, however other factors may influence decision-making.</td>
</tr>
</tbody>
</table>
### Table 9. Summary of Evidence for the use of Rotarix™:

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Number of Participants</th>
<th>Outcomes</th>
<th>Level of Evidence</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evidence for the Safety of Rotarix™</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dennehy et al. 2005(46)</td>
<td>Double blinded randomized controlled trial</td>
<td>529 enrolled</td>
<td>• Solicited daily record for 15 days post vaccination</td>
<td>I</td>
<td>Good North American Population Small sample size</td>
</tr>
<tr>
<td></td>
<td></td>
<td>421 immunized 108 placebo group</td>
<td>• Unsolicited record for within 43 days of vaccine receipt</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Serious adverse events (10-12 months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Gastroenteritis from first dose until 2 months after 2 dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruiz-Palacios et al. 2006(49)</td>
<td>Double blinded randomized controlled trial</td>
<td>63 225 enrolled</td>
<td>Clinical – including: Severe gastroenteritis, hospitalizations using MedRHA</td>
<td>I</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td></td>
<td>31 673 immunized 31 552 placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linhares et al. 2008(51)</td>
<td>Double blinded randomized controlled trial</td>
<td>15 183 enrolled</td>
<td>Clinical – including: Severe gastroenteritis, hospitalizations through active, hospital based surveillance</td>
<td>I</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 699 immunized 7 493 placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Evidence for the Efficacy of Rotarix™</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruiz-Palacios et al. 2006(49)</td>
<td>Double blinded randomized controlled trial</td>
<td>20 169 enrolled</td>
<td>RT-PCR in cases of gastroenteritis</td>
<td>I</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 159 immunized 10 010 placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vesikari et al. 2007(50)</td>
<td>Double blinded randomized controlled trial</td>
<td>3994 enrolled</td>
<td>Clinical – any severity gastroenteritis, hospitalization, health care visit</td>
<td>I</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 646 immunized 1 348 placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linhares et al. 2008(51)</td>
<td>Double blinded randomized controlled trial</td>
<td>20 160 enrolled</td>
<td>Clinical – hospitalized, severe gastroenteritis Vesikari scale used</td>
<td>I</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 397 immunized 7 218 placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Étude Plan d’étude Nombre de participants Résultats Niveau de preuve Qualité

#### Données à l’appui de l’innocuité de Rotarix<sup>MC</sup>:

<table>
<thead>
<tr>
<th>Étude</th>
<th>Plan d’étude</th>
<th>Nombre de participants</th>
<th>Résultats</th>
<th>Niveau de preuve</th>
<th>Qualité</th>
</tr>
</thead>
</table>
| Dennehy et coll., 2005<sup>(46)</sup> | Essai comparatif randomisé à double insu | 529 inscrits 421 vaccinés 108 sujets placebo | • Relevé quotidien sollicité pendant les 15 jours suivant la vaccination  
• Consignation non sollicitée des données pendant les 43 jours suivant la vaccination  
• Événements indésirables graves (10 12 mois)  
• Gastro entérite, de la première dose jusqu’à 2 mois après la 2e dose | I | Bonne Population nord-américaine Échantillon de petite taille |
| Ruiz-Palacios et coll., 2006<sup>(49)</sup> | Essai comparatif randomisé à double insu | 63 225 inscrits 31 673 vaccinés 31 552 placebo | Cliniques – notamment : gastro entérite grave, hospitalisations à l’aide de MedRHA | I | Bonne |
| Linhares et coll., 2008<sup>(51)</sup> | Essai comparatif randomisé à double insu | 15 183 inscrits 7 669 vaccinés 7 493 placebo | Cliniques – notamment : gastro entérite grave, hospitalisations par le biais d’une surveillance active en milieu hospitalier | I | Bonne |

#### Données à l’appui de l’efficacité de Rotarix<sup>MC</sup>:

<table>
<thead>
<tr>
<th>Étude</th>
<th>Plan d’étude</th>
<th>Nombre de participants</th>
<th>Résultats</th>
<th>Niveau de preuve</th>
<th>Qualité</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruiz-Palacios et coll., 2006&lt;sup&gt;(49)&lt;/sup&gt;</td>
<td>Essai comparatif randomisé à double insu</td>
<td>20 169 inscrits 10 159 vaccinés 10 010 placebo</td>
<td>RT-PCR dans les cas de gastro entérite</td>
<td>I</td>
<td>Bonne</td>
</tr>
<tr>
<td>Vesikari et coll., 2007&lt;sup&gt;(50)&lt;/sup&gt;</td>
<td>Essai comparatif randomisé à double insu</td>
<td>3994 inscrits 2 646 vaccinés 1 348 placebo</td>
<td>Cliniques – gastro entérite de toute gravité, hospitalisations, consultation d’un dispensateur de soins</td>
<td>I</td>
<td>Bonne</td>
</tr>
</tbody>
</table>
| Linhares et coll., 2008<sup>(51)</sup> | Essai comparatif randomisé à double insu | 20 160 inscrits 7 397 vaccinés 7 218 placebo | Cliniques – hospitalisations, gastro entérite grave  
Échelle de Vesikari utilisée | I | Bonne |

#### Données à l’appui de l’immunogénicité de Rotarix<sup>MC</sup>:

<table>
<thead>
<tr>
<th>Étude</th>
<th>Plan d’étude</th>
<th>Nombre de participants</th>
<th>Résultats</th>
<th>Niveau de preuve</th>
<th>Qualité</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dennehy et coll., 2005&lt;sup&gt;(46)&lt;/sup&gt;</td>
<td>Essai comparatif randomisé à double insu</td>
<td>529 inscrits 421 vaccinés 108 sujets placebo</td>
<td>IgA &gt;20 U/ml à l’ELISA</td>
<td>I</td>
<td>Bonne</td>
</tr>
</tbody>
</table>
Références


Belongia, EA. Update on RotaTeq. ACIP Meeting June 2008.


(53) Esparza-Aguilar M et al. Analysis of the mortality due to diarrhoea in younger children, before and after the introduction of the rotavirus vaccine. Salud Publica Mex;51:285-290

(54) Strens D et al. To investigate the effect of pediatric vaccination on rotavirus disease burden in Belgium. 27th Annual meeting of the European Society of Pediatric Infectious Diseases, Brussels, Belgium, 9-13 June 2009.


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CPS
Recommendations
Recommendations for the use of rotavirus vaccines in infants

M Salvadori, N Le Saux; Canadian Paediatric Society, Infectious Diseases and Immunization Committee

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

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

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

CLINICAL DISEASE

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

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

EPIDEMIOLOGY OF ROTAVIRUS DISEASE

It is estimated that all children will experience at least one episode of rotavirus infection by five years of age. Because rotavirus gastroenteritis is not a nationally notifiable disease, the exact prevalence and associated disease burden are not known. These are estimated by several Canadian studies that examine acute rotavirus diarrhea in children seen in family physician offices, paediatric clinics, emergency departments and hospital admissions. It is estimated that one in 62 (6) to one in 312 (7) children younger than
five years of age will be hospitalized with rotavirus infection. More than one-half of rotavirus hospitalizations occur in the six- to 24-month age group (8).

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

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

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

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

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

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

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

THE VIRUS

Rotaviruses are double-stranded RNA viruses. The serotype is defined by two outer capsid proteins – VP7, the glycoprotein (G protein) and VP4, the protease-cleaved protein (P protein). Most human infections to date have been caused mainly by four rotavirus serotypes: G1P[8], G2P[4], G3P[8] and G4P[8]; however, some regions have had more variability, with other serotypes (G9, G5, G6 and G8) presenting. The prevalence of rotavirus serotypes varies geographically and from year to year.

DIAGNOSIS

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

ROTAVIRUS VACCINATION

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

Efficacy of current vaccines

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

The first, RotaTeq, manufactured by Merck Frosst Canada, was approved in 2006. This is a live, oral, pentavalent vaccine that contains five live reassortant rotaviruses from human and bovine sources. The vaccine contains antigens G1, G2, G3, G4 and P1[8]. It is supplied in single prefilled 2 mL tubes given in three oral doses starting at six weeks of age, with a minimal interval between doses of four weeks. This vaccine can be given simultaneously with other regularly scheduled routine childhood immunizations.

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

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

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

SAFETY

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

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

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

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

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Selected differences and characteristics of two licensed vaccines in Canada</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RotaTeq (Merck Frosst Canada)</td>
</tr>
<tr>
<td>Type and origin of vaccine virus</td>
<td>Human-bovine pentavalent G1-G4P[8]</td>
</tr>
<tr>
<td>How vaccine is supplied and administered</td>
<td>Supplied as a liquid in a squeezable latex-free dosing tube.</td>
</tr>
<tr>
<td>Volume per dose</td>
<td>2 mL</td>
</tr>
<tr>
<td>Number of doses required</td>
<td>3</td>
</tr>
<tr>
<td>Minimum age at dose 1</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Maximum age at dose 1</td>
<td>14 weeks plus 6 days</td>
</tr>
<tr>
<td>Minimum interval between doses</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Maximum age for last dose</td>
<td>8 months plus 0 days</td>
</tr>
<tr>
<td>Storage</td>
<td>Should be stored in a refrigerator at 2°C to 8°C. After removal from refrigeration, use as soon as possible (&lt;4 h) and only if temperature has not exceeded 25°C</td>
</tr>
</tbody>
</table>

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

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

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

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

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

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

- Rotavirus vaccination is recommended for all infants because it significantly decreases the incidence and morbidity associated with rotavirus infection. Although these vaccines may not prevent all cases of rotavirus diarrhea, they do prevent severe disease and significantly decrease the risk of dehydration and hospitalization in vaccinated infants. Either vaccine is safe and efficacious. There are no interchangeability data, so whenever possible, the rotavirus vaccination series should be completed with the same product. (I-A)

- Vaccination must be started between six and 14 weeks plus six days of age, with the series completed by eight months of age. Adherence to recommendations regarding the time of administration should be ensured because the safety of rotavirus vaccine administration outside of these recommendations is unknown.

- Canadian physicians should advocate for universal funding and integration of this vaccine into provincial programs to ensure equitable access for all children.

- Advocating for the availability of rotavirus vaccination programs in the developing world should be a priority because the impact on global childhood mortality and morbidity due to rotavirus infections in this context is expected to be the greatest.

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

REFERENCES

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The recommendations in this statement do not indicate an exclusive course of treatment or procedure to be followed. Variations, taking into account individual circumstances, may be appropriate. All Canadian Paediatric Society position statements and practice points are reviewed, revised or retired as needed on a regular basis. Please consult the “Position Statements” section of the CPS website (www.cps.ca/english/publications/statementsindex.htm) for the most current version.
ACIP Statement
Prevention of Rotavirus Gastroenteritis Among Infants and Children
Recommendations of the Advisory Committee on Immunization Practices (ACIP)
Introduction .............................................................................. 1
Background ............................................................................... 2
Rotavirus Vaccines ..................................................................... 4
Methodology ............................................................................... 4
Pentavalent Human-Bovine Reassortant Rotavirus Vaccine
(RotaTeq® [RV5]) ................................................................. 4
Monovalent Human Rotavirus Vaccine (Rotarix® [RV1]) .......... 12
Recommendations for the Use of Rotavirus Vaccine .............. 16
References ............................................................................... 21

On the cover: Negative-stain electron micrograph of rotavirus A.
Courtesy of Charles D. Humphrey, CDC.
Prevention of Rotavirus Gastroenteritis Among Infants and Children

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

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Summary
Rotavirus is the most common cause of severe gastroenteritis in infants and young children worldwide. Before initiation of the rotavirus vaccination program in the United States in 2006, approximately 80% of U.S. children had rotavirus gastroenteritis by age 5 years. Each year during the 1990s and early 2000s, rotavirus resulted in approximately 410,000 physician visits, 205,000–272,000 emergency department visits, and 55,000–70,000 hospitalizations among U.S. infants and children, with total annual direct and indirect costs of approximately $1 billion. In February 2006, a live, oral, human-bovine reassortant rotavirus vaccine (RotaTeq® [RV5]) was licensed as a 3-dose series for use among U.S. infants for the prevention of rotavirus gastroenteritis, and the Advisory Committee on Immunization Practices (ACIP) recommended routine use of RV5 among U.S. infants (CDC. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 2006;55[No. RR-12]). In April 2008, a live, oral, human attenuated rotavirus vaccine (Rotarix® [RV1]) was licensed as a 2-dose series for use among U.S. infants, and in June 2008, ACIP updated its rotavirus vaccine recommendations to include use of RV1. This report updates and replaces the 2006 ACIP statement for prevention of rotavirus gastroenteritis. ACIP recommends routine vaccination of U.S. infants with rotavirus vaccine. RV5 and RV1 differ in composition and schedule of administration. RV5 is to be administered orally in a 3-dose series, with doses administered at ages 2, 4, and 6 months. RV1 is to be administered orally in a 2-dose series, with doses administered at ages 2 and 4 months. ACIP does not express a preference for either RV5 or RV1. The recommendations in this report also address the maximum ages for doses, contraindications, precautions, and special situations for the administration of rotavirus vaccine.

Introduction
Rotavirus is the most common cause of severe gastroenteritis in infants and young children worldwide. Rotavirus causes approximately half a million deaths each year among children aged <5 years, with >80% of deaths occurring in developing countries (1). In the United States during the prevaccine era, rotavirus gastroenteritis resulted in relatively few childhood deaths (approximately 20–60 deaths per year among children aged <5 years) (2–5). However, before initiation of the rotavirus vaccination program in 2006, nearly every child in the United States was infected with rotavirus by age 5 years; the majority had gastroenteritis, resulting annually during the 1990s and early 2000s in approximately 410,000 physician visits, 205,000–272,000 emergency department (ED) visits, 55,000–70,000 hospitalizations, and total annual direct and indirect costs of approximately $1 billion (5–9) (Figure 1). This report presents the recommendations of the Advisory Committee on Immunization Practices (ACIP) for use of two

FIGURE 1. Estimated number of annual deaths, hospitalizations, emergency department visits, and episodes of rotavirus gastroenteritis among children aged <5 years before introduction of rotavirus vaccine — United States

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rotavirus vaccines among U.S. infants: RotaTeq® (RV5) (Merck and Company, Whitehouse Station, New Jersey), which was licensed by the Food and Drug Administration (FDA) in February 2006 (10) and Rotarix® (RV1) (GlaxoSmithKline [GSK] Biologicals, Rixensart, Belgium), which was licensed by FDA in April 2008 (11). This report updates and replaces the 2006 ACIP statement for prevention of rotavirus gastroenteritis (12).

**Background**

**Clinical and Epidemiologic Features of Rotavirus Disease in the Prevaccine Era**

In the prevaccine era, rotavirus infected almost all children by age 5 years; severe dehydrating gastroenteritis caused by rotavirus occurred primarily among children aged 4–23 months (13–15). Rotavirus infects the proximal small intestine, where it elaborates an enterotoxin and destroys the epithelial surface, resulting in blunted villi, extensive damage, and shedding of massive quantities of virus in stool (13). The estimated incubation period for rotavirus diarrheal illness is <48 hours (16). Under experimental conditions, adults who became ill had massive quantities of virus in stool (17). The clinical spectrum of rotavirus illness in children ranges from mild, watery diarrhea of limited duration to severe diarrhea with vomiting and fever than can result in dehydration with shock, electrolyte imbalance, and death (19). The illness usually begins with acute onset of fever and vomiting, followed 24–48 hours later by frequent, watery stools (20,21). Up to one third of children with rotavirus illness have a temperature of >102°F (>39°C) (22,23). Vomiting usually lasts <24 hours; other gastrointestinal symptoms generally resolve in 3–7 days. Rotavirus protein and ribonucleic acid (RNA) have been detected in blood, organs, and cerebrospinal fluid, but the clinical implications of these findings are not clear (20,24).

Rotaviruses are shed in high concentrations (i.e., 10^{12} virus particles per gram of stool during the acute illness) in the stools of infected children before and several days after clinical disease (25). Rotavirus is transmitted primarily by the fecal-oral route, both through close person-to-person contact and through fomites (26). Very few infectious virions are needed to cause disease in susceptible hosts (25). Spread is common within families. Of adult contacts of infected children, 30%–50% become infected, although infections in adults often are asymptomatic because of immunity from previous exposure (27–29). Transmission of rotavirus through contaminated water or food is likely to be rare (30,31). Transmission through airborne droplets also has been hypothesized but remains unproven (21,30,32).

In the United States, rotavirus causes winter seasonal peaks of gastroenteritis, with activity beginning usually in the southwestern states during December–January, moving across the country, and ending in the northeastern states in April–May (33–35). Rotavirus might account for up to 10% of gastroenteritis episodes among children aged <5 years (36). Infants and children with rotavirus gastroenteritis are likely to have more severe symptoms than those with nonrotavirus gastroenteritis (22,23,37,38). In the prevaccine era, rotavirus accounted for 30%–50% of all hospitalizations for gastroenteritis among U.S. children aged <5 years and up to 70% of hospitalizations for gastroenteritis during the seasonal peak months (7,14,39–44). Of all the rotavirus hospitalizations that occurred among children aged <5 years in the United States during the prevaccine era, 17% occurred during the first 6 months of life, 40% by age 1 year, and 75% by age 2 years (Figure 2). Rotavirus accounted for 20%–40% of outpatient clinic visits during the rotavirus season (14,45,46). Before the initiation of the rotavirus vaccination program, four of five children in the United States had rotavirus gastroenteritis by age 5 years (36,39,47), one in seven required a clinic or ED visit, one in 70 were hospitalized, and one in 200,000 died from this disease (3,8). Active, population-based surveillance from early 2006 and before vaccine was used provided annual rotavirus hospitalization and ED visit rates of 22.4 and 301

per 10,000 children aged <3 years, respectively (14). Rotavirus also was an important cause of hospital-acquired gastroenteritis among children (48).

In a recent study, factors associated with increased risk for hospitalization for rotavirus gastroenteritis among U.S. children included lack of breastfeeding, low birth weight (a likely proxy for prematurity), daycare attendance, the presence of another child aged <24 months in the household, and either having Medicaid insurance or having no medical insurance (49). Another study identified low birth weight, maternal factors (e.g., young age, having Medicaid insurance, and maternal smoking), and male gender as risk factors for hospitalization with viral gastroenteritis (50). These studies suggest that preterm infants are at higher risk for severe rotavirus disease. Children and adults who are immunocompromised because of congenital immunodeficiency or because of bone marrow or solid organ transplantation sometimes experience severe or prolonged rotavirus gastroenteritis (51–56). The severity of rotavirus disease among children infected with human immunodeficiency virus (HIV) might be similar to that among children without HIV infection (57). Whether the incidence rate of severe rotavirus disease among HIV-infected children is similar to or greater than that among children without HIV infection is not known.

**Laboratory Testing for Rotavirus**

Because the clinical features of rotavirus gastroenteritis do not differ distinctly from those of gastroenteritis caused by other pathogens, confirmation of rotavirus infection by laboratory testing of fecal specimens is necessary for reliable rotavirus surveillance and can be useful (e.g., for infection-control purposes) in clinical settings. The most widely used diagnostic laboratory method is antigen detection in the stool by an enzyme immunoassay (EIA) directed at an antigen common to all group A rotaviruses (i.e., those that are the principal cause of human disease). Certain commercial EIA kits are available that are easy to use, rapid, and highly sensitive, making them suitable for rotavirus surveillance and clinical diagnosis. Other techniques, including electron microscopy, RNA electrophoresis, reverse transcription–polymerase chain reaction (RT-PCR), sequence analysis, and culture are used primarily in research settings.

Serologic methods that detect a rise in serum antibodies, primarily EIA for rotavirus serum immunoglobulin G (IgG) and immunoglobulin A (IgA) antibodies, have been used to confirm recent infections primarily in the research setting. In vaccine trials, the immunogenicity of rotavirus vaccines has been assessed by measuring rotavirus-specific IgG, IgA and neutralizing antibodies to the serotypes of the vaccine strains (58–60).

**Morphology, Antigen Composition, and Immune Response**

Rotaviruses are 70-nm nonenveloped RNA viruses in the family Reoviridae (61,62). The viral nucleocapsid is composed of three concentric shells that enclose 11 segments of double-stranded RNA. The outermost layer contains two structural viral proteins (VP): VP4, the protease-cleaved protein (P protein) and VP7, the glycoprotein (G protein). These two proteins define the serotype of the virus and are considered critical to vaccine development because they are targets for neutralizing antibodies that are believed to be important for protection (61,62). Because the two gene segments that encode these proteins can segregate independently, a typing system consisting of both P and G types has been developed (63). Although characterizing G serotypes by traditional methods is straightforward, using these methods for determining P serotypes is more difficult. Consequently, molecular methods are used almost exclusively to define genetically distinct P genotypes by nucleotide sequencing. These genotypes correlate well with known serotypes, but they are designated in brackets (e.g., P[8]) to distinguish them from P serotypes determined by antigenic analyses. In the United States, viruses containing six distinct P and G combinations are most prevalent: P[8]G1, P[4]G2, P[8]G3, P[8]G4, P[8]G9, P[6]G9 (64–67) (Figure 3).

Several animal species (e.g., primates and cows) are susceptible to rotavirus infection and suffer from rotavirus diarrhea, but animal strains of rotavirus differ from those that infect humans. Although human rotavirus strains that possess a high degree of genetic homology with animal strains have been identified (63,68–71), animal-to-human transmission appears...
to be uncommon. However, natural reassortant animal-human strains have been identified in humans (63), and some are being developed as vaccine candidates (72).

Although children can be infected with rotavirus several times during their lives, initial infection after age 3 months is most likely to cause severe gastroenteritis and dehydration (15,73–75). After a single natural infection, 38% of children are protected against subsequent infection with rotavirus, 77% are protected against subsequent rotavirus gastroenteritis, and 87% are protected against severe rotavirus gastroenteritis; second and third infections confer progressively greater protection against rotavirus gastroenteritis (75). Rotavirus infection in healthy full-term neonates often is asymptomatic or results in only mild disease, perhaps because of protection from passively transferred maternal antibody (13,76).

The immune correlates of protection from rotavirus infection and disease are not understood fully. Both serum and mucosal antibodies probably are associated with protection, and in some studies, serum antibodies against VP7 and VP4 have correlated with protection (58,59). However, in other studies, including vaccine studies, correlation between serum antibody and protection has been poor (77). First infections with rotavirus generally elicit a predominantly homotypic, serum-neutralizing antibody response, and subsequent infections typically elicit a broader, heterotypic response (21,78). The influence of cell-mediated immunity is understood less clearly but probably is related both to recovery from infection and to protection against subsequent disease (79,80).

**Rotavirus Vaccines**

**Background**

In 1998, ACIP recommended Rotashield® (RRV-TV) (Wyeth Lederle Vaccines and Pediatrics, Marietta, Pennsylvania) (81), a rhesus-based tetravalent rotavirus vaccine, for routine vaccination of U.S. infants, with 3 doses administered at ages 2, 4, and 6 months (82). However, RRV-TV was withdrawn from the U.S. market within 1 year of its introduction because of its association with intussusception (83). At the time of its withdrawal, RRV-TV had not yet been introduced in any other national vaccination program globally. The risk for intussusception was most elevated (>20-fold increase) within 3–14 days after receipt of dose 1 of RRV-TV, with a smaller (approximately fivefold) increase in risk within 3–14 days after receipt of dose 2 (84). Overall, the estimated risk associated with dose 1 of RRV-TV was approximately one case per 10,000 vaccine recipients (85). After they reassessed the data on RRV-TV and intussusception, certain researchers suggested that the risk for intussusception was age-dependent and that the absolute number of intussusception events, and possibly the relative risk for intussusception associated with dose 1 of RRV-TV increased with increasing age at vaccination (86,87). However, after reviewing all the available data, the World Health Organization (WHO) Global Advisory Committee on Vaccine Safety (GACVS) concluded that the risk for RRV-TV–associated intussusception was high in infants vaccinated after age 60 days and that insufficient evidence was available to conclude that the use of RRV-TV at age <60 days was associated with a lower risk (88). GACVS noted that the possibility of an age-dependent risk for intussusception should be taken into account in assessing rotavirus vaccines.

**Methodology**

The ACIP rotavirus vaccine workgroup was reestablished in July 2007, after submission of the Biologics License Application (BLA) for RV1 to FDA in June 2007. The workgroup held teleconferences at least monthly to review published and unpublished data on the burden and epidemiology of rotavirus disease in the United States, the safety and efficacy of RV1 and RV5, and cost-effectiveness analyses. Recommendation options were developed and discussed by ACIP's rotavirus vaccine work group. The opinions of workgroup members and other experts were considered when data were lacking. Programmatic aspects related to implementation of the recommendations were taken into account. Presentations were made to ACIP during meetings in October 2007 and February 2008. The final proposed recommendations were presented to ACIP at the June 2008 ACIP meeting; after discussion, minor modifications were made, and the recommendations were approved.

**Pentavalent Human-Bovine Reassortant Rotavirus Vaccine (RotarTeq® [RV5])**

RV5, which was licensed in the United States in 2006, is a live, oral vaccine that contains five reassortant rotaviruses developed from human and bovine parent rotavirus strains (Box) (10,89). Four reassortant rotaviruses express one of the outer capsid proteins (G1, G2, G3, or G4) from the human rotavirus parent strains and the attachment protein (P7[5]) from the bovine rotavirus parent strain. The fifth reassortant virus expresses the attachment protein (P1A[8]) from the human rotavirus parent strain and the outer capsid protein (G6) from the bovine rotavirus parent strain. The parent bovine rotavirus strain, Wistar Calf 3 (WC3), was isolated in 1981 from a calf with diarrhea in Chester County, Pennsylvania,
and was passaged 12 times in African green monkey kidney cells (90). The reassortants are propagated in Vero cells using standard tissue culture techniques in the absence of antifungal agents. The licensed vaccine is a ready-to-use 2 ml solution that contains \( \geq 2.0 - 2.8 \times 10^6 \) infectious units (IU) per individual reassortant dose, depending on serotype.

The RV5 BLA contained three phase III trials (91). Data from these trials on the immunogenicity, efficacy, and safety of RV5 are summarized below.
**Immunogenicity**

A relation between antibody responses to rotavirus vaccination and protection against rotavirus gastroenteritis has not been established. In clinical trials, a rise in titer of rotavirus group-specific serum IgA antibodies was used as one of the measures of the immunogenicity of RV5. Sera were collected before vaccination and at 2–6 weeks after dose 3, and seroconversion was defined as a threefold or greater rise in antibody titer from baseline. Seroconversion rates for IgA antibody to rotavirus were 93%–100% among 439 RV5 recipients compared with 12%–20% in 397 placebo recipients in phase III studies (94).

Antibody responses to concomitantly administered vaccines were evaluated in a study with a total of 662 RV5 recipients and 696 placebo recipients. Different subsets of infants were evaluated for specific antibody responses. A 3-dose series of RV5 did not diminish the immune response to concomitantly administered Haemophilus influenzae type b conjugate (Hib) vaccine, inactivated poliovirus vaccine (IPV), hepatitis B (HepB) vaccine, pneumococcal conjugate vaccine (PCV), and diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine (10,91).

**Efficacy**

The efficacy of the final formulation of RV5 has been evaluated in two phase III trials among healthy infants (92,93). Administration of oral polio vaccine (OPV) was not allowed; concomitant administration of other vaccines was not restricted. The large Rotavirus Efficacy and Safety Trial (REST) included a clinical efficacy substudy (Tables 1 and 2). In this substudy, 4,512 infants from Finland and the United States were included in the primary per-protocol efficacy analysis (consisting of evaluable subjects for whom there was no protocol violation) through one rotavirus season. The primary efficacy endpoint was the prevention of wild type G1–G4 rotavirus gastroenteritis occurring ≥14 days after completion of a 3-dose series through the first full rotavirus season after vaccination. A case of rotavirus gastroenteritis was defined as production of three or more watery or looser-than-normal stools within a 24-hour period or forceful vomiting, along with rotavirus detection by ELISA in a stool specimen obtained within 14 days after the onset of symptoms. G serotypes were identified by RT-PCR followed by sequencing. Severe gastroenteritis was defined as a score of ≥16 on an established 24-point severity scoring system (Clark score) on the basis of intensity and duration of fever, vomiting, diarrhea, and changes in behavior.

The efficacy of RV5 against G1–G4 rotavirus gastroenteritis of any grade of severity through the first full rotavirus season after vaccination was 74.0% (95% confidence interval [CI] = 66.8–79.9) and against severe G1–G4 rotavirus gastroenteritis was 98.0% (CI = 88.3–100.0) (Table 2). RV5 reduced office or clinic visits for G1–G4 rotavirus gastroenteritis by 86.0% (CI = 73.9–92.5). In a trial that evaluated RV5 at the end of its shelf life, the efficacy estimates for RV5 based on per-protocol analysis of data from 551 RV5 recipients and 564 placebo recipients were similar to those identified in the clinical efficacy substudy (10,92,93). Among the limited number of infants from phase III trials who received at least 1 dose of RV5 (n = 144) or placebo (n = 135) >10 weeks after a previous dose, the estimate of efficacy of the RV5 series for protection against G1–G4 rotavirus gastroenteritis of any severity was 63% (CI = 53%–94%) (94).

In the health-care utilization cohort of REST, data from 57,134 infants from 11 countries were included in the per-protocol analysis of the efficacy of RV5 in reducing the need for hospitalization or ED care for rotavirus gastroenteritis (93). The efficacy of the RV5 series against ED visits for G1–G4 rotavirus gastroenteritis was 93.7% (CI = 88.8–96.5), and efficacy against hospitalization for G1–G4 rotavirus gastroenteritis was 95.8% (CI = 90.5–98.2) (Table 2). Efficacy was observed against all G1–G4 and G9 serotypes (Table 3); relatively few non-G1 rotavirus cases were detected. The efficacy of RV5 against all gastroenteritis-related hospitalizations was 58.9% (CI = 51.7–65.0) for the period that started after dose 1.

Breastfeeding did not appear to diminish the efficacy of a 3-dose series of RV5. Post-hoc analyses of the clinical efficacy substudy found that the efficacy of RV5 against G1–G4 rotavirus gastroenteritis of any severity through the first rotavirus season was similar among the 1,632 infants (815 in the vaccine group and 817 in the placebo group) who never were breastfed (68.3%; CI = 46.1–82.1) and the 1,566 infants (767 in the vaccine group and 799 in the placebo group) who were exclusively breastfed (68.0%; CI = 53.8–78.3) (95). Efficacy against severe G1–G4 rotavirus gastroenteritis was also similar among infants who never were breastfed (100.0%; CI = 48.3–100.0) and those who were exclusively breastfed (100.0%; CI = 79.3–100.0).

In posthoc analyses of data from the clinical efficacy substudy of REST, efficacy also was estimated among 73 healthy preterm infants (gestational age of <37 weeks) who received RV5 and 78 healthy preterm infants who received placebo (96). The efficacy through the first full season against rotavirus gastroenteritis of any severity (all serotypes combined) was 73.0% (CI = -2.2–95.2); three cases occurred among RV5 recipients, and 11 cases occurred among placebo recipients. In the healthcare utilization cohort, the efficacy against rotavirus gastroenteritis–attributable hospitalizations (all serotypes combined) for healthy preterm infants was 100.0% (CI = 53.0–100.0); no cases were identified among 764 preterm infants who received
RV5 and nine cases were identified among 818 preterm infants who received placebo. Efficacy against rotavirus gastroenteritis—attributable ED visits was 100% (CI = 66.6–100.0), with no cases identified among RV5 recipients and 12 cases identified among placebo recipients (96).

### Adverse Events After Vaccination

#### Intussusception

REST was designed as a large trial to permit evaluation of safety with respect to intussusception; 69,625 enrolled infants received at least 1 dose of RV5 or placebo (10,93). No increased risk for intussusception was observed in this trial after administration of RV5 when compared with placebo. For the prespecified period of days 0–42 after any dose, six confirmed intussusception cases occurred among 34,837 infants who received RV5, and five confirmed intussusception cases occurred among 34,788 infants who received placebo (relative risk adjusted for group sequential design: 1.6; CI = 0.4–6.4). None of the infants with confirmed intussusception in either treatment group had onset during days 1–21 after dose 1.

### Other Adverse Events

Serious adverse events (SAEs) and deaths were evaluated in infants enrolled in phase III trials (10,97). Among RV5 and placebo recipients, the incidence of SAEs within 42 days of any dose (2.4% of 36,150 and 2.6% of 35,536, respectively) was similar. Across the studies, the incidence of death was similar among RV5 recipients (<0.1% [n = 25]) and placebo recipients (<0.1% [n = 27]). The most common cause of death (accounting for 17 (32.7%) of 52 deaths) was sudden infant death syndrome (SIDS), which was observed in eight RV5 recipients and nine placebo recipients.

Gastroenteritis occurring anytime after a dose was reported as an SAE in 76 (0.2%) RV5 recipients and in 129 (0.4%) placebo recipients. Seizures reported as SAEs occurred in 27 (<0.1%) vaccine recipients and in 18 (<0.1%) placebo recipients (difference not statistically significant). Pneumonia occurring anytime after a dose was reported as an SAE in 59 (0.2%) of RV5 recipients and in 62 (0.2%) of placebo recipients; hospitalization for pneumonia within 7 days after any dose occurred in 11 (<0.1%) RV5 recipients and in 14 (<0.1%) placebo recipients (91).

A subset of 11,711 infants was studied in detail to assess other potential adverse experiences (10). In the 42-day period postvaccination of any dose of RV5, the incidence of fever reported by parents and guardians of RV5 recipients and placebo recipients (42.6% and 42.8%, respectively) was similar, as was the incidence of hematochezia reported as an adverse experience (0.6% in both RV5 recipients and placebo recipients). Some (e.g., diarrhea, vomiting) adverse events occurred at a statistically higher incidence within 42 days of any dose in RV5 recipients (Table 4). Statistical significance was determined using 95% CIs on the risk difference; intervals with a
### TABLE 2. Efficacy of Rotarix® (RV1) and RotaTeq® (RV5) against rotavirus gastroenteritis (GE) in major efficacy trials, by severity and season

<table>
<thead>
<tr>
<th>Rotavirus disease severity</th>
<th>No. of cases†</th>
<th>% efficacy</th>
<th>(95% CI§)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rotavirus GE of any severity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RV1 Europe‡</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Through 1st season</td>
<td>24 (2,572)</td>
<td>94 (1,302)</td>
<td>87.1</td>
</tr>
<tr>
<td>2nd season</td>
<td>61 (2,554)</td>
<td>110 (1,294)</td>
<td>71.9</td>
</tr>
<tr>
<td>Through 2nd season**</td>
<td>85 (2,572)</td>
<td>204 (1,302)</td>
<td>78.9</td>
</tr>
<tr>
<td><strong>RV5 REST¶¶¶</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Through 1st full season (types G1–G4)</td>
<td>82 (2,207)</td>
<td>315 (2,305)</td>
<td>74.0</td>
</tr>
<tr>
<td>2nd full season (types G1–G4)</td>
<td>36 (813)</td>
<td>88 (756)</td>
<td>62.6</td>
</tr>
<tr>
<td><strong>Severe rotavirus GE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RV1 Latin America¶¶¶</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>To age 1 year: clinical***</td>
<td>12 (9,009)</td>
<td>77 (8,858)</td>
<td>84.7</td>
</tr>
<tr>
<td>To age 1 year: Vesikari ≥11</td>
<td>11 (9,009)</td>
<td>71 (8,858)</td>
<td>84.8</td>
</tr>
<tr>
<td>2nd season: Vesikari ≥11</td>
<td>19 (7,175)</td>
<td>101 (7,062)</td>
<td>81.5</td>
</tr>
<tr>
<td>To age 2 years: Vesikari ≥11</td>
<td>28 (7,205)</td>
<td>154 (7,081)</td>
<td>82.1</td>
</tr>
<tr>
<td><strong>RV1 Europe</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Through 1st season: Vesikari ≥11</td>
<td>5 (2,572)</td>
<td>60 (1,302)</td>
<td>95.8</td>
</tr>
<tr>
<td>2nd season: Vesikari ≥11</td>
<td>19 (2,554)</td>
<td>67 (1,294)</td>
<td>85.6</td>
</tr>
<tr>
<td>Through 2nd season: Vesikari ≥11</td>
<td>24 (2,572)</td>
<td>127 (1,302)</td>
<td>90.4</td>
</tr>
<tr>
<td><strong>RV5 REST</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Through 1st full season: Clark&gt;16 (types G1–G4)¶¶¶</td>
<td>1 (2,207)</td>
<td>51 (2,305)</td>
<td>98.0</td>
</tr>
<tr>
<td>2nd full season: Clark&gt;16 (types G1–G4)</td>
<td>2 (813)</td>
<td>17 (756)</td>
<td>88.0</td>
</tr>
<tr>
<td><strong>Hospitalization for rotavirus GE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RV1 Latin America¶¶¶</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>To age 1 year</td>
<td>9 (9,009)</td>
<td>59 (8,858)</td>
<td>85.0</td>
</tr>
<tr>
<td>2nd year</td>
<td>15 (7,175)</td>
<td>80 (7,062)</td>
<td>81.5</td>
</tr>
<tr>
<td>To age 2 years</td>
<td>22 (7,205)</td>
<td>127 (7,081)</td>
<td>83.0</td>
</tr>
<tr>
<td><strong>RV1 Europe</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Through 1st season</td>
<td>0 (2,572)</td>
<td>12 (1,302)</td>
<td>100.0</td>
</tr>
<tr>
<td>2nd season</td>
<td>2 (2,554)</td>
<td>13 (1,294)</td>
<td>92.2</td>
</tr>
<tr>
<td>Through 2nd season</td>
<td>2 (2,572)</td>
<td>26 (1,302)</td>
<td>96.0</td>
</tr>
<tr>
<td><strong>RV5 REST</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health-care use cohort (types G1–G4)¶¶¶</td>
<td>6 (28,646)</td>
<td>144 (28,488)</td>
<td>95.8</td>
</tr>
</tbody>
</table>

---

* Because trials were conducted in different countries and have other differences (including different case definitions and durations of follow-up), efficacy results between trials cannot be directly compared. Efficacy assessment periods began 2 weeks after the last dose of the series in the per-protocol analyses. The number of persons with rotavirus cases and the number of infants who contributed to the analyses are presented; vaccine efficacy results are based on analyses using the follow-up time contributed by each subject. Selected results are presented.

† Numbers in parentheses represent the number of persons who received either vaccine or placebo and were included in the per-protocol analysis.

‡ Confidence interval.

§ Confidence interval.


** Efficacy results for “through second season” based on 2,572 RV1 recipients and 1,302 placebo recipients who entered the first efficacy period (from 2 weeks after dose 2 up to the end of the first rotavirus season) and on 2,554 RV1 recipients and 1,294 placebo who entered the second efficacy period (from the visit at the end of the first rotavirus season up to the visit at the end of the second rotavirus season).

†† Rotavirus Efficacy and Safety Trial.


*** Defined as diarrhea (three or more loose or watery stools within 24 hours), with or without vomiting, that required overnight hospitalization or rehydration therapy equivalent to World Health Organization plan B (oral rehydration) or plan C (intravenous rehydration) in a medical facility.

††† Defined as ≥11 on this 20-point clinical scoring system, based on the intensity and duration of symptoms of fever, vomiting, diarrhea, degree of dehydration, and treatment needed.

†††† Efficacy results for “to age 2 years” are based on 7,205 RV1 recipients and 7,081 placebo recipients who entered the first efficacy period (from 2 weeks after dose 2 up to age 1 year) and on 2,572 RV1 recipients and 7,062 placebo recipients who entered the second efficacy period (from age 1 year up to age 2 years).

†††‡ Efficacy results are based on G1–G4 rotavirus-related hospitalizations among 28,646 RV5 recipients and 28,488 placebo recipients in the health-care utilization cohort analysis contributing approximately 35,000 person-years of total follow-up during the first year and on a subset of the cohort (2,502 infants total) contributing approximately 1,000 person-years of follow-up during the second year.

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8 MMWR February 6, 2009
TABLE 3. Efficacy of Rotarix® (RV1) and RotaTeq® (RV5) against G type-specific rotavirus gastroenteritis in major efficacy trials, by severity and season*

<table>
<thead>
<tr>
<th>Rotavirus type</th>
<th>No. of cases†</th>
<th>% Efficacy</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vaccine</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td><strong>G1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV5 REST</td>
<td>Through 1st full season</td>
<td>72</td>
<td>286 (2,207)</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV1 Latin America††</td>
<td>To age 1 yr: clinical§§</td>
<td>3</td>
<td>36 (8,858)</td>
</tr>
<tr>
<td></td>
<td>RV1 Latin America††</td>
<td>To age 1 yr: Vesikari ≥11¶¶</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>RV1 Latin America††</td>
<td>To age 2 yrs: clinical***</td>
<td>10</td>
</tr>
<tr>
<td>RV1 Europe†††</td>
<td>Through 1st season: Vesikari ≥11</td>
<td>2</td>
<td>28 (1,302)</td>
</tr>
<tr>
<td></td>
<td>Through 2nd season: Vesikari ≥11¶¶</td>
<td>4</td>
<td>132 (8,858)</td>
</tr>
<tr>
<td>RV5 REST</td>
<td>Hospitalization/ED visits****</td>
<td>16</td>
<td>328 (28,488)</td>
</tr>
<tr>
<td><strong>G2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV5 REST</td>
<td>Through 1st full season</td>
<td>6</td>
<td>17 (2,207)</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV1 Latin America</td>
<td>To age 1 yr: clinical§§</td>
<td>6</td>
<td>10 (8,858)</td>
</tr>
<tr>
<td></td>
<td>RV1 Latin America</td>
<td>To age 1 yr: Vesikari ≥11¶¶</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>RV1 Latin America</td>
<td>To age 2 yrs: clinical***</td>
<td>5</td>
</tr>
<tr>
<td>RV1 Europe</td>
<td>Through 1st season: Vesikari ≥11</td>
<td>1</td>
<td>2 (1,302)</td>
</tr>
<tr>
<td></td>
<td>Through 2nd season: Vesikari ≥11¶¶</td>
<td>2</td>
<td>45.4 (2,848)</td>
</tr>
<tr>
<td>RV5 REST</td>
<td>Hospitalization/ED visits****</td>
<td>16</td>
<td>8 (28,488)</td>
</tr>
<tr>
<td><strong>G3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV5 REST</td>
<td>Through 1st full season</td>
<td>1</td>
<td>6 (2,207)</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV1 Latin America</td>
<td>To age 1 yr: clinical§§</td>
<td>1</td>
<td>8 (8,858)</td>
</tr>
<tr>
<td></td>
<td>RV1 Latin America</td>
<td>To age 2 yrs: clinical***</td>
<td>3</td>
</tr>
<tr>
<td>RV1 Europe</td>
<td>Through 1st season: Vesikari ≥11</td>
<td>0</td>
<td>5 (1,302)</td>
</tr>
<tr>
<td></td>
<td>Through 2nd season: Vesikari ≥11¶¶</td>
<td>1</td>
<td>2 (1,302)</td>
</tr>
<tr>
<td>RV5 REST</td>
<td>Hospitalization/ED visits****</td>
<td>16</td>
<td>15 (28,488)</td>
</tr>
<tr>
<td><strong>G4</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV5 REST</td>
<td>Through 1st full season</td>
<td>3</td>
<td>6 (2,207)</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV1 Latin America</td>
<td>To age 1 yr: clinical§§</td>
<td>1</td>
<td>2 (8,858)</td>
</tr>
<tr>
<td></td>
<td>RV1 Latin America</td>
<td>To age 2 yrs: clinical***</td>
<td>7</td>
</tr>
<tr>
<td>RV1 Europe</td>
<td>Through 1st season: Vesikari ≥11</td>
<td>0</td>
<td>7 (1,302)</td>
</tr>
<tr>
<td></td>
<td>Through 2nd season: Vesikari ≥11¶¶</td>
<td>1</td>
<td>11 (1,302)</td>
</tr>
<tr>
<td>RV5 REST</td>
<td>Hospitalization/ED visits****</td>
<td>2</td>
<td>18 (28,488)</td>
</tr>
<tr>
<td><strong>G9</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV5 REST</td>
<td>Through 1st full season</td>
<td>1</td>
<td>3 (2,207)</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV1 Latin America</td>
<td>To age 1 yr: clinical§§</td>
<td>2</td>
<td>21 (8,858)</td>
</tr>
<tr>
<td></td>
<td>RV1 Latin America</td>
<td>To age 2 yrs: clinical***</td>
<td>9</td>
</tr>
<tr>
<td>RV1 Europe</td>
<td>Through 1st season: Vesikari ≥11</td>
<td>2</td>
<td>19 (1,302)</td>
</tr>
<tr>
<td></td>
<td>Through 2nd season: Vesikari ≥11¶¶</td>
<td>13</td>
<td>44 (1,302)</td>
</tr>
<tr>
<td>RV5 REST</td>
<td>Hospitalization/ED visits****</td>
<td>0</td>
<td>14 (28,488)</td>
</tr>
</tbody>
</table>

See Table 3 footnotes on next page.
TABLE 3. (Continued) Efficacy of Rotarix® (RV1) and RotaTeq® (RV5) against G type-specific rotavirus gastroenteritis in major efficacy trials, by severity and season*

* Because trials were conducted in different countries and have other differences (including different case definitions and durations of follow-up), efficacy results between trials cannot be directly compared. Efficacy assessment periods began 2 weeks after the last dose of the series in the per-protocol analyses. The number of persons with rotavirus cases and the number of infants who contributed to the analyses are presented; vaccine efficacy results are based on analyses using the follow-up time contributed by each subject. Selected results are presented.

† Numbers in parentheses represent the number of persons who received either vaccine or placebo and were included in the per-protocol analysis.

§ Confidence interval.

¶†††† Not available.

Shedding and Transmission of Vaccine Virus

Fecal shedding of rotavirus vaccine virus was evaluated by plaque assays with electrophenotyping in a subset of infants enrolled in the large phase III trial by obtaining a single stool sample during days 4–6 after each dose of RV5 (93). Vaccine virus was detected in 17 (12.7%) of 134 infants after dose 1, zero of 109 infants after dose 2, and zero of 99 infants after dose 3. Shedding of vaccine virus also was assessed for phase III studies overall, including that detected by plaque assays.

lower bound above zero were considered statistically significant. Adverse events also were solicited from parents and guardians within the first week after each dose. RV5 recipients had a small but statistically significantly greater (p-value <0.05) rate of diarrhea and vomiting after specific doses or after any dose (Table 5). Among the limited number of infants from phase III trials who received at least 1 dose of RV5 or placebo >10 weeks after a previous dose (depending on dose number and specific adverse event monitored, the number of infants evaluated in either the RV5 or placebo group ranged from 211–1,182), the proportion of infants with adverse events appeared generally similar among the RV5 and placebo recipients (94).

In the phase III clinical trials, infants were followed for up to 42 days of vaccine dose. Kawasaki disease was reported in five of 36,160 RV5 recipients and in one of 35,536 placebo recipients (unadjusted relative risk: 4.9; CI = 0.6–239.1) (10).

Preterm Infants

In posthoc analyses of data from REST, adverse events were examined among healthy preterm infants with gestational age of 25–36 weeks (median: 34 weeks) (10,96). At least one SAE was reported within 42 days after any dose in 55 (5.5%) of the 1,005 preterm infants who received RV5 and in 62 (5.8%) of the 1,061 preterm infants who received placebo. Among the preterm infants with gestational age of <32 weeks, at least one SAE was reported within 42 days of any dose in 6 (8.1%) of the 74 RV5 recipients and in 9 (9.8%) of the 92 placebo recipients. No confirmed intussusception occurred in a preterm infant during the study. Two deaths occurred in the RV5 group (one from SIDS and one from a motor-vehicle crash), and two occurred in the placebo group (one from SIDS and one from an unknown cause). The incidence of solicited adverse events (fever, vomiting, diarrhea, and irritability) within 7 days after each dose administration was assessed in preterm infants; depending on dose number and specific adverse event monitored, the number of infants evaluable in either the RV5 or placebo group varied (range: 108–154). The rates appeared generally similar between the RV5 and placebo recipients.
of rotavirus-antigen positive stools from infants evaluated for possible gastroenteritis. Shedding was observed as early as 1 day and as late as 15 days after a dose (10). The potential for transmission of vaccine virus to other persons was not assessed.

**Postlicensure Rotavirus Surveillance Data from the United States**

Rotavirus surveillance data from two systems, the National Respiratory and Enteric Virus Surveillance System (NREVSS) and the New Vaccine Surveillance Network (NVSN), indicated that the 2007–08 season was substantially delayed in onset and diminished in magnitude compared to the seasons before substantial uptake of RV5 among U.S. infants (98). NREVSS is a voluntary network of U.S. laboratories that provides CDC with weekly reports of the number of tests performed and positive results obtained for a variety of pathogens. For rotavirus, results of EIAs are reported. Compared with the 15 previous seasons spanning 1991–2006, rotavirus activity during the 2007–08 season appeared delayed in onset by 2–4 months (Figure 4). Further, data from the 32 laboratories that consistently reported results during July 2000–May 2008 indicated that the number of tests positive for rotavirus during the 2007–08 season (January 1, 2008–May 3, 2008) was lower by more than two thirds compared with the median number positive during the same weeks in the seven preceding rotavirus seasons.

Since 2006, NVSN has conducted prospective, population-based surveillance for rotavirus gastroenteritis among children aged <3 years residing in three U.S. counties. Among children with gastroenteritis enrolled during January–April of each year, the overall percentage of fecal specimens testing positive for rotavirus was 51% in 2006, 54% in 2007, and 6% in 2008.

Although nationally representative data on vaccine coverage are not yet available, information from population-based immunization information system sentinel sites indicates that mean coverage with 1 dose of rotavirus vaccine among infants aged 3 months was 49.1% in May 2007 and 56.0% in March 2008. Additional surveillance and epidemiologic studies are underway to monitor the impact of rotavirus vaccination in the United States.

**Postlicensure Safety Monitoring Data from the United States**

During February 2006–March 2008, approximately 14 million doses of RV5 were distributed in the United States (99). Results from two safety monitoring systems have been reported. The U.S. Vaccine Adverse Event Reporting System (VAERS), a national passive surveillance system managed

### TABLE 4. Number and percentage of infants with adverse events that occurred at a statistically higher incidence among recipients of RotaTeq® (RV5) compared with placebo, by event

<table>
<thead>
<tr>
<th>Event</th>
<th>RV5†</th>
<th>Placebo§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>1,479 (24.1)</td>
<td>1,186 (21.3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>929 (15.2)</td>
<td>758 (13.6)</td>
</tr>
<tr>
<td>Otitis media</td>
<td>887 (14.5)</td>
<td>724 (13.0)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>422 (6.9)</td>
<td>325 (5.8)</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>66 (1.1)</td>
<td>40 (0.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1,479 (24.1)</td>
<td>1,186 (21.3)</td>
</tr>
<tr>
<td>Vomiting</td>
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</tr>
<tr>
<td>Nasopharyngitis</td>
<td>422 (6.9)</td>
<td>325 (5.8)</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>66 (1.1)</td>
<td>40 (0.7)</td>
</tr>
</tbody>
</table>


† Events that occurred at a statistically higher incidence within 42 days of any dose. Statistical significance was determined using 95% confidence intervals on the risk difference; intervals with a lower bound above zero were considered statistically significant. Coadministration of routine infant vaccines was allowed in studies that provided these data. Parents and guardians were asked to report adverse events on a vaccination report card.

§ N = 6,138.

**TABLE 5. Solicited adverse events within the first week after doses 1, 2, and 3 of RotaTeq® (RV5) and placebo, by event and dose**

<table>
<thead>
<tr>
<th>Event</th>
<th>RV5† (n = 5,703)</th>
<th>Placebo§ (n = 5,725)</th>
<th>RV5† (n = 5,496)</th>
<th>Placebo§ (n = 4,989)</th>
<th>RV5† (n = 6,130)</th>
<th>Placebo§ (n = 5,560)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>5.0%</td>
<td>4.4%</td>
<td>3.6%</td>
<td>3.2%</td>
<td>3.6%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8.6%</td>
<td>6.4%</td>
<td>6.1%</td>
<td>5.4%</td>
<td>11.6%</td>
<td>9.9%</td>
</tr>
<tr>
<td>Irritability</td>
<td>6.0%</td>
<td>6.5%</td>
<td>4.3%</td>
<td>4.5%</td>
<td>12.9%</td>
<td>10.5%</td>
</tr>
<tr>
<td>Elevated temperature</td>
<td>17.1%</td>
<td>19.4%</td>
<td>18.2%</td>
<td>17.6%</td>
<td>35.3%</td>
<td>34.1%</td>
</tr>
</tbody>
</table>

**REFERENCES:**

1. Coadministration of routine infant vaccines was allowed in studies that provided these data. Parents and guardians were asked to monitor for these adverse events and record information on a vaccination report card.

2. Statistically significantly higher compared to rate in placebo recipients (p<0.05).

3. Temperature ≥100.5°F (≥38.1°C) rectal equivalent obtained by adding 1°F (0.55°C) to otic and oral temperatures and 2°F (1.1°C) to axillary temperatures.

* 2008 data current through week ending May 3, 2008. Data from July 2006–June 2007 were excluded from the (1991–2006) prevaccine baseline data because some persons tested likely received vaccine during that period.

jointly by FDA and CDC, receives reports of adverse events after vaccination from multiple sources, including health-care providers, vaccine recipients and parents and guardians of vaccine recipients, and manufacturers (100,101). Reported cases of intussusception among vaccine recipients are classified as confirmed if Brighton Collaboration Level 1 criteria are met (102). In VAERS analyses, the number of confirmed intussusception cases reported after vaccination is compared with the number of cases expected to occur by chance alone. This latter number is determined from estimates of the background rates of intussusception among infants and estimates of the total number of doses of RV5 that have been administered to infants. As of March 31, 2008, the number of confirmed cases of intussusception reported to VAERS during either the 1–21 day period or the 1–7 day period after receipt of any dose (doses 1, 2, and 3 combined) of RV5 did not exceed the number of cases expected to occur by chance alone after vaccination (99,103). A relative increase in intussusception reports in the first week after receipt of dose 1 of RV5, compared with the second and third weeks after dose 1, has been noted; whether this phenomenon is related to better reporting for intussusception during the first week after vaccination or represents a small increased risk for intussusception during the first week after dose 1 of RV5 is not clear (99,103).

Because VAERS is not designed to provide a definitive assessment of risk, the safety of RV5 also is monitored in the Vaccine Safety Datalink (VSD), a collaborative project between CDC and several large U.S. health maintenance organizations that links computerized patient-level vaccination data to medical outcomes, including potential adverse events (104). VSD is able to test hypotheses suggested by VAERS reports and prelicensure trials. With >200,000 doses of RV5 administered to infants in the VSD system during May 21, 2006–May 24, 2008, the number of cases of intussusception identified that occurred within a 30-day period after receipt of any dose of RV5 was not greater than the number of cases expected to occur by chance alone (105). No case of intussusception was identified that occurred within the first week after receipt of the first dose of RV5 in VSD (out of approximately 77,000 first doses) nor in the prelicensure REST. The data suggest that, if any associated risk exists, the risk for intussusception associated with the first dose of RV5 within the first week after vaccination is not greater than one in 25,000–50,000 first doses (105).

Other adverse events monitored in VAERS, VSD, or both include hematochezia, Kawasaki syndrome, seizures, meningitis and encephalitis, myocarditis and gram-negative sepsis. The data do not indicate that RV5 is associated with an increased risk for these adverse events (99,105).

**Monovalent Human Rotavirus Vaccine (Rotarix® [RV1])**

RV1 is a live, oral vaccine licensed in 2008 for use in the United States that contains a human rotavirus strain (type G1P1A[8]) (Box). It was developed from a strain of rotavirus (termed 89-12) that was isolated in 1988 from a child in Cincinnati, Ohio, and that was first attenuated by passaging 33 times in African green monkey kidney cells (106); it was then cloned and further passaged in a Vero cell line and renamed RIX4414 (107). The licensed vaccine is prepared as a lyophilized powder that is reconstituted with 1 ml of a calcium bicarbonate buffer to a titer of ≥106.0 CCID50 per dose (11). The BLA contained six phase II trials and five phase III trials (108). Data from these trials on the immunogenicity, efficacy, and safety of RV1 are summarized below.

**Immunogenicity**

A relation between antibody responses to rotavirus vaccination and protection against rotavirus gastroenteritis has not been established. In two clinical trials, seroconversion was defined as the appearance of antirotavirus IgA antibodies (concentration of ≥20 U/ml) postvaccination in the serum of infants previously negative for rotavirus IgA antibodies. In the two studies, 1–2 months after a 2-dose series, 681 (86.5%) of 787 RV1 recipients seroconverted compared with 28 (6.7%) of 420 placebo recipients, and 302 (76.8%) of 393 RV1 recipients seroconverted compared with 33 (9.7%) of 341 placebo recipients, respectively (11).

One U.S. study was designed specifically to evaluate the antibody responses to vaccines (DTaP-HepB-IPV, PCV7 and Hib) coadministered with RV1. A total of 180 infants received...
the 2 doses of RV1 coadministered with the other vaccines, and 137 infants who received the 2 RV1 doses 1 month after the other vaccines were included in the ATP cohort. Noninferiority criteria were met for all antigens, indicating that coadministration of RV1 with routine childhood vaccines did not diminish the immune responses to any of these vaccine antigens (11,108).

Efficacy

The efficacy of the licensed formulation of RV1 has been evaluated in two large phase III trials among healthy infants, one conducted in 11 Latin American countries (109) and one conducted in six European countries (110) (Table 1). OPV was not coadministered; other routine childhood vaccines could be administered concomitantly. In both studies, both breast and formula feeding were permitted.

In the Latin American trial, 17,867 infants enrolled into the safety study also were part of the efficacy analysis and were included in the per-protocol efficacy analysis (Table 1) (109). The primary efficacy endpoint in this study was prevention of severe wild-type rotavirus gastroenteritis from 2 weeks after second dose until age 1 year. Wild-type rotavirus gastroenteritis was defined as an episode of gastroenteritis in which rotavirus other than vaccine strain was identified in a stool sample collected no later than 7 days after symptom onset. A clinical definition for severe rotavirus gastroenteritis was used: diarrhea (three or more loose or watery stools within 24 hours), with or without vomiting, in which rotavirus other than vaccine strain was identified in a stool sample and that required overnight hospitalization or rehydration equivalent to WHO plan B (oral rehydration) or plan C (intravenous rehydration) in a medical facility. Stools were tested for the presence of rotavirus antigen by enzyme-linked immunosorbent assay (ELISA). Stools that tested positive by ELISA were analyzed further for G and P type determination by RT-PCR, followed by reverse hybridization assay or optional sequencing (108).

For certain outcomes, severe rotavirus gastroenteritis also was defined as a score of ≥11 on an established 20-point severity scoring system (Vesikari scale) on the basis of the intensity and duration of symptoms of fever, vomiting, diarrhea, degree of dehydration, and treatment needed (109).

In the Latin American trial, the efficacy of RV1 against severe rotavirus gastroenteritis (clinical definition) after completion of a 2-dose series until age 1 year was 84.7% (CI = 71.7–92.4) (109) (Table 2); the efficacy results were similar when severe rotavirus gastroenteritis was defined as an episode of rotavirus gastroenteritis with a Vesikari score of ≥11 (84.8%; CI = 71.1–92.7). The efficacy against severe rotavirus gastroenteritis (clinical definition) after completion of a 2-dose series until age 2 years was 80.5% (CI = 71.3–87.1). Efficacy against non-G1 strains was observed; few cases from certain strains were detected (Table 3). The efficacy against G2 was greater than zero for subjects followed to age 1 year and those followed to age 2 years, but the 95% CIs included zero.

The efficacy against rotavirus gastroenteritis of any severity was not measured in the Latin American trial. For the first year follow-up period, the efficacy for 2 doses of RV1 against severe gastroenteritis (clinical definition) from any cause was 40.0% (CI = 27.7–50.4) (109). In the European trial, efficacy was assessed among 3,874 infants who received either RV1 or placebo (110). The primary efficacy endpoint in this study was prevention of wild-type rotavirus gastroenteritis of any grade of severity occurring from 2 weeks after dose 2 until the end of the first rotavirus season. In general, efficacy results were somewhat higher in the European trial than in the Latin American trial (Tables 2 and 3). The efficacy against rotavirus gastroenteritis of any severity after the 2-dose regimen until the end of the first rotavirus season was 87.1% (CI = 79.6–92.1), and efficacy against severe rotavirus gastroenteritis (score of ≥11 on the Vesikari scale) was 95.8% (CI = 89.6–98.7) (Table 2). The efficacy after 2 doses of RV1 through the end of the second rotavirus season was 78.9% (CI = 72.7–83.8) against rotavirus gastroenteritis of any severity, and 90.4% (CI = 85.1–94.1) against severe rotavirus gastroenteritis (score of ≥11 on the Vesikari scale). Efficacy against non-G1 strains was observed; few cases from certain strains were detected (Table 3). For the second season and for the combined first and second season, the efficacy against severe disease from G2 was positive with a 95% CI that did not include zero. For the first season follow-up period, the efficacy for 2 doses of RV1 against hospitalization for gastroenteritis of any cause was 74.7% (CI = 45.5–88.9).

The efficacy of RV1 against rotavirus gastroenteritis of any severity through the first season among infants in the European trial that breastfed at the time of at least 1 dose (86.0%; CI = 76.8–91.9) was similar to the efficacy among infants not breastfed at the time of either dose (90.8%; CI = 72.5–97.7) (108). Efficacy against severe rotavirus gastroenteritis through the first season also was similar for the two groups (breastfed at the time of at least 1 dose: 95.7% [CI = 88.2–98.9] compared with not breastfed at the time of either dose: 96.2% [CI = 74.1–99.9]). Data on the efficacy of RV1 among preterm infants are not available.

Adverse Events After Vaccination

Intussusception

The Latin American trial was designed as a large trial to permit evaluation of safety with respect to intussusception;
63,225 infants (including 2,060 infants from Finland) received at least 1 dose of RV1 or placebo (109). No increased risk for intussusception was observed after administration of RV1 when compared with placebo. For the prespecified period days 0–30 after either dose, on the basis of the date of diagnosis, six confirmed intussusception cases occurred among 31,673 infants who received RV1 and seven occurred among 31,552 infants who received placebo (relative risk [RR]: 0.85; CI = 0.30–2.42). On the basis of the date of intussusception onset, seven confirmed intussusception cases occurred among RV1 recipients and seven occurred among placebo recipients for the period days 0–30 after either dose (108). None of the confirmed intussusception cases in either vaccine or placebo group had onset from days 0–14 after dose 1.

Other Adverse Events

During the entire course of eight clinical studies, 68 (0.19%) deaths occurred among 36,755 RV1 recipients, and 50 (0.15%) deaths occurred among 34,454 placebo recipients (11). The most commonly reported cause of death after vaccination was pneumonia, which occurred in 19 (0.05%) RV1 recipients and 10 (0.03%) placebo recipients (RR: 1.7; CI = 0.8–4.2).

Infants were monitored for SAEs that occurred in the 31-day period after vaccination in eight clinical studies (11). Severe disease from one or more SAE occurred in 627 (1.7%) of 36,755 RV1 recipients compared with 659 (1.9%) of 34,454 placebo recipients (RR: 0.9; CI = 0.8–1.0). Diarrhea (RV1: 0.02%; placebo: 0.07%), dehydration (RV1: 0.02%; placebo: 0.06%), and gastroenteritis (RV1: 0.2%; placebo: 0.3%) occurred at a statistically higher (CI for relative risk excluded 1.0) incidence among placebo recipients compared with RV1 recipients. SAEs were coded with Medical Dictionary for Regulatory Activities (MedDRA) terms on the basis of information collected by study investigators from parental reports or medical records. Rates of SAEs were similar or the same between RV1 and placebo recipients for SAEs coded with the preferred MedDRA term “pneumonia” (RV1: 0.3%; placebo: 0.4%) and “convulsions” (RV1: 0.02%; placebo: 0.02%) (108). In the Latin American trial, no notable differences were observed in the vaccinated versus placebo groups in rates of nonfatal pneumonia events and pneumonia hospitalizations (108). However, an increase was observed in pneumonia deaths (using combined pneumonia-related preferred terms) during the period between dose 1 and visit 3 (visit 3 took place 30–90 days after dose 2); 16 (0.05%) such deaths occurred among RV1 recipients, and six (0.02%) occurred among placebo recipients (risk difference: 3.2 per 10,000 infants; exact p = 0.035) (108). In the European trial, no deaths were reported (108); rates of SAEs with the preferred term “pneumonia” reported from dose 1 to the end of the second rotavirus season were significantly greater among RV1 recipients than among placebo recipients (0.9% and 0.3%, respectively) (risk difference: 61 per 10,000 infants; p = 0.03). In the RV1 group, 71% of the pneumonia SAEs occurred ≥153 days from the last dose of RV1 (111) (GSK, unpublished data, 2008). In all other clinical trials in the BLA, and in the core integrated safety summary, statistically significant differences were not noted in the vaccine versus placebo groups for pneumonia or other pneumonia-related SAEs within the 31-day postvaccination period or for the full study period (111) (GSK, unpublished data, 2008). Excluding the Latin American safety and efficacy trial, for all other BLA trials combined, no statistically significant differences were noted among the vaccine versus placebo groups in pneumonia-related deaths during the full study period. The significance of these pneumonia-related findings is unclear. Additional data are expected from studies nearing completion in Asia and Africa (Leonard Friedland, GSK, personal correspondence, June 2008).

In the Latin American trial, statistically significantly more events coded with the preferred term “convulsions” were reported from dose 1 to visit 3 in RV1 recipients (16 [0.05%]) compared with placebo recipients (6 [0.02%]; p = 0.03) (108). When convulsion-related preferred terms were combined, no statistically significant difference in these events occurred in RV1 recipients compared with placebo recipients in three periods that were analyzed: from dose 1 to visit 3 (RV1: 20 [0.06%]; placebo: 12 [0.04%]), within 31 days after any dose (RV1: seven [0.02%]; placebo: nine [0.03%]), and 43 days after any dose (RV1: 12 [0.04%]; placebo: nine [0.03%]). In the European trial, no statistically significant difference was observed between convulsion-related SAEs in the RV1 group compared with the placebo group within 31 or 43 days after any dose (one event in each group; 0.04% and 0.07%, respectively) (108).

In seven clinical studies, detailed safety information for solicited adverse events was collected by parents and guardians for the day of vaccination and the next 7 days. Adverse events among RV1 recipients and placebo recipients occurred at similar rates, with the exception of Grade 3 (i.e., those that prevented normal everyday activities) cough or runny nose, which was slightly but statistically significantly higher in the RV1 group (108) (Table 6). During the 31-day period after vaccination, the following unsolicited adverse events occurred at a statistically higher incidence among RV1 recipients compared with placebo recipients: irritability (11.4% in RV1 group compared with 8.7% in the placebo group) and flatulence (2.2% in RV1 group compared with 1.3% in the placebo group) (11).
TABLE 6. Percentage of infants with solicited adverse events (any intensity and Grade 3*) within 8 days following any dose of Rotarix® (RV1) or placebo†

<table>
<thead>
<tr>
<th>Event</th>
<th>RV1 (n = 3,286)</th>
<th>Placebo (n = 2,015)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Any intensity</td>
<td>% Grade 3</td>
</tr>
<tr>
<td>Fever§</td>
<td>39.8</td>
<td>0.9</td>
</tr>
<tr>
<td>Fussiness/irritability</td>
<td>62.2</td>
<td>6.3</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>34.8</td>
<td>1.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17.6</td>
<td>3.4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Cough/runny nose†</td>
<td>44.2</td>
<td>3.6**</td>
</tr>
</tbody>
</table>


* Those that prevented normal everyday activities.
† Percentages are per subject. Coadministration of routine infant vaccines allowed in studies that provided these data. Parents/guardians were asked to monitor for these events and record on a diary card.
§ Fever, any intensity defined as temperature of ≥100.4 F (≥38.0°C) rectally or ≥99.5 F (≥37.5°C) orally/axillary. Grade 3 fever is defined as temperature of ≥103.1 F (≥39.5°C) rectally or ≥102.2 F (≥39.0°C) orally/axillary.
† This event was solicited among 2,584 RV1 recipients and 1,899 placebo recipients.
** Statistically significantly higher (95% confidence interval for relative risk excluded 1.0) in RV1 group compared with placebo group.

In the placebo-controlled trials (including some that were not 1:1 randomized), Kawasaki disease was reported in 17 (0.03%) RV1 recipients and nine (0.02%) placebo recipients (RR: 1.7; CI = 0.7−4.4); one case occurred within 30 days after study dose in RV1 recipients and one in the placebo recipients (RR: 1.0; CI = 0.01−78.4) (*11). Among RV1 recipients, the time of onset after study dose varied (range: 3 days−19 months).

Preterm Infants

A limited number of preterm infants (reported gestational age of ≤36 weeks) who received RV1 were followed for serious adverse events up to 30−90 days after dose 2. Serious adverse events were observed in seven (5.2%) of 134 preterm RV1 recipients compared with six (5.0%) of 120 preterm placebo recipients (*11). No deaths or cases of intussusception were reported among these infants. Additional data are expected in the near future.

Shedding and Transmission of Vaccine Virus

Rotavirus antigen shedding in stools postvaccination was evaluated in all or a subset of infants from seven phase II or III studies in various countries (RV1 administered at $10^{6.5}−10^{6.8}$ CCID<sub>50</sub> per dose, with 26−152 infants evaluated per study) (*108). After dose 1, rotavirus antigen shedding was detected by ELISA in 50.0%−80.0% (depending on study) of infants at approximately day 7, 19.2%−64.1% at approximately day 15, 0−24.3% at approximately day 30, and 0−2.6% at approximately day 60. After dose 2, rotavirus antigen shedding was detected in 4.2%−18.4% (depending on study) of infants at approximately day 7, 0−16.2% at approximately day 15, 0−1.2% at approximately day 30, and 0 at approximately day 45 (day 45 was assessed in only one study).

Shedding of live rotavirus was assessed in two BLA studies in which RV1 was administered at $10^{6.5}$ CCID<sub>50</sub> per dose (*108). In both studies, stool samples that were collected from a subset of infants at approximately day 7 after dose 1 were tested by ELISA. Stools that were rotavirus-antigen positive were tested subsequently for live virus by focus forming unit assay if enough sample was available. Live virus was detected in six (46.2%) of 13 and 15 (45.5%) of 33 rotavirus-antigen positive stools, for an estimated 26% of vaccinated infants shedding live virus at approximately day 7 after dose 1.

The potential for transmission of vaccine virus to other persons was not assessed.

Cost-Effectiveness of Rotavirus Vaccination

In a 2006 analysis that considered rotavirus disease burden, vaccine efficacy, vaccine coverage rates, and health costs, investigators estimated that a national rotavirus vaccination program in which 3 doses of RV5 were administered at ages 2, 4, and 6 months would result in 255,000 fewer physician visits, 137,000 fewer ED visits, 44,000 fewer hospitalizations, and 13 fewer deaths among children in one U.S. birth cohort followed to age 5 years (*5). From the health-care perspective (i.e., evaluating medical costs only), the vaccination program was estimated to be cost-saving if the total cost per child (including administration costs) was less than $66 (in 2004 dollars) for a complete series and would incur a net cost at $143 per child. From the societal perspective (i.e., evaluating medical and nonmedical costs), vaccination was likely to be cost-saving at a total cost per child of less than $156 and would be a net cost to society if total cost of vaccination was more than $238 per child. At the manufacturer’s price of $62.50 (in 2006 dollars) per dose, a rotavirus vaccination program with RV5 would cost an estimated $197,190 per life-year saved and $138 per case averted from the societal perspective. This analysis was repeated in 2008 for RV1 administered at ages 2 and 4 months (*112). A national program with either the 3-dose RV5 series or the 2-dose RV1 series will have similar cost-effectiveness estimates. Assuming a total cost of $208 per child for RV1 and $218 per child for RV5 (in 2006 dollars; one extra $10 administration cost for RV5), RV1 was slightly more cost-effective than RV5 (e.g., from a societal perspective,
median estimates of $94 compared with $139 per case averted and $128,400 compared with $198,546 per life-year saved, respectively). However, because of uncertainty in cost per dose, administration, and shipping for each product and of the field vaccine effectiveness of a product’s full or partial series, these differences in median estimates between the vaccines might not translate into a true difference for a program.

Rationale for Rotavirus Vaccination and Development of Updated Recommendations

The rationale for adopting vaccination of infants as the primary public health measure for prevention of rotavirus disease, especially severe rotavirus disease, in the United States is threefold. First, rates of rotavirus illness among children in industrialized and less developed countries were similar, indicating that clean water supplies and good hygiene have little effect on virus transmission; therefore, further improvements in hygiene in the United States were unlikely to have a substantial impact on disease prevention (36, 75, 113–116). Second, in the United States, a high level of rotavirus morbidity continued in the prevaccine era despite available therapies. For example, the rate of hospitalizations for gastroenteritis in young children declined only modestly during 1979–1995 (8, 117) despite the widespread availability of oral rehydration solutions in the treatment of dehydrating gastroenteritis (118, 119). Third, studies of natural rotavirus infection indicated that initial infection protects against subsequent severe gastroenteritis, although subsequent asymptomatic infections and mild disease still might occur (75, 76, 120). Therefore, vaccination early in life, which mimics a child’s first natural infection, will not prevent all subsequent disease but should prevent the majority of cases of severe rotavirus disease and their sequelae (e.g., dehydration, physician visits, hospitalizations, and deaths).

In drafting and updating rotavirus vaccine recommendations for consideration by ACIP, the rotavirus vaccine work group acknowledged that differences existed in the design of the vaccine trials and studies and that these differences and the lack of a head-to-head trial between the two licensed vaccines limited direct comparisons of some study results. One aspect that differed in the trials was the maximum ages for doses of vaccine. The maximum age for dose 1 in the trial protocols differed by approximately 3 weeks (Table 1). In addition, because the RV1 series has only 2 doses of vaccine whereas the RV5 series has 3 doses, the maximum age for the last dose for the RV1 trials was younger than that for the RV5 trial. When developing the recommendations for the maximum ages for doses, the workgroup considered the vaccines’ safety and efficacy data and also the effect that having the same or different maximum ages for the products would have on the ability of practitioners to follow the recommendations. After reviewing the options, the workgroup considered that harmonization of the maximum ages for doses of the two vaccines, as presented in the recommendations, would be unlikely to affect the safety and efficacy of the vaccines and would be programmatically advantageous.

Changes to Recommendations from the 2006 ACIP Statement

- ACIP provides recommendations for use of a second rotavirus vaccine, RV1, to be administered in a 2-dose series at ages 2 and 4 months.
- The maximum age for dose 1 of rotavirus vaccine* is 14 weeks and 6 days (previous recommendation: 12 weeks).
- The maximum age for the last dose of rotavirus vaccine is 8 months and 0 days (previous recommendation: 32 weeks).
- The minimum interval between doses of rotavirus vaccine is 4 weeks; no maximum interval is set (previous recommendation: interval of 4–10 weeks between doses).
- Considerations that support rotavirus vaccination of HIV-exposed or infected infants are described below.
- Rotavirus vaccine may be administered at any time before, concurrent with, or after administration of any blood product, including antibody-containing products, following the routinely recommended schedule for rotavirus vaccine (previous recommendation: defer vaccination for 42 days after receipt of an antibody-containing product, if possible).

Recommendations for the Use of Rotavirus Vaccine

Routine Administration

ACIP recommends routine vaccination of U.S. infants with rotavirus vaccine (Table 7). Two different rotavirus vaccine products are licensed for use in infants in the United States, RV5 and RV1. The products differ in composition and schedule of administration. Safety and efficacy were demonstrated for both vaccines in prelicensure clinical trials. Efficacy studies demonstrated that rotavirus vaccine was 85%–98% protective against severe rotavirus disease and 74%–87% protective against rotavirus disease of any severity through approximately the first rotavirus season (93, 109, 110). ACIP does not express a preference for either RV5 or RV1.

*In these recommendations, the term “rotavirus vaccine” is used to refer to both RV5 and RV1.
RV5 is to be administered orally in a 3-dose series, with doses administered at ages 2, 4, and 6 months. RV1 is to be administered orally in a 2-dose series, with doses administered at ages 2 and 4 months (Table 8). The minimum age for dose 1 of rotavirus vaccine is 6 weeks; the maximum age for dose 1 is 14 weeks and 6 days. Vaccination should not be initiated for infants aged 15 weeks and 0 days or older because of insufficient data on safety of dose 1 of rotavirus vaccine in older infants. The minimum interval between doses of rotavirus vaccine is 4 weeks; no maximum interval is set. All doses should be administered by age 8 months and 0 days.

For infants to whom dose 1 of rotavirus vaccine is administered inadvertently at age 15 weeks and 0 days or older, the rest of the rotavirus vaccination series should be completed according to the schedule and by age 8 months and 0 days because timing of dose 1 should not affect the safety and efficacy of any subsequent dose(s). Infants who have had rotavirus gastroenteritis before receiving the full series of rotavirus vaccination should still start or complete the schedule according to the age and interval recommendations because the initial rotavirus infection might provide only partial protection against subsequent rotavirus disease.

RV5 is to be administered orally in a 3-dose series, with doses administered at ages 2, 4, and 6 months. RV1 is to be administered orally in a 2-dose series, with doses administered at ages 2 and 4 months (Table 8). The minimum age for dose 1 of rotavirus vaccine is 6 weeks; the maximum age for dose 1 is 14 weeks and 6 days. Vaccination should not be initiated for infants aged 15 weeks and 0 days or older because of insufficient data on safety of dose 1 of rotavirus vaccine in older infants. The minimum interval between doses of rotavirus vaccine is 4 weeks; no maximum interval is set. All doses should be administered by age 8 months and 0 days.

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No restrictions are placed on the infant’s feeding before or after receipt of rotavirus vaccine. Breastfed infants should be vaccinated according to the same schedule as nonbreastfed infants. The efficacy of the rotavirus vaccine series is similar among breastfed and nonbreastfed infants. As with all other vaccines, rotavirus vaccine can be administered to infants with minor acute illness (e.g., mild gastroenteritis or mild upper-respiratory tract infection, with or without fever).

**Simultaneous Administration**

Rotavirus vaccine can be administered together with DTaP vaccine, Hib vaccine, IPV, hepatitis B vaccine, and pneumococcal conjugate vaccine. Available evidence suggests that rotavirus vaccine does not interfere with the immune response to these vaccines (for each rotavirus vaccine, see Immunogenicity). The infant’s immune response to influenza vaccine administered at the same time as rotavirus vaccine has not been studied. However, ACIP has recommended previously that an inactivated vaccine (e.g., inactivated influenza vaccine) may be administered either simultaneously or at any time before or after a different inactivated vaccine or live vaccine (e.g., rotavirus vaccine) (121).

**Interchangeability of Rotavirus Vaccines**

ACIP recommends that the rotavirus vaccine series be completed with the same product whenever possible. However, vaccination should not be deferred because the product used
for a previous dose(s) is not available or is unknown. In these situations, the provider should continue or complete the series with the product available. If any dose in the series was RV5 or the vaccine product is unknown for any dose in the series, a total of 3 doses of rotavirus vaccine should be administered. All doses should be administered by age 8 months and 0 days.

No studies address the interchangeability of the two rotavirus vaccine products. However, no theoretic reason exists to expect that the risk for adverse events would be increased if the series included more than one product, compared with the risk for adverse events of a series containing only one product. Further, although it is possible that effectiveness of a series that contained both products could be reduced compared with a complete series with one product, the effectiveness of a series that contains both products is likely to be greater than an incomplete series with one product.

Contraindications

Rotavirus vaccine should not be administered to infants who have a history of a severe allergic reaction (e.g., anaphylaxis) after a previous dose of rotavirus vaccine or to a vaccine component. Latex rubber is contained in the RV1 oral applicator, so infants with a severe (anaphylactic) allergy to latex should not receive RV1. The RV5 dosing tube is latex-free.

Precautions

Altered Immune Competence

Practitioners should consider the potential risks and benefits of administering rotavirus vaccine to infants with known or suspected altered immune competence (121); consultation with an immunologist or infectious diseases specialist is advised. Children and adults who are immunocompromised because of congenital immunodeficiency, hematopoietic transplantation, or solid organ transplantation sometimes experience severe or prolonged rotavirus gastroenteritis. However, no safety or efficacy data are available for the administration of rotavirus vaccine to infants who are immunocompromised or potentially immunocompromised, including 1) infants with primary and acquired immunodeficiency states, cellular immunodeficiencies, and hypogammaglobulinemic and dysgammaglobulinemic states; 2) infants with blood dyscrasias, leukemia, lymphomas, or other malignant neoplasms affecting the bone marrow or lymphatic system; 3) infants on immunosuppressive therapy (including high-dose systemic corticosteroids); and 4) infants who are HIV-exposed or infected. However, two considerations support vaccination of HIV-exposed or infected infants: first, the HIV diagnosis might not be established in infants born to HIV-infected mothers before the age of the first rotavirus vaccine dose (only 1.5%–3% of HIV-exposed infants in the United States will be determined to be HIV-infected); and second, vaccine strains of rotavirus are considerably attenuated.

Acute Gastroenteritis

In usual circumstances, rotavirus vaccine should not be administered to infants with acute moderate or severe gastroenteritis until the condition improves. However, infants with mild acute gastroenteritis can be vaccinated, particularly if the delay in vaccination might be substantial and might make the infant ineligible to receive vaccine (e.g., aged ≥15 weeks and 0 days before the vaccine series is started). Rotavirus vaccine has not been studied among infants with concurrent acute gastroenteritis. In these infants, the immunogenicity and efficacy of rotavirus vaccine theoretically could be compromised. For example, in some instances, infants who received OPV during an episode of acute gastroenteritis had diminished poliovirus antibody responses (122).

Moderate or Severe Acute Illness

As with all other vaccines, the presence of a moderate or severe acute illness with or without fever is a precaution to administration of rotavirus vaccine. Infants with a moderate or severe acute illness should be vaccinated as soon as they have recovered from the acute phase of the illness. This precaution avoids superimposing any potential adverse effects of the vaccine on the underlying illness or mistakenly attributing a manifestation of the underlying illness to the vaccine. Vaccination should not be delayed because of the presence of mild respiratory tract illness or other mild acute illness with or without fever.

Pre-existing Chronic Gastrointestinal Diseases

Infants with pre-existing gastrointestinal conditions (e.g., congenital malabsorption syndromes, Hirschsprung’s disease, or short-gut syndrome) who are not undergoing immuno-

<table>
<thead>
<tr>
<th>TABLE 8. Schedule for administration of rotavirus vaccines</th>
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<td><strong>Characteristic</strong></td>
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<tr>
<td>No. doses in series</td>
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<tr>
<td>Recommended ages for doses</td>
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<tr>
<td>Minimum age for first dose</td>
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<td>Maximum age for first dose</td>
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<tr>
<td>Minimum interval between doses</td>
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<tr>
<td>Maximum age for last dose</td>
</tr>
<tr>
<td>* RotaTeq®.</td>
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<td>† Rotarix®.</td>
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CONSIDERATION
Suppressive therapy should benefit from receiving rotavirus vaccine, and ACIP considers the benefits to outweigh the theoretic risks. However, no data are available on the safety and efficacy of rotavirus vaccine for infants with preexisting chronic gastrointestinal conditions.

**Previous History of Intussusception**

Practitioners should consider the potential risks and benefits of administering rotavirus vaccine to infants with a previous history of intussusception. Available data do not indicate that RV5 or RV1 are associated with intussusception. A previously licensed rotavirus vaccine that is no longer available in the United States, RRV-TV, was associated with an increased risk for intussusception. Compared with infants who have never had intussusception, infants with a history of intussusception are at higher risk for a repeat episode of intussusception. No data are available on the administration of rotavirus vaccine to infants with a history of intussusception.

**Infants with Spina Bifida or Bladder Exstrophy**

Latex rubber is contained in the RV1 oral applicator whereas the RV5 dosing tube is latex-free. Therefore, some experts prefer that infants with spina bifida or bladder exstrophy, who are at high risk for acquiring latex allergy, receive RV5 instead of RV1 to minimize latex exposure in these children. However, if RV1 is the only rotavirus vaccine available, it should be administered, because the benefit of vaccination is considered to be greater than the risk for sensitization.

**Special Situations**

**Preterm Infants (<37 Weeks’ Gestation)**

ACIP considers the benefits of rotavirus vaccination of preterm infants (those born at <37 weeks’ gestation) to outweigh the risks of adverse events. Data suggest that preterm infants are at increased risk for hospitalization from rotavirus or other viral pathogens associated with gastroenteritis during their first one to two years of life. In clinical trials, rotavirus vaccine appeared to be generally well tolerated in preterm infants, although a relatively small number of preterm infants have been evaluated (for each rotavirus vaccine, see Adverse Events After Immunization).

ACIP supports vaccination of preterm infants according to the same schedule and precautions as full-term infants and under the following conditions: the infant’s chronological age meets the age requirements for rotavirus vaccine (e.g., age 6 weeks–14 weeks and 6 days for dose 1), the infant is clinically stable, and the vaccine is administered at the time of discharge from the neonatal intensive care unit [NICU] or nursery, or after discharge from the NICU or nursery. Although the lower level of maternal antibody to rotavirus in very preterm infants theoretically could increase the risk for adverse reactions from rotavirus vaccine, ACIP believes the benefits of vaccinating the infant when age-eligible, clinically stable, and no longer in the hospital outweigh the theoretic risks.

Vaccine strains of rotavirus are shed in stools of vaccinated infants (for each rotavirus vaccine, see Shedding and Transmission of Vaccine Virus), so if an infant were to be vaccinated with rotavirus vaccine while still needing care in the NICU or nursery, at least a theoretic risk exists for vaccine virus being transmitted to infants in the same unit who are acutely ill (moderate or severe acute illness is a precaution for vaccination) and to preterm infants who are not age-eligible for vaccine. ACIP considers that, in usual circumstances, the risk from shedding outweighs the benefit of vaccinating the infant who is age-eligible for vaccine but who will remain in the NICU or nursery after vaccination.

**Exposure of Immunocompromised Persons to Vaccinated Infants**

Infants living in households with persons who have or are suspected of having an immunodeficiency disorder or impaired immune status can be vaccinated. Vaccine virus (attenuated rotavirus) is shed in the stools of infants after rotavirus vaccination. However, no data are available on the risk for transmission of vaccine virus to household contacts and the risk for any subsequent disease. Vaccine virus is shed more commonly and for longer periods after RV1 than after RV5 (for each rotavirus vaccine, see Shedding and Transmission of Vaccine Virus). ACIP believes that the protection of the immunocompromised household member afforded by vaccinating the infant in the household and preventing wild-type rotavirus disease outweighs the small risk for transmitting vaccine virus to the immunocompromised household member and any subsequent theoretic risk for vaccine virus-associated disease. Vaccine virus is shed during the first weeks after administration of rotavirus vaccine; handwashing after diaper changing is always recommended.

**Exposure of Pregnant Women to Vaccinated Infants**

Infants living in households with pregnant women should be vaccinated according to the same schedule as infants in households without pregnant women. Because the majority of women of childbearing age have preexisting immunity to rotavirus, the risk for infection and any subsequent theoretic risk for disease from potential exposure to the attenuated vaccine virus is considered to be very low.
Regurgitation of Vaccine

The practitioner should not readminister a dose of rotavirus vaccine to an infant who regurgitates, spits out, or vomits during or after administration of vaccine. No data exist on the benefits or risks associated with readministering a dose. The infant should receive the remaining recommended doses of rotavirus vaccine following the routine schedule (with a 4-week minimum interval between doses).

Hospitalization After Vaccination

If a recently vaccinated infant is hospitalized for any reason, no precautions other than standard precautions need to be taken to prevent spread of vaccine virus in the hospital setting.

Infants Who Have Recently Received or Will Receive an Antibody-Containing Blood Product

Rotavirus vaccine may be administered at any time before, concurrent with, or after administration of any blood product, including antibody-containing products, following the routinely recommended schedule for rotavirus vaccine among infants who are eligible for vaccination. No data are available on the immune response to rotavirus vaccine in infants who have recently received a blood product. In theory, infants who have recently received an antibody-containing blood product might have a reduced immunologic response to a dose of oral rotavirus vaccine. However, 2 or 3 doses of vaccine are administered in the full rotavirus vaccine series, and no increased risk for adverse events is expected.

Reporting of Adverse Events

Any clinically significant or unexpected adverse event that occurs after administration of rotavirus vaccine should be reported to VAERS, even if a causal relation to vaccination is not certain. The National Childhood Vaccine Injury Act requires health-care providers to maintain permanent immunization records and to report to VAERS occurrences of specific adverse events that follow selected vaccines, including rotavirus vaccine (available at http://vaers.hhs.gov/reportable.htm). VAERS reporting forms and information are available electronically at http://vaers.hhs.gov or by telephone, 1-800-822-7967. Web-based reporting by providers is encouraged and is available at https://secure.vaers.org/VaersDataEntryinto.htm.

Enhanced Postlicensure Surveillance for Adverse Events

Monitoring for adverse events after introduction of rotavirus vaccine into routine vaccination programs is important, particularly in light of the previous experience with RRV-TV and its association with intussusception. The monitoring after introduction of RV1 will be similar to that conducted for RV5 and will include manufacturer-sponsored phase IV studies and enhanced review of adverse events reported to VAERS.

National Vaccine Injury Compensation Program

The National Vaccine Injury Compensation Program (VICP), established by the National Childhood Vaccine Injury Act of 1986, is a no-fault system through which persons thought to have suffered an injury or death as a result of administration of a covered vaccine can seek compensation. Persons of all ages who receive a VICP-covered vaccine are eligible to file a claim.

The program relies on a vaccine injury table listing the vaccines covered by the program and the injuries, disabilities, illnesses, and conditions (including death) for which compensation can be awarded. Claimants also can prevail for conditions not listed in the table if they can prove causation. For a claimant to be eligible for compensation, claims must be filed within a specific time period after the injury.

Rotavirus vaccine is covered by VICP under the general category of rotavirus vaccines in Category XI of the Vaccine Injury Table (available at http://www.hrsa.gov/vaccinecompensation/table.htm). In this category, no condition is specified for compensation. Additional information about the program is available at http://www.hrsa.gov/vaccinecompensation or by telephone, 1-800-338-2382.

Areas for Study Related to Rotavirus Vaccination

Surveillance of Rotavirus Gastroenteritis

Rotavirus gastroenteritis is not a reportable disease in the United States, and testing for rotavirus infection is not always performed when a child seeks medical care for acute gastroenteritis. Rotavirus disease surveillance systems need to be adequately sensitive and specific to document the effectiveness of the vaccination program. Methods of surveillance for rotavirus disease at the national level include review of national hospital discharge databases for rotavirus-specific or rotavirus-compatible diagnoses, surveillance for rotavirus disease at three sites that participate in NVSN, and reports of rotavirus detec-
tion from a sentinel system of laboratories \((6,7,14)\). At the state and local levels, surveillance efforts at sentinel hospitals or by review of hospital discharge databases can be used to monitor the impact of the vaccine program. Special studies \(e.g.,\) case-control studies and retrospective cohort studies \) will be used to measure the effectiveness of rotavirus vaccine under routine use in the United States.

**Detection of Unusual Strains of Rotavirus**

CDC has established a national strain surveillance system of sentinel laboratories to monitor circulating rotavirus strains before and after the introduction of rotavirus vaccine \((64–66)\). This system is designed to detect new or unusual strains causing gastroenteritis that might not be prevented effectively by vaccination, which might affect the success of the vaccination program.

**Research**

Additional studies would be valuable to evaluate the safety and efficacy of rotavirus vaccine administered to infants who are born preterm, have immune deficiencies, live in households with immunocompromised persons, have chronic gastrointestinal disease, or start the series late. Postlicensure studies also could determine the relative effectiveness of rotavirus vaccine when less than the full series is administered and evaluate possible secondary transmission of vaccine virus.

**Acknowledgments**

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ACIP Rotavirus Vaccine Working Group

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Q & A on PCV1
Drugs and Health Products

Questions and Answers - Porcine Circovirus Found in Rotavirus Vaccines

1. What is rotavirus?
Rotavirus is a virus that has been known to cause rotavirus gastroenteritis in infants. Rotavirus gastroenteritis is a highly infectious form of diarrhoea in infants and young children that can cause severe vomiting and dehydration resulting in hospitalization and can be life-threatening. Children under five years of age, especially those between six months and two years, are most vulnerable to the disease.

Rotavirus is the most common cause of severe diarrhoea in infants and young children globally but severe diarrhoea is not a major public health issue in Canada. Rotaviruses are estimated to be responsible for approximately 527,000 deaths each year, with most of these deaths occurring in low-income countries in Africa and Asia, and over two million people are hospitalized each year with pronounced dehydration.

2. What are the symptoms of rotavirus infection?
Rotavirus infects the intestines. The illness usually begins with fever, an upset stomach, and vomiting, followed by diarrhoea, and generally lasts three to eight days.

3. How is rotavirus infection treated?
There is no specific treatment for the rotavirus infection. Symptoms are treated mostly by oral rehydration to prevent dehydration, the most serious problem caused by the disease. Oral rehydration therapy is a simple treatment for dehydration that consists of a solution of salts and sugars which is taken by mouth. Severe cases of dehydration require administration of intravenous fluids in a hospital.

4. Can rotavirus disease be prevented?

Rotavirus disease can be prevented by vaccination.

5. Are there rotavirus vaccines in Canada?

In Canada, two rotavirus vaccines are authorized to protect against the human rotavirus that cause vomiting and diarrhoea in infants, Rotarix (GlaxoSmithKline) and RotaTeq (Merck Frosst).

The RotaTeq and Rotarix product monographs can be found on the Health Canada website.

Currently, Rotarix and RotaTeq are not part of the routine immunization programs in Canada. For more information on routine immunization programs, please contact your provincial or territorial public health authority.

6. What is porcine circovirus types 1 and 2?

Porcine circovirus-1 and porcine circovirus-2 are both small, circular viruses composed of a single strand of DNA.

Porcine circovirus-1 and porcine circovirus-2 are common in pigs. Porcine circovirus-1 does not cause illness in any animal but porcine circovirus-2 may cause illness in pigs. Humans may be exposed to porcine circoviruses through diet or from exposure to farm animals but porcine circoviruses are not known to cause illness in humans.

7. Why is porcine circovirus found in rotavirus vaccines?

Porcine circovirus DNA can be a contaminant of an enzyme obtained from pig pancreas. This enzyme is used during some manufacturing steps in the production of rotavirus vaccines. As such, porcine circovirus is considered a contaminant in rotavirus vaccines.

8. Are the rotavirus vaccines safe for my child?

Yes, neither porcine circovirus-1 nor porcine circovirus-2 are known to cause illness in humans. In fact, Health Canada has no evidence that either porcine circovirus-1 or porcine circovirus-2 poses a safety risk. Both vaccines have a successful track record of safety and effectiveness. The benefits of the vaccines for infants are substantial, and
include prevention of hospitalization for severe rotavirus disease in Canada.

9. **Should my child see a doctor if he/she has received a rotavirus vaccine?**

Health Canada currently has no evidence to suggest that human rotavirus vaccines containing DNA from the porcine circovirus (PCV-1 or PCV-2) pose a safety risk. Canadians should contact their health care professional if they have questions or concerns about rotavirus vaccine.

Both Rotarix (GlaxoSmithKline) and RotaTeq (Merck Frosst Canada) vaccines have strong safety records, including clinical trials involving tens of thousands of patients and clinical experience with millions of patients.

10. **Are porcine circovirus -1 and porcine circovirus -2 pig material?**

No, porcine circovirus is not pig or other animal material. Porcine circovirus is a virus.

Porcine circovirus has sometimes been referred to as the 'pig virus' by the media but this is only because the virus is commonly found in pigs.

11. **What illness does porcine circovirus -2 cause in pigs?**

Porcine circovirus type 2 (PCV-2) is a DNA virus that infects pigs and contributes to the development of post-weaning multisystemic wasting syndrome (PMWS) in pigs aged four to fourteen weeks old. Symptoms of the condition are poor growth rate and/or acute malnutrition and weight loss.

While porcine circovirus- 2 infect swine worldwide, only a small proportion of pigs develop post-weaning multisystemic wasting syndrome and other porcine circovirus- 2 associated diseases.

It is important to remember that humans may be exposed to porcine circoviruses through diet or from exposure to farm animals but porcine circoviruses are not known to cause illness in humans.

12. **Why was porcine circovirus DNA not detected in rotavirus vaccines earlier?**

The identification of DNA fragments by the academic researchers has only recently become possible due to new technological developments.

Health Canada stresses that the findings do not present a Canadian public health threat. However, given that DNA fragment testing is now available, Health Canada and other international regulatory agencies now expect the manufacturers to establish a
plan to manufacture porcine circovirus-free vaccines.

13. What are Health Canada and the vaccine manufacturers doing about porcine circovirus DNA contamination in rotavirus vaccines?

Health Canada has been working closely with vaccine manufacturers and other international regulators, including the US Food and Drug Administration and the World Health Organization, to facilitate an international response to this issue.

On March 26, 2010, GlaxoSmithKline posted information on their website relating to the manufacture of Rotarix and the presence of PCV-1. Health Canada then posted a statement to our website that same day to notify Canadians and health care professionals that no lots of Rotarix were on the market in Canada and that the Canadian RotaTeq vaccine was not known to be contaminated with PCV-1.

On May 7, 2010, Merck posted information on their website relating to the presence of PCV-1 and PCV-2 in their RotaTeq vaccine and GlaxoSmithKline posted an information update on their website disclosing the presence of PCV-1 in their Rotarix vaccine. That same day, Health Canada issued an information update for Canadians and health care professionals that indicated that the Department had become aware that extremely low levels of two types of porcine circovirus DNA (PCV-1 and PCV-2) have been detected in the Canadian RotaTeq vaccine.

Since this time, Health Canada has continued to work closely with rotavirus vaccine manufacturers, GlaxoSmithKline and Merck Frosst. Both manufacturers have conducted an investigation on this issue, updated their product labelling to reflect the presence of porcine circovirus DNA and informed health care practitioners of the new labelling. This information can now be found on the Health Canada website for both Rotarix and RotaTeq.

New information will be communicated to Canadians and health care professionals as it becomes available and Health Canada will take appropriate regulatory action as needed. Canadians should contact their health care professional if they have questions or concerns about rotavirus.

Date Modified: 2010-08-17
July 12, 2010

Dear Health Care Professional

Subject: Presence of Porcine Circovirus, Type 1 (PCV-1) in ROTARIX™
(Human Rotavirus, live, attenuated, oral vaccine)

ROTARIX™ is an orally administered vaccine that is authorized for the active immunization of infants from the age of 6 weeks for the prevention of gastroenteritis caused by rotavirus types G1P[8], G2P[4], G3P[8], G4P[8] and G9P[8].

GlaxoSmithKline Inc. (GSK), in consultation with Health Canada, would like to inform healthcare professionals of new information on the composition of its Human Rotavirus vaccine, ROTARIX™ (live, attenuated, oral vaccine).

- GSK has identified the presence of material from porcine circovirus, Type 1 (PCV-1) in its ROTARIX™ vaccine.
- According to scientific literature, PCV-1 is a virus commonly found in pigs and pork products. PCV-1 does not replicate in humans and is not known to cause illness in humans or any other animals.\(^{1,2}\)
- Available evidence, obtained before and after the marketing authorization, supports the safety and effectiveness of ROTARIX™.
- GSK’s Vaccine Safety Monitoring Board has reviewed all data and has concluded that the benefit/risk profile of the vaccine remains unchanged to date.

The safety and effectiveness of ROTARIX™ has been extensively studied. The safety profile of ROTARIX™ is based on extensive clinical data from the largest vaccine clinical trial program conducted by GSK, enrolling more than 90,000 participants in Europe, Latin America, Asia, Africa and the US. The discovery of PCV-1 in the vaccine is a new finding which GSK continues to investigate. Since material from PCV-1 has been present in ROTARIX™ since the initial stages of its development, the established safety profile therefore reflects exposure to material from PCV-1. ROTARIX™ was authorized in Canada in October 2007 based on data from 12 clinical studies involving over 76,000 subjects.

Post marketing surveillance data of the product reflects more than 69 million doses which have been distributed globally since its launch five years ago. The Canadian Product Monograph for ROTARIX™ will be updated to reflect the discovery of PCV-1. The benefit/risk profile of the vaccine remains unchanged and GSK will continue to work closely with Health Canada on this issue.

Managing marketed health product-related adverse reactions depends on health care professionals and consumers reporting them. Reporting rates determined on the basis of spontaneously reported post-marketing adverse reactions are generally presumed to underestimate the risks associated with health product treatments. Any case of serious or unexpected adverse reactions in patients receiving ROTARIX™ should be reported to your local public health authority, GlaxoSmithKline or the Public Health Agency of Canada as follows:
REPORTING SUSPECTED VACCINE ADVERSE EVENTS

If a patient experiences an adverse event following immunization, please complete the Adverse Events Following Immunization (AEFI) Form and send it to your local Health Unit in your province/territory.

Contact information for each provincial/territorial public health jurisdiction can be found through the following link:


The national AR Reporting Form and the AEFI Reporting Guidelines can be found on the Public Health Agency of Canada web site: http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php

Contact Information:
By toll-free telephone:  1-866-844-0018
By toll-free fax:             1-866-844-5931
Email Address: caefi@phac-aspc.gc.ca

Mail:
Vaccine Safety Section
Centre for Immunization and Respiratory Infectious Diseases
Public Health Agency of Canada  A/L 6502A
130 Colonnade Road
Ottawa, Ontario
K1A 0K9

or to

GlaxoSmithKline Inc.
7333 Mississauga Road North
Mississauga, Ontario, L5N 6L4
Tel: 1-800-387-7374

For other inquiries related to this communication, please contact Health Canada at:

Biologics and Genetic Therapies Directorate
E-mail: BGTD_ORA_Enquiries@hc-sc.gc.ca
Tel: (613) 957-1722

Sincerely,

original signed by

Dr. Tjark Reblin
Vice President, Medical and Chief Medical Officer
GlaxoSmithKline Canada
References:
Rotavirus
Promotional Materials
To order English or French Rotarix branded promotional material please contact GSK’s customer service:

Phone: 1 800 387 7374

Email: cacsu@gsk.com
Additional Non-Branded Resources:

Public Health Agency of Canada; National Advisory Committee Updated Statement on the use of Rotavirus Vaccines:


Canadian Paediatric Society Recommendations for the use of Rotavirus Vaccines in Infants:

http://www.cps.ca/English/Media/NewsReleases/2010/Rotavirus.htm

Canadian Paediatric Society: Caring for Kids information on Rotavirus Vaccines:

http://www.caringforkids.cps.ca/immunization/Rotavirus.htm
**Rotarix™ Fact Sheet**

<table>
<thead>
<tr>
<th>Brand</th>
<th>Rotarix™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-proprietary name/ dosage form</td>
<td>Human rotavirus, live, attenuated, oral vaccine for oral suspension</td>
</tr>
<tr>
<td>Active immunizing agent</td>
<td></td>
</tr>
<tr>
<td>Manufacturer</td>
<td>GlaxoSmithKline Inc.</td>
</tr>
<tr>
<td>Indication</td>
<td>For active immunization of infants from the age of 6 weeks for the prevention of gastroenteritis caused by rotavirus types G1P[8], G2P[4], G3P[8], G4P[8] and G9P[8]. The results from clinical trials suggest that the vaccine’s efficacy may vary with the type of rotavirus causing the infection.</td>
</tr>
<tr>
<td>Packaging</td>
<td>Available in an oral applicator with a plunger stopper in pack sizes of 1, 5, 10, 25 or 100.</td>
</tr>
<tr>
<td>DIN</td>
<td>02300591</td>
</tr>
<tr>
<td>062021 11930 7</td>
<td></td>
</tr>
<tr>
<td>UPC</td>
<td>0 62021 11930 7</td>
</tr>
<tr>
<td>GSK Item #</td>
<td>11930</td>
</tr>
<tr>
<td>Customer Service/Med Info</td>
<td>1-800-387-7374</td>
</tr>
<tr>
<td>Demonstrated Efficacy</td>
<td>In a clinical study demonstrated 95.8% efficacy against severe RGE (Vesikari score ≥11) after 1 season (p&lt;0.05 vs. placebo n=2572 Rotarix™ vaccines and n=1,302 placebo).1,2†</td>
</tr>
<tr>
<td>Statistically significant efficacy against severe RGE for 5 rotavirus serotypes (p&lt;0.05)1* G1P[8] 96.4%<em>, G2P[4] 85.5%</em>, G3P[8] 93.7%<em>, G4P[8] 95.4%</em> and G9P[8] 85.0%* over 2 rotavirus seasons1 (n=2,572 Rotarix™ vaccines and n=1,302 placebo).1†</td>
<td></td>
</tr>
<tr>
<td>Rotarix™ vaccine helps provide cross protection against infection due to non-G1 serotypes.3</td>
<td></td>
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<tr>
<td>Studies have demonstrated considerable reductions in overall burden of illness following implementation of a ROTARIX™ immunization program.3</td>
<td></td>
</tr>
<tr>
<td>Storage and Stability</td>
<td>2°C to 8°C in a refrigerator.</td>
</tr>
<tr>
<td>Do not freeze.</td>
<td></td>
</tr>
<tr>
<td>Store in the original package to protect from light.</td>
<td></td>
</tr>
<tr>
<td>Do not use beyond the expiry date indicated on the label and packaging.</td>
<td></td>
</tr>
<tr>
<td>The vaccine is ready to use (no reconstitution or dilution is required).</td>
<td></td>
</tr>
<tr>
<td>Dosage Form</td>
<td>Available as an oral suspension (1.5mL).</td>
</tr>
<tr>
<td>Composition</td>
<td>Each 1.5 mL dose is formulated to contain not less than 10⁶⁰ CCID₅₀ of human rotavirus RIX4414 strain (live, attenuated), produced on Vero cells. Each dose also contains Dulbecco's Modified Eagle Medium (DMEM), sucrose, di-sodium adipate and sterile water.</td>
</tr>
<tr>
<td>Usual Dose</td>
<td>Vaccination course consists of two doses. The first dose can be administered from the age of 6 weeks. There should be an interval of at least 4 weeks between doses. The administration of the two doses should be completed by the age of 24 weeks.</td>
</tr>
<tr>
<td>ROTARIX™ may be given to preterm infants following the same vaccination course.</td>
<td></td>
</tr>
<tr>
<td>It is strongly recommended that infants who receive a first dose of Rotarix™ vaccine complete the 2 dose regimen with Rotarix™ vaccine.</td>
<td></td>
</tr>
<tr>
<td>Administration</td>
<td>The vaccine is administered orally. Under no circumstance should Rotarix™ vaccine be administered by injection. Please consult product monograph for special handling instructions.</td>
</tr>
</tbody>
</table>

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*Statistically significant (p<0.05) 
† Multicentre, multicountry, double-blinded, randomized, placebo controlled study, two oral doses n=2,572 Rotarix™ vaccines and n=1,302 placebo.
What are the Warnings and Precautions associated with Rotarix™ vaccine?
The administration of Rotarix™ vaccine should be postponed in infants suffering from acute severe febrile illness and infants suffering from diarrhea or vomiting. No safety or efficacy data are available for the administration of Rotarix to immunocompromised patients or individuals who have received a blood transfusion or blood products, including immunoglobulins, within 42 days. Rotarix™ vaccine is for oral use only and under no circumstances should Rotarix™ vaccine be injected. Rotarix™ vaccine does not protect against gastroenteritis due to other pathogens than rotavirus.

In post-marketing experience, cases of intussusception have been reported within seven days following the first dose. No casual relationship has been established Rotarix™ vaccine should be administered with caution to individuals with immunodeficient dose contacts such as individuals with malignancies, or who are otherwise immunocompromised or receiving immunosuppressive therapy. Please consult product monograph for complete warnings and precautions.

Are there any contraindications to Rotarix™ vaccine?

- Infants who are hypersensitive to this drug or to any ingredient in the formulation or component of the container.
- For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- Infants who experienced hypersensitivity after previous administration of rotavirus vaccines.
- Infants with uncorrected congenital malformation (such as Meckel’s diverticulum) of the gastrointestinal tract that would predispose for intussusception.

Can Rotarix™ vaccine be given with other vaccines at the same time?
Rotarix™ vaccine can be given concomitantly with any of the following monovalent or combination vaccines (including hexavalent vaccines (DTPa-HBV-IPV/Hib): diphtheria-tetanus-acellular pertussis vaccine (DTPa), Haemophilus influenzae type b vaccine (Hib), inactivated polio vaccine (IPV), hepatitis B vaccine (HBV), pneumococcal conjugate vaccine and meningococcal serogroup C conjugate vaccines. Concomitant administration of Rotarix™ vaccine and oral polio vaccine (OPV) does not affect the immune response to the polio antigens but may reduce that to Rotarix™ vaccine. The immune response to Rotarix™ vaccine is unaffected when OPV is administered two weeks apart from Rotarix™ vaccine.

What adverse reactions have been reported with Rotarix™ vaccine?
As with any vaccine, a protective immune response may not be elicited in all vaccinees. The most common adverse events after dose 1 in a clinical trial were irritability/fussiness 32.7%, fever 14.6%, loss of appetite 13.8%, cough/runny nose 6.3%, vomiting 4.8% and diarrhea 2.0%. Common side effects which may occur between ≥1% and <10% include diarrhea. Uncommon side effects which may occur between ≥0.1% and <1% include flatulence, abdominal pain and dermatitis. For more information, please contact Medical Information at GlaxoSmithKline 1-800-387-7334.

If an infant spits out or regurgitates most of the vaccine dose, can a replacement dose be given?
In the unlikely event that an infant spits out or regurgitates Rotarix™ vaccine, a single replacement dose may be given at the same vaccination visit.

Can breastfeeding continue during the vaccination period?
There is no evidence to suggest that breast feeding would reduce the protection against rotavirus gastroenteritis afforded by Rotarix™ vaccine. Therefore, breastfeeding may be continued during the vaccination schedule.

Are there any restrictions on an infant’s consumption of food or liquid before or after vaccination?
There are no restrictions to an infant’s consumption of food or liquid including breast milk before or after vaccination.

References
1. Rotarix™ vaccine Product Monograph, GlaxoSmithKline, August 3, 2010

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Rotarix™ vaccine may provide completion of rotavirus immunization as early as 2.5 months of age in just 2 oral doses.¹

Rotarix™ vaccine is indicated for active immunization of infants from the age of 6 weeks for the prevention of gastroenteritis caused by rotavirus types G1P[8], G2P[4], G3P[8], G4P[8] and G9P[8].¹

Rotarix™ vaccine should not be used in children with an intolerance to some sugars, born with malformation of the gastrointestinal tract that would predispose for intussusception, have any disease that reduces resistance to infections, have severe infection with a high temperature or have diarrhea or is vomiting.¹

Following immunization with Rotarix™ vaccine, some children may experience very common adverse reactions (>10% of doses) such as irritability and loss of appetite. Common adverse reactions (1-10% of doses) include fever, fatigue, diarrhea, vomiting or regurgitation of food, flatulence and abdominal pain.¹

Ask your doctor for more information about Rotarix™ vaccine and help protect your child against rotavirus infection.

References:
1. Rotarix™ vaccine Product Monograph, GlaxoSmithKline August 8, 2008

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About Rotavirus

What is rotavirus infection?
Rotavirus infection is the most common cause of severe diarrhea in infants and young children. Most children with rotavirus diarrhea recover on their own. However, in some instances, some children become very ill with severe vomiting, diarrhea and life-threatening loss of fluids that requires hospitalization.1

How is rotavirus infection spread?
Rotavirus may be highly contagious and it is easily spread from hand-to-mouth due to contact with stools from an infected person.1

What are the symptoms of a typical rotavirus infection?
Symptoms may last from 3 to 8 days.2
Symptoms may include:2
- severe watery diarrhea (defined as more than three loose stools per day)
- severe vomiting
- abdominal pain or cramps
- fever

Prevention

What can be done to help protect your child?
Primary infection after 3 months of age usually causes the most disease.1 Vaccination can help to prevent severe diarrhea and vomiting due to rotavirus.

The vaccine is given by mouth to babies starting from as young as six weeks old. Two Rotarix™ vaccine doses are required.1

About ROTARIX™
Rotarix™ vaccine is a viral vaccine, containing live, attenuated human rotavirus, that helps to protect your child against gastroenteritis (diarrhea and vomiting) caused by rotavirus infection.1

When a person is given the vaccine, the immune system (the body’s natural defences) will make antibodies against the most commonly occurring types of rotavirus. These antibodies protect against disease caused by these types of rotavirus and should protect your child from infection.1

As with all vaccines, ROTARIX™ may not completely protect all people who are vaccinated against rotavirus infections, it is intended to prevent.1

Recommended Dose and Dosage Adjustment1

Please note that your healthcare provider will administer Rotarix™ vaccine to your child. Under no circumstances is Rotarix™ vaccine to be administered by injection.