Rotavirus Vaccines for Children in Developing Countries: Results of Clinical Trials

9th International Rotavirus Symposium

August 2, 2010
GAVI and the Rotavirus Vaccine Program

A public/private global health partnership launched in 2000 to improve access to immunization for children in impoverished countries.

PATH Rotavirus Vaccine Program

- Accelerated Development and Introduction Plan (ADIP) established with generous grant from GAVI Alliance.
- Partnership with WHO and US CDC.
- Mission: *To reduce child mortality and morbidity from diarrheal disease by accelerating the availability of rotavirus vaccines appropriate for use in developing countries.*
Study Partners

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Low resource countries in Asia and Africa carry the greatest rotavirus disease burden

Global annual rotavirus deaths: 527,000—predominantly in developing countries
Clinical trials of rotavirus vaccines in Africa and Asia

- In 2005, RCT showed high efficacy of Rotarix™ and RotaTeq® in U.S., Latin America and Europe.
- In 2005, recommendation for use of RV in regions above, and call for data in other regions.
- From 2005-2009, 3 RCT conducted that included over 12,000 children at sites in 7 countries.

Source: WHO Statistical Information System (WHOSIS)
Clinical trials of rotavirus vaccines in Africa and Asia

- Publications of primary efficacy results:
  - Madhi/Cunliffe, Steele et al. January 28, 2010 NEJM
  - Zaman, Anh, Victor et al. August 6, 2010 The Lancet
  - Armah, Sow, Breiman et al. August 6, 2010 The Lancet

- Multiple presentations to WHO and at international meetings
  - ESPID 2009 and 2010
  - VED 2009
  - ASTMH 2009
  - WHO’s SAGE, Global Vaccine Research Forum, Global Immunization Meeting

- 9 posters at this symposium
A primary goal: Design and execute clinical trials that will inform policy

- Which vaccine?
- Where? Are the populations broadly representative?
- Who? Are the participants broadly representative?
- Efficacy or effectiveness?
- Outcome measure?
- Logistical considerations
SAGE recommends the inclusion of rotavirus vaccination of infants into all national immunization programs.

Rotavirus vaccination

Data from trials in Latin America, Europe and the United States of 2 oral, live, attenuated rotavirus vaccines, Rotarix (GlaxoSmithKline) and RotaTeq (Merck & Co., Inc.) were reviewed by SAGE in 2005. Noting the variable efficacy of live, oral vaccines in different populations, SAGE considered that the introduction of vaccines would be appropriate only in regions where successful phase III efficacy trials had been conducted. SAGE therefore recommended that rotavirus vaccines be included in national immunization programmes in countries where data on vaccine efficacy suggest a significant public health impact; SAGE also noted the need to urgently generate such data in Africa and Asia.

Vaccination antirotavirus

En 2005, le SAGE a examiné les données d’essais cliniques menés en Amérique latine, en Europe et aux États Unis concernant 2 vaccins antirotavirus vivants atténués pour voie orale, le Rotarix (GlaxoSmithKline) et le RotaTeq (Merck & Co. Inc.). Notant que l’efficacité des vaccins vivants pour voie orale variait selon les populations, le SAGE a estimé judicieux de les adopter seulement dans les Régions où des essais d’efficacité de phase III avaient été effectués avec succès. Il a par conséquent recommandé que les vaccins antirotavirus soient inclus dans les programmes de vaccination nationaux des pays où les données sur l’efficacité des vaccins semblent indiquer qu’ils ont des répercussions importantes en santé publique; il a par ailleurs noté qu’il était urgent d’obtenir des données de ce type en Afrique et en Asie.
# Efficacy against severe rotavirus gastroenteritis in the first year of life

<table>
<thead>
<tr>
<th>Region</th>
<th>Vaccine</th>
<th>Countries</th>
<th>VE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>Rotarix™</td>
<td>Malawi, South Africa</td>
<td>61.7</td>
<td>44.0, 73.2</td>
</tr>
<tr>
<td>Africa</td>
<td>RotaTeq®</td>
<td>Ghana, Kenya, Mali</td>
<td>64.2</td>
<td>40.2, 79.4</td>
</tr>
<tr>
<td>Asia</td>
<td>RotaTeq®</td>
<td>Bangladesh, Vietnam</td>
<td>51.0</td>
<td>12.8, 73.3</td>
</tr>
</tbody>
</table>

† Madhi/Cunliffe, Steele et al. January 28, 2010 NEJM
How will efficacy translate into impact on a population level?

Estimates of cumulative impact of rotavirus vaccines, 2010-2025

Source: “Accelerating the Introduction of Rotavirus Vaccines into GAVI-Eligible Countries: Investment Case for GAVI Secretariat,” Submitted by PATH’s Rotavirus Vaccine Program in collaboration with WHO and the US CDC, October 2006.
From 1999 – 2009: Over 5 million children died from rotavirus disease

Global annual rotavirus deaths: 527,000—predominantly in developing countries


Global mortality figure: WHO. Weekly Epidemiological Record. 82(32).
There is a lot of disease left to prevent: Will clinical trial data help us to understand and maximize impact of vaccines?

- Regional and country differences
- Apparent waning of efficacy in second year of life
- OPV and maternal antibody effects
- Correlate of protection or predictors of vaccine failure
- Co-infections
- HIV effects
- Strain diversity
- Timing of infections
- Timing of vaccine doses
Clinical Trials: Lessons Learned

- Dr. George Armah: Additional measures of impact
- Dr. Nigel Cunliffe: Strain diversity
- Dr. K. Zaman: Highlights from Asia trial
PRV in low resource countries: Measuring the impact

- Dr. George Armah
## Efficacy of RotaTeq® against Severe RVGE of Any Serotype in the First Year of Life by Country, Per Protocol and Intention to Treat Populations

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of Severe RVGE Cases PP</th>
<th>Number of Severe RVGE Cases ITT</th>
<th>Efficacy (%) Per Protocol PP</th>
<th>Efficacy (%) Per Protocol ITT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vaccine</td>
<td>Placebo</td>
<td>Vaccine</td>
<td>Placebo</td>
</tr>
<tr>
<td>Ghana</td>
<td>15</td>
<td>42</td>
<td>15</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>(35.5, 81.9)</td>
<td></td>
<td>(35.8, 82.0)</td>
<td></td>
</tr>
<tr>
<td>Kenya</td>
<td>2</td>
<td>12</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>(25.5, 98.2)</td>
<td></td>
<td>(14.1, 95.7)</td>
<td></td>
</tr>
<tr>
<td>Mali</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>(&lt;0.0, 81.6)</td>
<td></td>
<td>(&lt;0.0, 87.7)</td>
<td></td>
</tr>
</tbody>
</table>

Efficacy of PRV against All Cause Severe Gastroenteritis in Africa and Asia
Combined 5 Country Analyses

<table>
<thead>
<tr>
<th>All Cause GE</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>Severe (Vesikari≥11)</td>
<td><strong>23.0% (5.4%, 37.3)</strong></td>
<td><strong>11.2% (-17.7, 33.0)</strong></td>
<td><strong>15.3% (1.7, 27.1)</strong></td>
</tr>
</tbody>
</table>

Breiman, R., Efficacy of the Oral Pentavalent Rotavirus Vaccine: Ad-hoc Analyses from the 5 Sites Participating in the Africa and Asia Clinical Trials. 9th International Rotavirus Symposium.
Vaccine “Probe” Analysis

- Given vaccine efficacy of 23% against all cause severe GE during first year of life, and assuming vaccine efficacy of 59% against severe RVGE during first year of life:

  If \( X = \) the proportion of severe GE which is caused by rotavirus, then 
  \[ X = \frac{0.23}{0.59} = 38.9\% \]

- Our results suggest that approximately 39% of severe GE was caused by rotavirus during the first year of life for participants of the trial.
Alternative measures of impact: Kenya

- Data on acute gastroenteritis (GE) episodes were collected during monthly home-visits to remind mothers to bring children into clinic
  - Data collection included illnesses, hospitalizations, and medication use in the past 2 weeks
  - >15,000 monthly household visits were made
  - Severe and moderate dehydration were defined according to WHO IMCI definitions
### Vaccine Efficacy (VE) of PRV against All Diarrhoea Episodes and Dehydration as Determined by Household Visits through the Entire Follow-up Period

<table>
<thead>
<tr>
<th></th>
<th>Vaccine</th>
<th>Placebo</th>
<th>Vaccine Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong># Monthly follow-up visits</strong></td>
<td>7,655</td>
<td>7,648</td>
<td></td>
</tr>
<tr>
<td>All AGE episodes</td>
<td>1653(22%)</td>
<td>1775(23%)</td>
<td>7.0% (1.3 – 12)</td>
</tr>
<tr>
<td>AGE with severe dehydration</td>
<td>92 (1.2%)</td>
<td>123 (1.6%)</td>
<td>25.3% (57 – 98)</td>
</tr>
<tr>
<td>AGE with moderate dehydration</td>
<td>259 (3.4%)</td>
<td>271 (3.5%)</td>
<td>4.5% (-13 – 19)</td>
</tr>
</tbody>
</table>

1\textsuperscript{st} year of life: VE against severe dehydration: 29% (3-48%)

2\textsuperscript{nd} year of life: VE against severe dehydration: 15% (-43%-50%)
Applying the VE for severe-RVGE at healthcare facilities (63.9%) to the VE of PRV against GE with severe-dehydration at home visits (25%), we can deduce that 39% of the severe GE illness occurring at Kenyan homes, in the Siaya district, were due to rotavirus.
Additional measures of impact

- Ad-hoc analyses confirm rotavirus as an important cause of severe diarrheal disease in low resource countries.
- In Kenya, rotavirus vaccine prevented a significant number of severe diarrhea episodes among children who never attended the clinic.
Strain Diversity

- Dr. Nigel Cunliffe
Rotavirus Genotype Strain Distribution (%) among RVGE Cases, Regardless of Severity, by Country

Ghana, n=139
- G1P[8]: 33.8%
- G1P[6]: 29.5%
- G2P[4]: 11.5%
- G8P[6]: 11.5%
- G9P[6]: 5.8%
- G9P[8]: 5.8%
- Others: 7.9%

Kenya, n=93
- G2P[6]: 36.6%
- G1P[6]: 22.6%
- G2P[4]: 20.3%
- Others: 11.5%

Mali, n=370
- G3P[8]: 54.3%
- G2P[6]: 22.2%
- G3P[6]: 8.4%
- G1P[6]: 4.6%
- Others: 6.2%

Bangladesh, n=158
- G1P[8]: 31.6%
- G2P[4]: 30.4%
- G9P[6]: 19.7%
- Others: 15.8%

Vietnam, n=43
- G3P[8]: 62.8%
- G3P[6]: 14%
- Others: 23.2%

n, total number of rotavirus positive stool samples
Serotype distribution among placebo recipients in study sites during trial

Madhi/Cunliffe, Steele et al. January 28, 2010 NEJM
Vaccine efficacy against severe rotavirus GE due to different serotypes: South Africa

- G1WT: 69.8%
- G2: 91.8%
- G3: 83.5%
- G8: 100%
- G12: 75.3%
- P[4]: 94.5%
- P[6]: 75.3%
- P[8]: 70.8%
- Non G1: 85.9%

N = 1944 (Rotarix)
N = 960 (Placebo)
Vaccine efficacy against severe rotavirus GE due to different serotypes: Malawi

N = 1030 (Rotarix)
N = 483 (Placebo)
Distribution of rotavirus G types, Blantyre, Malawi 1997 - 2007

N = 1130

N = 1130

Courtesy of Nigel Cunliffe; presented in Mauritius July 2008
Strain Diversity

- Tremendous strain diversity in trial sites, but efficacy generally maintained across strains
- Natural variation in strains from year-to-year
- Need to be cautious in attributing changes in relative percentages of strains isolated to vaccine introduction
- Studies planned to further characterize strains isolated as part of clinical trials
Impact of PRV in low resource countries in Asia

Dr. K. Zaman
## Efficacy against RVGE and GE in Asia

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Total Follow-up Period Efficacy (95% CI)</th>
<th>Rate Reduction per 100 person-years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any severity RVGE</td>
<td>42.5 (21.1–58.4)</td>
<td>4.1 (1.8–6.4)</td>
</tr>
<tr>
<td>Severe RVGE (Vesikari ≥ 11)</td>
<td>48.3 (22.3–66.1)</td>
<td>3.0 (1.2–4.8)</td>
</tr>
<tr>
<td>Severe RVGE (Vesikari ≥ 15)</td>
<td>70.0 (31.8–88.3)</td>
<td>1.5 (0.6–2.6)</td>
</tr>
<tr>
<td>Severe GE any etiology</td>
<td>27.0 (1.6–46.0)</td>
<td>3.0 (0.3–5.8)</td>
</tr>
</tbody>
</table>

Zaman, Anh, Victor et al. August 6, 2010 The Lancet
# Efficacy of RotaTeq® against Severe RVGE of Any Serotype in the First Year of Life 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>346</td>
<td>343</td>
<td>17</td>
<td>31</td>
</tr>
<tr>
<td>Vietnam‡</td>
<td>260</td>
<td>252</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Pooled</td>
<td>606</td>
<td>595</td>
<td>19</td>
<td>38</td>
</tr>
</tbody>
</table>

*Vesikari score of ≥11

† N = 556 evaluable subjects in the vaccine group; 556 evaluable subjects in the placebo group.
‡ N = 440 evaluable subjects in the vaccine group; 428 evaluable subjects in the placebo group.
Efficacy and severe RVGE cases prevented through the first year of life

- Asia: 2.0 cases prevented
- Bangladesh: 2.5 cases prevented
- Vietnam: 1.2 cases prevented
Impact of PRV in low resource countries in Asia

- Efficacy of PRV in Asia increases as disease severity increases

- Immunogenicity and efficacy lower in Bangladesh than Vietnam

- Due to higher incidence of severe disease, absolute number of RVGE cases prevented per 100 vaccinees was greater in Bangladesh than Vietnam