Rotavirus Vaccines -- Current Status & Value of a Correlate of Protection

Umesh D. Parashar
CDC, Atlanta, GA
Two New Rotavirus Vaccines Licensed in 2006

- Efficacy of 85%-98% against severe disease in Europe and Americas

Vesikari et al and Ruiz-Palacios et al, NEJM 2006
National RV introductions, 79 countries*

*As of Oct 1, 2015

- Not Gavi-eligible [43]
- Gavi-eligible [36]
Impact on All-Cause and Rotavirus-Specific Gastroenteritis Hospitalizations in USA

![Graph showing hospitalizations](image_url)

Payne DC, unpublished 2014
Impact on Rotavirus and All-Cause Gastroenteritis Hospitalizations in Children, El Salvador

70-80% reduction in rotavirus hospitalizations children < 5 years

![Graph showing reduction in hospitalizations after vaccination]

De Palma, BMJ, 2010
Effect of Rotavirus Vaccination on Death from Childhood Diarrhea in Mexico

Richardson et al, NEJM 2010
How well will live oral rotavirus vaccines work in the developing world?
Hurdles to Immunization for a Live Oral Rotavirus Vaccine

Factors that lower viral titer

- Breast milk
- Stomach acid
- Maternal antibodies
- OPV

Factors that impair immune response

- Malnutrition - Zn, Vit A
- Interfering microbes - viruses and bacteria
- Other infections - HIV, malaria, TBC

Slide: R Glass
## Moderate Efficacy of Rotavirus Vaccines in Africa and Asia

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Region</th>
<th>Countries</th>
<th>Efficacy (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RotaTeq</td>
<td>Africa</td>
<td>Ghana, Kenya, Mali</td>
<td>64% (40%-79%)</td>
</tr>
<tr>
<td>RotaTeq</td>
<td>Asia</td>
<td>Bangladesh, Vietnam</td>
<td>51% (13%-73%)</td>
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<tr>
<td>Rotarix</td>
<td>Africa</td>
<td>South Africa, Malawi</td>
<td>62% (44%-73%)</td>
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</table>

Armah et al. Lancet 2010  
Zaman et al. Lancet 2010  
Madhi et al NEJM 2010
Monthly count of diarrhea hospitalizations among children <5 years of age, Soweto, South Africa, 2006-2013

Groome et al, CID in press
Diarrhea hospitalizations by month among children <5 years of age at 24 district hospitals, Rwanda, 2009-2014

Annual reductions of 17%-23% in diarrhea hospitalizations following rotavirus vaccine introduction

Ngabo et al Lancet GH, 2016
How well will vaccines protect against range of strains?
RotaTeq is Pentavalent & Rotarix is Monovalent

RotaTeq

- G1
- G2
- G3
- G4
- P[8]

Five bovine-human rotavirus strains

Rotarix

- G1P[8]

Single human rotavirus strain
Seroconversion rates for serum neutralizing antibodies differed against human serotypes in RotaTeq, REST Trial
RotaTeq efficacy was similar against different G types

**Table 2. Reduction in the Numbers of Hospitalizations and Emergency Department Visits in the Per-Protocol Population of the Large-Scale Study, According to G Serotype Identified in the Subject’s Stool.**

<table>
<thead>
<tr>
<th>Serotype</th>
<th>No. of Cases of Rotavirus Gastroenteritis</th>
<th>Percent Rate Reduction (95% CI)</th>
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<tbody>
<tr>
<td></td>
<td>Vaccine Group (N=34,035)</td>
<td>Placebo Group (N=34,003)</td>
</tr>
<tr>
<td>G1</td>
<td>16</td>
<td>328</td>
</tr>
<tr>
<td>G2</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>G3</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>G4</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>G9</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>G12</td>
<td>0</td>
<td>1</td>
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Great Strain Diversity in African Rotarix Trial

Malawi

- G1P8: 27%
- G9P8: 24.19%
- G8P4: 24%
- G12P6: 6%
- G2+P4: 6%
- Other: 13%

South Africa

- G1P8: 57%
- G12P6: 10%
- G8P4: 17%
- G2P4: 17%
- Other: 13%

Madhi et al. NEJM 2010; Steele et al BMC Pediatrics 2013
Rotarix (G1P8) Efficacy Similar Against Disease Caused by Vaccine & Non-Vaccine Strains

Efficacy

Madhi et al. NEJM 2010; Steele et al BMC Pediatrics 2013
## High Rotarix (G1P8) Effectiveness against Non-Vaccine Strains in Several Countries

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<tr>
<td>Bolivia</td>
<td>G9P[8]</td>
<td>84% (64, 92)</td>
</tr>
<tr>
<td></td>
<td>G2P[4]</td>
<td>71% (19, 90)</td>
</tr>
<tr>
<td></td>
<td>G3P[8]</td>
<td>92% (60, 98)</td>
</tr>
<tr>
<td></td>
<td>G9P[6]</td>
<td>87% (-10, 98)</td>
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Value of a Correlate of Protection
Key Issue – Vaccine Supply and Cost

- Big Pharma
  - Merck
  - GSK
- Emerging Manufactures
  - Brazil
  - Indonesia
  - China
  - Germany
  - India
**Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian infants: a randomised, double-blind, placebo-controlled trial**


<table>
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<tr>
<th>Endpoints</th>
<th>ROTAVAC N= 4354</th>
<th>Placebo N= 2187</th>
<th>Vaccine Efficacy % (95% CI)</th>
<th>p value</th>
</tr>
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<td>Severe RV GE requiring hospitalization# or supervised rehydration therapy§</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Till 2 yrs of age</td>
<td>92 (2%)</td>
<td>102 (5%)</td>
<td>55.6% (40.5, 66.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Till 1 yr of age</td>
<td>57 (1%)</td>
<td>65 (3%)</td>
<td>56.3% (36.7, 69.9)</td>
<td>&lt;0.0001</td>
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Drug firms cut vaccine prices to the developing world*

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<th>United States</th>
<th>PAHO</th>
<th>GAVI / UNICEF</th>
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<td><strong>GSK</strong></td>
<td>$120 – $200/child</td>
<td>$15/child</td>
<td>$5/child [up to 125 M doses; over 5 yrs]</td>
</tr>
<tr>
<td><strong>Merck</strong></td>
<td>$120 – $200/child</td>
<td>$15.45/child</td>
<td>$10.50/child [for volume over 30 M]</td>
</tr>
<tr>
<td><strong>Bharat Biotech</strong></td>
<td>–</td>
<td>–</td>
<td>~ $3/child</td>
</tr>
</tbody>
</table>

- 3 doses/child: Merck, Bharat Biotech
- 2 doses/child: GSK

* Applies to GAVI tenders
How will we license future rotavirus vaccines?

• All trials to date have been placebo controlled and relied on clinical endpoint
• Placebo controlled trials ethically complex given widespread global rollout of vaccine
• Non-inferiority studies with clinical endpoints large and expensive to conduct
• An immunologic correlate will simplify testing
Testing of interventions to improve rotavirus vaccine performance in developing countries

• Additional doses of vaccine
  – 3rd dose of RV1
  – Booster dose at 9 month of life

• Alternate vaccination schedules
  – Delaying vaccination to reduce interference with maternally acquire antibody

• Supplementation with micronutrients (e.g., zinc) or probiotics
Immunogenicity of Different RV1 Schedules in Ghana

Study Group

Group 1 – 2 RV1 doses at 6 and 10 weeks
Group 2 – 2 RV1 doses at 10 and 14 weeks
Group 3 – 3 RV1 doses at 6, 10, and 14 weeks

Proportion with IgA titers ≥ 20 U/mL post-vaccination (%)

G1 vs. G2: difference = 8.5, \( p = 0.16 \)
G1 vs. G3: difference = 14.5, \( p = 0.01 \)

Armah et al, JID
Serum IgA as a Correlate?
Relationship between under-5 child mortality and immune response to rotavirus vaccination

Relationship between anti-rotavirus serum IgA geometric mean titers/concentrations and rotavirus vaccine efficacy

Decline in vaccine efficacy between year 1 (open circles) and year 2 (solid circles) after rotavirus vaccination, by location and titers rotavirus IgA geometric mean titers/concentrations.

2-year efficacy = 44% (30-55)
Mean efficacy decline = 66%

2-year efficacy = 85% (82-90)
Mean efficacy decline = 7%

Summary

• Good impact of rotavirus vaccination
  – Efficacy lower in developing countries, but still substantial impact
  – Evidence of heterotypic protection

• Correlate of protection will
  – Simplify testing of future rotavirus vaccines
  – Help test interventions to improve vaccine performance