Rotavirus Vaccines

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Disease burden: United States

• Rotavirus accounted for approximately 2.7 million cases, 500,000 doctor visits, 270,000 ED visits, 70,000 hospitalizations, and 20-60 deaths each year.

• About 1 of every 50 children born in the United States was hospitalized with dehydration secondary to rotavirus infection.

Disease burden: Developing countries

• Rotavirus accounts for approximately 500,000 deaths each year.

• Therefore, about 2,000 children die every day from rotavirus-induced dehydration.

• Rotavirus is one of the most important killers of infants and young children in the world.
Immunity to natural rotavirus infection determines strategies to make a rotavirus vaccine

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Clinical characteristics

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Rotavirus</th>
<th>Non-rotavirus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>96%*</td>
<td>58%</td>
</tr>
<tr>
<td>Fever</td>
<td>77%</td>
<td>61%</td>
</tr>
<tr>
<td>Dehydration</td>
<td>83%*</td>
<td>40%</td>
</tr>
</tbody>
</table>

* p<0.01

Unique rotaviruses isolated from:

- Humans
- Mice
- Pigs
- Cows
- Antelope
- Dogs
- Monkeys
- Cats
- Horses
- Rats
- Rabbits
- Turkeys
- Chickens
- Goats
- Sheep
### RRV: Clinical trials

<table>
<thead>
<tr>
<th>Site</th>
<th>N</th>
<th>Severe</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td>200</td>
<td>67</td>
<td>38</td>
</tr>
<tr>
<td>Sweden</td>
<td>106</td>
<td>80</td>
<td>48</td>
</tr>
<tr>
<td>Rochester</td>
<td>176</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Venezuela</td>
<td>320</td>
<td>90</td>
<td>64</td>
</tr>
<tr>
<td>Rochester</td>
<td>223</td>
<td>-</td>
<td>66</td>
</tr>
</tbody>
</table>

### WC3: Clinical trials

<table>
<thead>
<tr>
<th>Site</th>
<th>N</th>
<th>Severe</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Philadelphia</td>
<td>104</td>
<td>100</td>
<td>76</td>
</tr>
<tr>
<td>Cincinnati</td>
<td>206</td>
<td>41</td>
<td>17</td>
</tr>
<tr>
<td>C. Africa Rep</td>
<td>472</td>
<td>36</td>
<td>0</td>
</tr>
</tbody>
</table>

### Construction of animal x human viruses

- Determine the rotavirus proteins responsible for evoking virus-specific neutralizing antibodies.
- Determine the rotavirus proteins responsible for viral virulence.
Rotavirus Structure

- Double-layered outer shell around a central core of genetic material (double-stranded RNA)
- Outer layer made of VP4 (P) and VP7 (G) neutralizing proteins

Figure adapted from Estes MK. J Infect Dis. 1996;174(Suppl 1):S37-S46.

Rotavirus gene reassortment *in vitro*

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>A x B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

Monkey Kidney Cells

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Functional properties of rotavirus proteins

- VP4 (P type) and VP7 (G type) each independently evoke antibodies that neutralize rotavirus infectivity
- Prevalent G and P types include G1, G2, G3, G4, G9, and P1
- Four genes required for virulence.
  Advance beyond Theiler's attenuation.
Simian rotavirus-based vaccine

Vaccine: Rotashield

Company: Wyeth-Lederle

Method of attenuation: Heterologous host virus (simian strain RRV).

Simian rotavirus-based vaccine

Construction: Contains 4 rotavirus strains.

3 simian-human reassortant viruses containing a simian (strain RRV) backbone and human rotavirus genes encoding G1, G2, and G4.

1 virus is simian strain RRV (similar to human G3 strains)
Rotashield - VAERS

- 15 cases if INT following Rotashield were reported to VAERS
- 13/15 cases occurred after the 1st dose
- 11/13 cases within 7 days of vaccine admin.
- 8/13 cases in children 2-3 months of age
Relative risk of INT by age after dose 1

<table>
<thead>
<tr>
<th>Interval</th>
<th>1-2 mo.</th>
<th>3-5 mo.</th>
<th>6-8 mo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-7 days</td>
<td>27*</td>
<td>25*</td>
<td>30*</td>
</tr>
<tr>
<td>8-14 days</td>
<td>6.9*</td>
<td>4.6*</td>
<td>2.4</td>
</tr>
<tr>
<td>15-21 days</td>
<td>1.2</td>
<td>0.8</td>
<td>1.0</td>
</tr>
</tbody>
</table>


Rotashield - ACIP

Withdrawal of Rotavirus Vaccine Recommendation

In July 1999, CDC recommended that health-care providers and parents postpone use of the meso rotavirus vaccine-rotavirus (Rotashield®), Wyeth Laboratories, Inc., Marietta, Pennsylvania, for infants, at least until November 1999. This action was based on reports to the Vaccine Adverse Event Reporting System of intussusception in type of bowel obstruction that occurs when the bowel folds in on itself) among 15 infants who received rotavirus vaccine. Also at that time, the manufacturer, in consultation with the Food and Drug Administration, voluntarily ceased further distribution of the vaccine.

On October 22, 1999, the Advisory Committee on Immunization Practices (ACIP).

Risks and benefits of Rotashield in US

Assumes risk of INT is 1 in 10,000 vaccine recipients

Estimates per million children

<table>
<thead>
<tr>
<th></th>
<th>No vaccine</th>
<th>Vaccine</th>
<th>Diff.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctor visits</td>
<td>143,000</td>
<td>30,000</td>
<td>113,000</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>16,000</td>
<td>100</td>
<td>15,900</td>
</tr>
<tr>
<td>Intussusception</td>
<td>580</td>
<td>680</td>
<td>(100)</td>
</tr>
<tr>
<td>Deaths</td>
<td>6-12</td>
<td>1</td>
<td>5-11</td>
</tr>
</tbody>
</table>
Rotashield for the developing world

- Results of a WHO meeting in February 2000, four months after the withdrawal of RotaShield from the United States

Bovine rotavirus-based vaccine

Vaccine: RotaTeq

Company: Merck and Co.

Method of attenuation: Heterologous host virus (bovine strain WC3).

RotaTeq vaccine trial in infants

Construction: Contains 5 rotavirus strains.

5 bovine-human reassortant rotaviruses containing a bovine rotavirus (strain WC-3) backbone and human rotavirus genes encoding either vp4 (P1) or vp7 proteins (G1, G2, G3, and G4).
Bovine rotavirus-based vaccine

Dose: $1.6 \times 10^6$ pfu per strain ($8 \times 10^6$ pfu total)

Administration: Three doses administered by mouth at 2, 4, and 6 months of age.

70,301 infants enrolled in 11 countries

Results of Phase III trial: RotaTeq

- Efficacy, any rotavirus disease: 74% (CI: 67-80)
- Efficacy, severe rotavirus disease: 98% (CI: 88-100).
- Efficacy, rota. hospitalization: 94%
- Efficacy, rota. doctor visits: 86%

Results of Phase III trial: Safety

- No clinically significant increase in fever, vomiting, diarrhea, listlessness, lethargy, or poor feeding vs. placebo


Results of Phase III trial: Intussusception

- Within 14 days of any dose: 1 V, 1P
- Within 42 days of any dose: 6V, 5P
- Within 1 year of any dose: 12V, 15P
- Post-licensure data


RotaTeq for the developing world

- Nicaraguan demonstration project of Clinton-Gates
- Completion of trials in Bangladesh, Vietnam, Ghana, and Mali.
- Impact of Bill and Melinda Gates
**Attenuated human rotavirus vaccine**

**Vaccine:** Strain RIX 4414 (RotaRix)

**Company:** GlaxoSmithKline

**Method of attenuation:** Cell culture adaptation (strain 89-12 further attenuated by serial passage in cell culture)

**Dose:** $5 \times 10^4$ pfu per strain ($5 \times 10^4$ pfu total)

**Administration:** Two doses administered by mouth at about 2-3 and 4-5 months of age.

**Construction:** Contains P1G1 only.

- Protection against rotavirus serotype G1 by inclusion of G1
- Protection against rotavirus serotypes G3, G4, and G9 by inclusion of P1.
RotaRix

- Study of 63,225 infants orally inoculated at 2 and 4 months of age
- Performed in 11 Latin American countries and Finland.


Results of Phase III trial: RotaRix

- Efficacy, severe rotavirus disease: 85% (CI: 72-92).
- Efficacy, rota. hospitalization: 85% (CI: 70-94)


Conclusions

- Current rotavirus vaccines include both bovine-human reassortants and attenuated human rotavirus strains
- Both strategies safely prevent rotavirus-induced disease and don’t cause intussusception
Recent development: Porcine circovirus

- Eric Delwart deep sequencing technology
- PCV-1 in RotaRix and response by FDA
- PCV-1 and PCV-2 sequences in RotaTeq
- Application of technology to grocery store
- Assessment of risk