The Pentavalent Rotavirus Vaccine, RotaTeq®: From Development to Licensure and Beyond

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Characteristics of RotaTeq®

- Oral pentavalent vaccine suspended in a liquid buffer/stabilizer.
- Administered directly from tube.
- 3-dose regimen that integrates easily into pre-established immunization schedules:
  - First dose age 6 to 12 weeks
  - Subsequent doses at 1 to 2 month intervals
  - Last dose to be given by 32 weeks of age
- Concomitant use: DTaP, DTwP, Hep B, Hib, IPV, Prevnar¹,², OPV³, Hexavalent⁴, Meningococcal C conjugate⁵
- Contains 5 human-bovine reassortants:
  - G serotypes - human G1, G2, G3, G4, and bovine G6

² Rodriguez et al., 2007. PIDJ, 26: 221-227
³ Ciarlet et al., 2008. PIDJ, 27: 874-880.
⁴ Ciarlet et al., PIDJ, 28: 177-181.
⁵ Vesikari et al., submitted to Human Vaccines.
Phase III Studies: Protocol 006 (Rotavirus Efficacy and Safety Trial [REST]), Protocol 007, and Protocol 009

Multi-centre, 11 countries on 3 continents, from 2001 to 2005
Randomised, double-blind study: RotaTeq® versus placebo controlled
Age at enrolment: 6 to 12 weeks of age, 3 oral doses provided every 4–10 weeks

71,799 Subjects Vaccinated
36,203 in RotaTeq® Group
35,596 in Placebo Group

Vesikari et al., 2006. IJID, 25 (Suppl 1): S42-A47
Dennehy et al., 2007. IJID 11 (Suppl 2): S36-S42.

REST Subjects Lost to Follow-Up: 81 (0.2%) V: 97 (0.3%) P
RotaTeq®: Consistent High Protection against Severe Rotavirus Gastroenteritis (RGE) and RGE of Any Severity

<table>
<thead>
<tr>
<th>Study Protocol</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composition; subject number</td>
<td>002 G1-3,P1A (n = 370)</td>
<td>005 G1-4,P1A (n = 499)</td>
</tr>
<tr>
<td>Severe RGE % Efficacy (95% CI)</td>
<td>100% (44-100)</td>
<td>100% (35-100)</td>
</tr>
<tr>
<td>Any RGE % Efficacy (95% CI)</td>
<td>75% (50-88)</td>
<td>74% (38-91)</td>
</tr>
</tbody>
</table>

Efficacy measured from 14 days after the third dose.
RGE cases with score >16/24 by Clark severity scale based on the intensity and duration of symptoms (fever, vomiting, diarrhoea, and behavioural changes).

Efficacy of RotaTeq® against Hospitalizations, Emergency Department Visits and Office Visits for (G1-G4) RGE up to 2 Years Postvaccination

<table>
<thead>
<tr>
<th>Type of Health Care Encounter</th>
<th>Number of Cases</th>
<th>% Rate Reduction</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vaccine</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Hospitalizations†</td>
<td>6</td>
<td>138</td>
<td>96</td>
</tr>
<tr>
<td>Emerg. Dept. Visits†</td>
<td>13</td>
<td>191</td>
<td>94</td>
</tr>
<tr>
<td>Office Visits‡</td>
<td>13</td>
<td>98</td>
<td>86</td>
</tr>
</tbody>
</table>

† N=34,035 vaccinated in vaccine group and 34,003 vaccinated in placebo group.
‡ N=2,834 vaccinated in vaccine group and 2,839 vaccinated in placebo group.

### Efficacy of RotaTeq® against Hospitalizations and Emergency Department Visits for RGE up to 2 Years Postvaccination by Geographic Region

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of Cases</th>
<th>% Rate Reduction</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vaccine</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Europe*</td>
<td>16</td>
<td>301</td>
<td>95%</td>
</tr>
<tr>
<td>US†</td>
<td>1</td>
<td>27</td>
<td>96%</td>
</tr>
<tr>
<td>Native Americans†</td>
<td>2</td>
<td>31</td>
<td>93%</td>
</tr>
<tr>
<td>Latin America/Caribbean‡</td>
<td>1</td>
<td>10</td>
<td>90%</td>
</tr>
</tbody>
</table>

* N = 14,018 RotaTeq®/ 13,984 Placebo
† N = 11,990 RotaTeq®/ 11,892 Placebo
‡ N = 294 RotaTeq®/ 287 Placebo
† N = 2,252 RotaTeq®/ 2237 Placebo.

Vesikari et al., 2007, IJID, 11, Suppl 2: S29-S35.
Serotype-Specific Rate Reduction of RotaTeq® in Reducing Hospitalizations and Emergency Department (ED) Visits

Per-Protocol Analysis (PP)

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Reduction %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>95%*</td>
<td>[92.97]</td>
</tr>
<tr>
<td>G2</td>
<td>88%</td>
<td>[&lt;0.99]</td>
</tr>
<tr>
<td>G3</td>
<td>93%*</td>
<td>[49.99]</td>
</tr>
<tr>
<td>G4</td>
<td>89%*</td>
<td>[52.98]</td>
</tr>
<tr>
<td>G9</td>
<td>100%*</td>
<td>[67.100]</td>
</tr>
</tbody>
</table>

Intention-to-Treat Analysis (ITT)

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Reduction %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>92%*</td>
<td>[88.95]</td>
</tr>
<tr>
<td>G2</td>
<td>92%*</td>
<td>[35.99]</td>
</tr>
<tr>
<td>G3</td>
<td>85%*</td>
<td>[50.96]</td>
</tr>
<tr>
<td>G4</td>
<td>90%*</td>
<td>[57.98]</td>
</tr>
<tr>
<td>G9</td>
<td>92%*</td>
<td>[66.98]</td>
</tr>
</tbody>
</table>

N=68,038 vaccinated infants 6-12 weeks who received 3 doses of vaccine or placebo in the PP population, or at least one dose in the ITT population


* Statistically significant
RotaTeq®: Efficacy between Doses

≥82% protection against hospitalisations and ED visits after administration of the first dose; provided complete 3-dose regimen is administered\(^1\)

REST + FES: Overall Efficacy of RotaTeq® against RVGE-Associated Hospitalizations and ED Visits, Regardless of Rotavirus Serotype, in the Per-Protocol (PP)† Population

In the Finnish Extension Study (FES)*, nearly 21,000 infants were followed for up to 3.1 years after their third dose in REST

- **REST** (up to 2 years): 95% (95% CI: 92, 97)
- **REST+FES** (up to 3.1 years): 94% (95% CI: 91, 96)

† Infants who received 3 doses of vaccine or placebo; follow-up started 14 days after dose 3.

## Clinical Trials and Demonstration Project in Developing Countries

<table>
<thead>
<tr>
<th>Studies</th>
<th>Country/Region</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Latin America</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral poliovirus Concomitant use</td>
<td>Brazil, Mexico, Costa Rica, and Guatemala</td>
<td>Completed¹</td>
</tr>
<tr>
<td><strong>Latin America</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open-label effectiveness demonstration</td>
<td>Nicaragua</td>
<td>Completed²</td>
</tr>
<tr>
<td><strong>Africa</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-positive</td>
<td>Tanzania, Zambia, Uganda, Zimbabwe, Botswana</td>
<td>Started Dec 2009</td>
</tr>
<tr>
<td><strong>Asia + Africa</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy, immunogenicity, and safety trial</td>
<td>Bangladesh, Ghana, Kenya, Mali, Vietnam</td>
<td>Completed³,⁴</td>
</tr>
</tbody>
</table>

RotaTeq®: Phase III Study of Efficacy, Safety, and Immunogenicity

Ghana (PI: Dr. George Armah)
Site: rural Navrongo DSS

Kenya (PI: Dr. Rob Breiman)
Site: rural Kisumu DSS

Mali (PI: Dr. Samba Sow)
Site: urban Bamako

Bangladesh (PI: Dr. K. Zaman)
Site: rural Matlab HDSS

Vietnam (PI: Dr. Duc Anh)
Site: urban and periurban Nha Trang DSS
Details of Clinical Trial of RotaTeq® in the Developing World

Africa

- Enrollment began April 28, 2007
- 5,468 infants vaccinated

Asia

- Enrollment began March 29, 2007
- 2,036 infants vaccinated

- Follow-up completed March 31, 2009
  - Nearly all children through at least one year of age
  - Majority of children through second year of life
- No safety concerns identified by the Data Safety Monitoring Board (DSMB)

Africa: Armah et al., 2010. The Lancet, in press.
Asia: Zaman et al., 2010. The Lancet, in press.
RotaTeq®: Efficacy and Severe RVGE Cases Prevented

**Efficacy and Severe RVGE Cases Prevented**

**First Year of Life**
- **Africa**: Efficacy: 64.2% (21V:58P) (95% CI: 40, 79)
- **Asia**: Efficacy: 51.0% (19V:38P) (95% CI: 13, 73)

**Up to 2 Years**
- **Africa**: Efficacy: 39.4% (79V:129P) (95% CI: 19, 55)
- **Asia**: Efficacy: 48.3% (38V:71P) (95% CI: 22, 66)

Severe RVGE Cases per 100 Vaccinees

- **Africa (First Year of Life)**
  - **Placebo**: 2.0 cases prevented
  - **Vaccine**: 1.5 cases prevented

- **Asia (First Year of Life)**
  - **Placebo**: 2.2 episodes prevented
  - **Vaccine**: 3.6 episodes prevented

- **Africa (Up to 2 Years)**
  - **Placebo**: 7 episodes prevented
  - **Vaccine**: 5 episodes prevented

- **Asia (Up to 2 Years)**
  - **Placebo**: 2 episodes prevented
  - **Vaccine**: 2 episodes prevented

Africa: Armah et al., 2010. The Lancet, in press.
Asia: Zaman et al., 2010. The Lancet, in press.
## Efficacy of RotaTeq® against RVGE in Africa and Asia

<table>
<thead>
<tr>
<th>RVGE</th>
<th>Year 1 Efficacy (95% CI)</th>
<th>Year 2 Efficacy (95% CI)</th>
<th>Total Follow-up Period Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Very Severe”</td>
<td>67.1% (37.0, 83.9)</td>
<td>33.8% (-15.7, 62.8)</td>
<td>51.2% (26.3, 68.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>58.9% (40.0, 72.3)</td>
<td>28.1% (2.3, 47.2)</td>
<td>42.5% (27.4, 54.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any severity</td>
<td>51.2% (36.6, 62.6)</td>
<td>21.1% (3.7, 35.5)</td>
<td>33.9% (22.7, 43.5)</td>
</tr>
</tbody>
</table>

Overview of Worldwide Efficacy of RotaTeq® against Severe RVGE, Regardless of Serotype

Vaccine Efficacy

<table>
<thead>
<tr>
<th>Region</th>
<th>Vaccine Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>100%</td>
</tr>
<tr>
<td>Finland</td>
<td>100%</td>
</tr>
<tr>
<td>US</td>
<td>100%</td>
</tr>
<tr>
<td>Finland</td>
<td>100%</td>
</tr>
<tr>
<td>Africa</td>
<td>50%</td>
</tr>
<tr>
<td>Asia</td>
<td>40%</td>
</tr>
</tbody>
</table>

Scoring System:
- Clark clinical score ≥17
- Vesikari clinical score ≥11

Data Collection:
- AGE Report Card
- Vaccination Report Cards and by home visits at days 7, 14, and 42
- Healthcare centers soliciting information from parents

Safety data Collection:
- Home visits at days 7 and 14 after any dose; monthly visits until end-of-study
- First full rotavirus season

Follow-up:
- First full rotavirus season
- First Year of Life

Large-Scale US Post-Licensure Safety Studies

- Useful to continue to assure medical community of vaccine safety
- Passive surveillance
  1. Vaccine Adverse Event Reporting System (VAERS) (CDC/FDA)
     - >21 million doses distributed through August 2008
- Database controlled studies
  2. Merck Safety Surveillance Study (Merck)
     - >210,000 doses administered
     - Large insured population
     - Automated medical claims database
  3. Vaccine Safety Datalink (CDC)
     - >207,000 doses administered (May 2008)
     - >650,000 doses administered (Oct 2009)
     - 8 health maintenance organizations (HMOs)
     - Large, linked database

Summary of Safety Profile of RotaTeq® since Licensure from Multiple Studies

• Large-scale safety surveillance in separate populations
  – Passive studies (VAERS)
  – Database controlled studies (Merck-sponsored, VSD)
• FDA/CDC VAERS
  – No safety concern of IS noted 21 days after any dose
  – 22,274,551 million doses (June 2008 ACIP¹)
• Merck-Sponsored & Vaccine Safety Datalink² (CDC study)
  – No increased risk of IS or other prespecified endpoints within 30 days or 1-7 post any dose
  – Over 860,000 doses analyzed to date in both studies

Effectiveness against Rotavirus Gastroenteritis (RVGE) in Routine Practice in a US National Claims Database

(2007 and 2008 Seasons)

Infants who received 3 doses of RotaTeq® vs DTaP recipients who did not

<table>
<thead>
<tr>
<th>Medical Setting</th>
<th>Incidence Rate per 1000 Person Years</th>
<th>Vaccine Effectiveness (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RotaTeq® (N = 33,140) (7700 person years)</td>
<td>0</td>
<td>100% (87 - 100)</td>
</tr>
<tr>
<td>Concurrent DTaP Cohort (N = 27,954) (5831 person years)</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>Combined (Hospitalizations + ED visits)</td>
<td>0.1</td>
<td>96% (76 - 100)</td>
</tr>
<tr>
<td>Physician Office Visit</td>
<td>3.4</td>
<td></td>
</tr>
</tbody>
</table>

Continued Decrease in 2009 Number of Seasonal RVGE Claims among Infants <1 Year of Age after Introduction of RotaTeq® in a Large Insured US Population (January 1, 2002 – June 30, 2009)

72% Decrease in Seasonal Average Peak RVGE Claims in 2008 & 2009

US Licensure February 2006
ACIP Recommendation MMWR August 2006

Mast et al., 44th National Immunization Conference, Atlanta, Georgia, April 19-22, 2010.
6 Independent US Hospital-Based Studies Reported 85-95% Reduction in Rotavirus Cases

2008 vs Previous Years

- Kansas City, MO⁴: 88% reduction in Hospitalization
- Galveston, TX³: 94% reduction in Hospitalization or ED
- Philadelphia, PA¹: 87% reduction in Community acquired cases (Children's Hospital of Philadelphia)
- New York State⁶: 85% reduction in Hospitalization/ED
- Worcester, MA⁵: 95% reduction in Hospitalization, ED, Outpatient
- Philadelphia, PA²: 94% reduction in Hospitalization (St Chris)

Conclusions – Postlicensure Safety Studies and Effectiveness Data

**Safety**
- Human-bovine formulation well tolerated
  - No statistically significant association detected between RotaTeq® and intussusception or Kawasaki Disease for any follow-up period or comparison
  - No specific general safety concerns
- Extensive prelicensure and active (>3 years) postlicensure safety data from US (>21 million doses)

**Impact**
- Vaccine 82-100% effective in routine use in US
- Consistent data from multiple sources show dramatic reduction in rotavirus disease in ~3 years of use in US
  - ↓ Rotavirus hospitalizations and emergency room visits
  - ↓ Laboratory testing for rotavirus
  - ↓ Costs associated with rotavirus disease
Summary

- RotaTeq® is consistently highly efficacious against RVGE of any severity (74%) and severe disease (98%), and also highly efficacious (>95%) in preventing hospitalizations and ED visits across studies, geographic regions, and populations (including premature infants).

- RotaTeq® substantially reduces the rate (91-100%) of hospitalizations and ED visits between doses starting ≥14 days Postdose 1.
  - Early onset of protection against severe RVGE may be particularly beneficial to infants vaccinated during RV seasons.

- RotaTeq® is efficacious for up 3 years postvaccination.

- RotaTeq® effectively reduces healthcare encounters in a postlicensure setting.

- RotaTeq® significantly reduces severe RVGE in African and Asian children through the first two years of life.
  - RotaTeq® can have significant impact on public health globally