Rotavirus Vaccines: Effectiveness & Impact

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CDC, Atlanta
Rotavirus Vaccines – RV1 & RV5

Human rotavirus

Rotarix (RV1)

Bovine rotavirus with single human rotavirus gene substitution

G1
G2
P[8]

G1
G3
G4

RotaTeq (RV5)
RV5 & RV1 Efficacy

• High and middle income countries
  – Good efficacy (85-100%) against severe RV diarrhea in pivotal trials

• Low income countries
  – Moderate efficacy (50-70%) against severe RV diarrhea in Asia and Africa
  – Trend toward reduced efficacy in 2\textsuperscript{nd} year of life
RV5: Strain-Specific Efficacy

Vesikari et al, NEJM, January 2006; Heaton, 7th Rotavirus Symposia, June 2006
RV1: Strain Specific Efficacy

Vaccine efficacy (%)

<table>
<thead>
<tr>
<th></th>
<th>Clinical</th>
<th>Vesikari scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>All wild-types</td>
<td>85 [71.7; 92.4]</td>
<td>85 [71.1; 92.7]</td>
</tr>
<tr>
<td>G1 wild-type</td>
<td>92 [74.1; 98.4]</td>
<td>91 [70.5; 98.2]</td>
</tr>
<tr>
<td>G9</td>
<td>91 [61.7; 98.9]</td>
<td>91 [61.7; 98.9]</td>
</tr>
<tr>
<td>G3</td>
<td>88 [8.3; 99.7]</td>
<td>86 [9.3; 99.7]</td>
</tr>
</tbody>
</table>

Key Remaining Issues

• Vaccine performance in routine use
  – Will we see indirect benefits?

• Effectiveness in low income settings
  – Will protection last in second year of life?

• Protection against diverse strains
  – Will vaccination lead to emergence of new strains?

• Impact on diarrhea mortality
  – Not assessed in trials
Challenge in Evaluating Rotavirus Vaccines

- No correlate of protection
  - Need efficacy/effectiveness data to evaluate vaccine performance
Countries with Rotavirus Vaccine in their Immunization Schedule*

Brazil: Mar 2006
Venezuela: Apr 2006
Panama: Mar 2006
ELS: Oct 2006
Mexico: May 2007
Nicaragua: Oct 2006
Ecuador, Oct 2007
Bolivia, Aug 2008
United States – Feb 2006 and Jun 2008

* Also Australia and few countries in Europe
Vaccine Performance in Routine Use – US Experience
Cortes J et al (unpublished data)
RotaTeq Effectiveness -- USA

• Case-control study (February-June 2008)
• Cases
  – Children <23 months with acute gastroenteritis (AGE) who tested positive for rotavirus by EIA
• Hospital Controls (two groups)
  – Rotavirus-negative AGE cases
  – Children with acute respiratory infection (ARI)

Boom et al.  IDSA 2008
Controls

• Rotavirus-negative AGE controls
  – Easy to identify as part of AGE surveillance
  – Similar health care seeking behavior to cases
  – Potential for misclassification if EIA fails to detect some rotavirus cases

• ARI controls
  – Abundant during same season as rotavirus cases
  – Require additional effort to enroll
# RotaTeq Effectiveness -- USA

<table>
<thead>
<tr>
<th>Vaccine Effectiveness</th>
<th>RV-negative AGE</th>
<th>ARI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 dose</td>
<td>65% (-11%, 89%)</td>
<td>65% (-7%, 89%)</td>
</tr>
<tr>
<td>2 doses</td>
<td>82% (15%, 96%)</td>
<td>72% (-37%, 94%)</td>
</tr>
<tr>
<td>3 doses</td>
<td>89% (70%, 96%)</td>
<td>85% (55%, 95%)</td>
</tr>
</tbody>
</table>
National Laboratory Surveillance

• Network of ~90 sentinel laboratories

• Weekly reporting
  – Number of rotavirus tests performed
  – Number that test rotavirus positive

Tate et al, Pediatrics 2008
Number of Total and Positive Rotavirus Tests, 2000-2008

- **Total N Tests**
- **Total N Positive**

RotaTeq introduced

- **2000**: Total N Tests and Total N Positive levels are relatively low.
- **2001**: A significant increase in the number of tests and positives, indicating a rise in rotavirus cases.
- **2002**: Slight decrease in cases followed by another peak.
- **2003**: Similar pattern as 2001, with a rise then fall in cases.
- **2004**: Another increase in cases, peaking in the middle of the year.
- **2005**: Similar pattern to previous years, with a peak around the middle of the year.
- **2006**: Further increase in cases, peaking near the end of the year.
- **2007**: Peak near the end of the year, similar to 2006.
- **2008**: The highest peak ever recorded, indicating a significant increase in rotavirus cases.

The overall trend shows a consistent increase in rotavirus cases, especially after the introduction of RotaTeq in 2006.
Active Rotavirus Surveillance

Payne et al, PAS 2009
Total AGE and Rotavirus AGE Hospitalizations NVSN, 2006-2008

Number of cases

2006: 181
- Total AGE
- Rotavirus: 91 (50% Rota+)

2007: 179
- Total AGE
- Rotavirus: 81 (45% Rota+)

2008: 139
- Total AGE
- Rotavirus: 9 (6% Rota+)
# Rotavirus Hospitalization Rates and Vaccine Coverage, 2006-2008

<table>
<thead>
<tr>
<th>Year</th>
<th>Rotavirus hospitalization rate (per 10,000 children &lt; 3 yrs)</th>
<th>Vaccine coverage (&gt;=1 doses among children &lt; 3 yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>22.5</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>2007</td>
<td>26.8</td>
<td>19%</td>
</tr>
<tr>
<td>2008</td>
<td>3.7</td>
<td>36%</td>
</tr>
</tbody>
</table>

*84% decline in rotavirus hospitalization rate

36% vaccine uptake*
### Age-Specific Rotavirus Hospitalization Rate Reduction and Vaccine Coverage

<table>
<thead>
<tr>
<th>Age</th>
<th>Decline in rotavirus hospitalization rate (2008 vs. 2006)</th>
<th>Rotavirus vaccine coverage in 2008 (&gt;=1 dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year</td>
<td>66%</td>
<td>56%</td>
</tr>
<tr>
<td>1 -&lt; 2 years</td>
<td>95%</td>
<td>44%</td>
</tr>
<tr>
<td>&gt;=5 years</td>
<td>85%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

*This age cohort was ineligible to receive rotavirus vaccine*
Was the Decline in Rotavirus Activity in 2008 all Due to Vaccine?
Vaccine Performance in Low Income Setting -- Nicaragua
Nicaragua

- Birth cohort: ~150,000
- Annual GNI: ~980 US$
- Low income country (GAVI eligible)
RotaTeq Launch in Nicaragua

• Donation of vaccine for 3-year period

• First GAVI country to introduce vaccine

• Launched in same calendar year as FDA approval/US launch
RotaTeq Effectiveness -- Nicaragua

- Case-control study (July 2007-June 2008)
- Active surveillance for AGE in children under 2 years at 4 pediatric hospitals

- Cases
  - overnight hospitalization for EIA confirmed rotavirus diarrhea

- 3 neighborhood & 3 hospital controls per case
  - matched on date of birth (+/- 4 weeks)

* Patel et al. JAMA, 2009
### RotaTeq Effectiveness -- Nicaragua

<table>
<thead>
<tr>
<th>No. of doses</th>
<th>Vaccine Effectiveness (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neighborhood</td>
</tr>
<tr>
<td>1 Dose</td>
<td>50% (12, 71)</td>
</tr>
<tr>
<td>2 Doses</td>
<td>49% (13, 70)</td>
</tr>
<tr>
<td>3 Doses</td>
<td>45% (14, 65)</td>
</tr>
</tbody>
</table>

* Patel et al. JAMA, 2009
### Effectiveness of 3 Doses of RotaTeq, by Age (Time Since Vaccination)

<table>
<thead>
<tr>
<th>Age</th>
<th>Vaccine effectiveness (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-11 months</td>
<td>69% (37, 95)</td>
</tr>
<tr>
<td>12-18 months</td>
<td>32% (-47, 68)</td>
</tr>
</tbody>
</table>

*Patel et al. JAMA, 2009*
RV1 Effectiveness Against G2P4 Strains

Ricardo O. Gurgel,*† Luis E. Cuevas,†‡
Sarah C.F. Vieira,* Vanessa C.F. Barros,*
Paula B. Fontes,* Eduardo F. Salustino,*
Osamu Nakagomi,§ Toyoko Nakagomi,§
Winifred Dove,† Nigel Cunliffe,†
and Charles A. Hart†

We identified 21 rotaviruses in 129 patients with diarrhea in a Brazilian city with high rotavirus vaccine coverage. All rotaviruses were genotype P[4]G2 with 1 mixed infection with P[NT]G9. Although virus predominance could have occurred randomly, the vaccine may be less protective against P[4]G2. Prospective surveillance is urgently needed.

Apparent extinction of non-G2 rotavirus strains from circulation in Recife, Brazil, after the introduction of rotavirus vaccine

T. Nakagomi · L. E. Cuevas · R. G. Gurgel · S. H. Elrokhsi · Y. A. Belkhir ·
M. Abugalia · W. Dove · F. M. U. Montenegro · J. B. Correia ·
O. Nakagomi · N. A. Cunliffe · C. A. Hart

*Gurgel et al EID 13(10):1571; 2007

*Nakagomi et al, Arch Vir 153(3); 2008
# RV1 Effectiveness Against Severe G2P[4] Rotavirus Diarrhea, by Age

<table>
<thead>
<tr>
<th>Age Group</th>
<th>VE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cases 6-11 months of age</strong></td>
<td></td>
</tr>
<tr>
<td>Rotavirus negative controls</td>
<td>77 (42 to 91)</td>
</tr>
<tr>
<td>ARI controls</td>
<td>77 (43 to 90)</td>
</tr>
<tr>
<td><strong>Cases &gt;=12 months of age</strong></td>
<td></td>
</tr>
<tr>
<td>Rotavirus negative controls</td>
<td>-24 (-190 to 47)</td>
</tr>
<tr>
<td>ARI controls</td>
<td>15 (-101 to 64)</td>
</tr>
</tbody>
</table>

T Nakagomi et al, VED 2009
G2P4 in Brazil -- Could it be Natural Shift?

El Salvador

2006: Pre-vaccine

81%

2008: Post-vaccine

P[8]G1
72%

*Patel et al EID 14(5):863; 2008
Future Priorities

• Further assess indirect benefits and possible changes in disease epidemiology (e.g., age shift)

• Fully assess duration of vaccine protection and burden of disease in 2\textsuperscript{nd} and later years of life

• Assess long-term vaccine impact on strains

• As African and Asian countries adopt vaccine, assess effectiveness in these challenging settings
Immune response to RV1 decreases with Income Level of the Country

### Table 2. Summary of the Immunogenicity Data (Mean Geometric Mean Concentrations [GMC] and Seroconversion) for Rotarix by World Bank Income Group

<table>
<thead>
<tr>
<th>Income group</th>
<th>No. of countries</th>
<th>GMC 1–2 months after second dose, a U/mL</th>
<th>Seroconversion, b %</th>
<th>Seroconversion, b %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Difference from high-income group (95% CI)</td>
<td>Mean</td>
<td>Difference from high-income group (95% CI)</td>
</tr>
<tr>
<td>High</td>
<td>9</td>
<td>205.6</td>
<td>...</td>
<td>86</td>
</tr>
<tr>
<td>Upper-middle</td>
<td>6</td>
<td>106.6</td>
<td>−99.1 (−195.0 to −3.0)</td>
<td>72</td>
</tr>
<tr>
<td>Lower-middle</td>
<td>6</td>
<td>90.5</td>
<td>−115.1 (−224.0 to −5.9)</td>
<td>75</td>
</tr>
<tr>
<td>Low</td>
<td>3</td>
<td>67.3</td>
<td>−138.3 (−276.4 to −1.0)</td>
<td>63</td>
</tr>
</tbody>
</table>

**NOTE.** Data were obtained GlaxoSmithKline [7]. CI, confidence interval.

- a Serum rotavirus IgA antibody concentrations 1–2 months after dose 2.
- b Defined as a GMC ≥20 U/mL.
Immune Response to RV1 by Age at Vaccination, S. Africa

6 week dose does little!

Acknowledgments

- PATH
- GAVI
- WHO/PAHO
- Ministries of Health (Nicaragua, Mexico)