Secondary Efficacy Endpoints of the Pentavalent Rotavirus Vaccine against Gastroenteritis in Asia

K Zaman, Dang Duc Anh, John C Victor, Md Yunus, Sunheang Shin, Shams El Arifeen, Mustafizur Rahman, Tajul Islam Bari, Kristen Lewis, David A Sack, A Duncan Steele, Kathleen M Neuzil, Max Ciarlet
Study sites

Dhaka

Matlab
Rotavirus in Bangladesh

- Estimated 2.4 million cases of rotavirus diarrhoea annually in children <5 years of age
- 40,000 hospitalizations for rotavirus AGE at icddr,b hospitals each year
  - ~ 40% of diarrhoea hospitalizations in children
  - Represents about 15% of community cases (0.5/child/year)
- Up to 10,000 deaths in children <5 each year

Black et al, 1982
Bangladesh has high Rotavirus Disease Burden$^{1,2}$

- It is estimated that in Bangladesh, Rotavirus Gastroenteritis is accountable for:
  - About 30% of Hospital admissions for Acute Gastroenteritis
  - 40% of outpatient visits due to Acute Gastroenteritis.

Number of diarrhea and rotavirus admissions in children aged 0-23 months to Matlab hospital from the icddr,b Demographic Surveillance area, 2011-2013

<table>
<thead>
<tr>
<th>Age (month)</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diarrh adm</td>
<td>RV adm</td>
<td>Diarrh adm</td>
</tr>
<tr>
<td>0-2</td>
<td>29</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td>3-5</td>
<td>65</td>
<td>13</td>
<td>97</td>
</tr>
<tr>
<td>6-11</td>
<td>260</td>
<td>107</td>
<td>281</td>
</tr>
<tr>
<td>12-17</td>
<td>156</td>
<td>65</td>
<td>156</td>
</tr>
<tr>
<td>18-23</td>
<td>65</td>
<td>22</td>
<td>60</td>
</tr>
<tr>
<td>Total</td>
<td>575</td>
<td>215</td>
<td>(37.4%)</td>
</tr>
</tbody>
</table>
Rotavirus in Bangladesh

- Year-round transmission, with seasonal peaks
  - January-February winter peak similar to US
  - July-August summer peak during monsoon

Zaman et al, Vaccine 2009
Age distribution of rotavirus cases in Matlab
Notes

- Graph shows the combined typing results from Dhaka and Matlab hospital surveillance
- Rotavirus year starts in June and ends in May of the following year
- Mixed infections excluded from this analysis
RotaTeq®: Phase III Study of Efficacy, Safety, and Immunogenicity

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

Vietnam (PI: Dr. Duc Anh)
Site: urban and periurban Nha Trang DSS
Objectives

To evaluate the secondary efficacy endpoints of the pentavalent rotavirus vaccine (PRV), RotaTeq®, against gastroenteritis in 2 countries in Asia
Blood collection- Pre-vaccination and 14 days after dose 3

- 2 ml blood by the medical officer
- Transferred to Matlab Hospital at +2 to +8°C
- Serum stored at -70°C
Study Design/Update

- Study period: March 2007 - March 2009
- Randomized, double-blinded, placebo controlled
- Study site: Matlab icddr,b intervention area and Vietnam Nha Trang
- Sample Size: 1136 + 900 = 2036
- 3 oral doses of RotaTeq™/placebo at 6-, 10-, 14-week (EPI schedule)
- Blood collection for immunogenicity
- Follow up weekly/monthly
- Surveillance for RV diarrhoea
Methods – Outcome Measures

Primary outcome: severe rotavirus gastroenteritis (RVGE) caused by any rotavirus serotype

Gastroenteritis: diarrhoea (3 or more looser-than-normal stools within 24 hours) and/or vomiting

Clinical Data Collection

Severity: Score ≥11 on 20-point Vesikari scale

Confirmation: Stools collected and analyzed for rotavirus by standard EIA

Rotavirus positive samples tested by RT-PCR to determine the G and P genotypes
Methods – secondary efficacy endpoints

- Efficacy against rotavirus gastroenteritis (RVGE) of any severity
- Efficacy against severe gastroenteritis of any aetiology
- Type-specific efficacy against severe RVGE through the first year of life, during the second year of life, and through the total follow-up period of nearly 2 years
2,119 subjects screened

2,036 subjects vaccinated (96%)

Vaccine group (n=1018)
At least one dose of vaccine

Participants included in and completing immunogenicity cohort (n=131)

Participants excluded from PPE analysis (n=27)

Participants included in the PPE analysis (n=991)

Placebo group (n=1018)
At least one dose of placebo

Participants included in and completing immunogenicity cohort (n=132)

Participants excluded from PPE analysis (n=40)

Participants included in the PPE analysis (n=978)

PPE - per protocol efficacy
Rotavirus Genotypes distribution in Bangladesh and Vietnam

(A) Bangladesh

- G1P[8]: 19.7%
- G2P[4]: 31.6%
- G9P[8]: 30.4%
- G12P[6]: 15.8%
- Others: 2.5%

(B) Vietnam

- G3P[8]: 62.8%
- G2P[4]: 23.2%
- G1P[8]: 14%

(A) Bangladesh

- G1P[8]: 2.5%
- G2P[4]: 31.6%
- G9P[8]: 15.8%
- G12P[6]: 30.4%
- Others: 19.7%
### Efficacy of RotaTeq® against Severe RVGE of Any Serotype in the Total Follow-up Period by Country

<table>
<thead>
<tr>
<th>Country</th>
<th>Follow-up (person-years)</th>
<th>Number of Severe RVGE Cases*</th>
<th>Efficacy (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vaccine</td>
<td>Placebo</td>
<td>Vaccine</td>
<td>Placebo</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>713</td>
<td>693</td>
<td>33</td>
<td>56</td>
</tr>
<tr>
<td>Vietnam</td>
<td>486</td>
<td>465</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Pooled</td>
<td>1198</td>
<td>1158</td>
<td>38</td>
<td>71</td>
</tr>
</tbody>
</table>

*Vesikari score of ≥11

Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in Asia: a randomised, double-blind, placebo-controlled trial


Lancet, 2010
### Efficacy of PRV against RVGE of any severity regardless of serotype in all countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Total Follow-Up Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Efficacy (95% CI)</td>
<td>Cases</td>
</tr>
<tr>
<td></td>
<td>Vaccine/Placebo</td>
<td>(95% CI)</td>
<td>Vaccine/placebo</td>
</tr>
<tr>
<td>Asia</td>
<td>29/63</td>
<td>54.7 (28.6, 71.9)</td>
<td>36/47</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>27/51</td>
<td>47.5 (14.7, 68.4)</td>
<td>28/35</td>
</tr>
<tr>
<td>Vietnam</td>
<td>2/12</td>
<td>83.8 (27.1, 98.2)</td>
<td>8/12</td>
</tr>
<tr>
<td>Country</td>
<td>Year 1 Cases</td>
<td>Year 1 Efficacy (95% CI)</td>
<td>Year 2 Cases</td>
</tr>
<tr>
<td>------------</td>
<td>--------------</td>
<td>--------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Asia</td>
<td>46/62</td>
<td>26.7 (&lt;0.0, 51.1)</td>
<td>26/34</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>41/53</td>
<td>23.5 (&lt;0.0, 50.4)</td>
<td>20/24</td>
</tr>
<tr>
<td>Vietnam</td>
<td>5/9</td>
<td>45.3 (&lt;0.0, 85.6)</td>
<td>6/10</td>
</tr>
</tbody>
</table>

Efficacy of PRV against severe gastroenteritis (score ≥11 Vesikari Clinical Scoring System) of any etiology in all countries.
Efficacy of PRV against severe RVGE (score ≥11 Vesikari Score) according to vaccine types, non-vaccine G types, non-vaccine P types

<table>
<thead>
<tr>
<th>Types</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Total Follow-Up Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Efficacy (95% CI)</td>
<td>Cases</td>
</tr>
<tr>
<td>Vaccine Types</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccine/Placebo</td>
<td>34/65</td>
<td>52.2 (12.4, 74.9)</td>
<td>17/30</td>
</tr>
<tr>
<td>Non-Vaccine G Types</td>
<td>6/16</td>
<td>62.8 (&lt;0.0, 88.1)</td>
<td>7/10</td>
</tr>
<tr>
<td>Non-Vaccine P Types</td>
<td>6/10</td>
<td>40.3 (&lt;0.0, 82.2)</td>
<td>2/6</td>
</tr>
</tbody>
</table>
## Type-specific efficacy of PRV against severe RVGE (≥11 Vesikari Clinical Scoring System)

<table>
<thead>
<tr>
<th>Rotavirus genotype</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Total Follow-Up Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Efficacy</td>
<td>Cases</td>
</tr>
<tr>
<td></td>
<td>Vaccine/Placebo</td>
<td></td>
<td>Vaccine/Placebo</td>
</tr>
<tr>
<td>G1</td>
<td>6/9</td>
<td>33.6</td>
<td>6/13</td>
</tr>
<tr>
<td>G2</td>
<td>4/6</td>
<td>33.5</td>
<td>1/1</td>
</tr>
<tr>
<td>G3</td>
<td>1/5</td>
<td>80.1</td>
<td>3/7</td>
</tr>
<tr>
<td>G9</td>
<td>6/15</td>
<td>60.3</td>
<td>6/8</td>
</tr>
<tr>
<td>P[8]</td>
<td>13/28</td>
<td>54.3*</td>
<td>15/26</td>
</tr>
<tr>
<td>P[4]</td>
<td>5/8</td>
<td>37.8</td>
<td>1/2</td>
</tr>
<tr>
<td>P[6]</td>
<td>1/2</td>
<td>50.1*</td>
<td>1/3</td>
</tr>
</tbody>
</table>

* P <0.05
Conclusion

- PRV significantly reduced RVGE through nearly two years of follow up; higher in first year of life compared to second year.

- Modest reductions against gastroenteritis of any aetiologies.

- PRV provides protection against severe-RVGE caused by diverse rotavirus genotypes.
This trial was funded by PATH’s Rotavirus Vaccine Program, established in 2003 with a generous grant from the GAVI Alliance. The trial was sponsored by Merck & Co., Inc.
icddr,b thanks its Core Donors

Australian Aid

Canada

SWEDEN

UKaid from the British people