Vaccines against Rotavirus & Norovirus

Umesh D. Parashar
CDC, Atlanta, GA
Rotavirus is the Leading Cause Of Severe Diarrhea in Children <5 Years Globally
Rotavirus is a Major Cause of Child Mortality Worldwide -- ~200,000 Annual Deaths

1 dot = 100 deaths
First Rotavirus Vaccine (Rotashield) Implemented in 1998 in US
A Setback – Rotashield Withdrawn Within 1 Year Because of Intussusception

1 intussusception per 10,000 vaccinated infants
Will other oral rotavirus vaccines also cause intussusception?
Two New Rotavirus Vaccines Licensed in 2006

- Trials of 60-70,000 infants each
- No increased risk of intussusception
- Efficacy of 85%-98% against severe disease

Vesikari et al and Ruiz-Palacios et al, NEJM 2006
National RV introductions, 81 countries*

*As of May 1, 2016
Rotavirus Vaccines in USA

- Feb 2006 – RotaTeq recommended
- June 2008 – Rotarix recommended
Impact on All-Cause and Rotavirus-Specific Gastroenteritis Hospitalizations in USA

Payne DC, unpublished 2014
## Age-Specific Rotavirus Hospitalization Rate Reduction and Vaccine Coverage, USA

<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>
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</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>2 -&lt; 3 years</td>
<td>85%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

*This age cohort was ineligible to receive rotavirus vaccine*

*Herd immunity?*
Impact on Rotavirus and All-Cause Gastroenteritis Hospitalizations in Children, El Salvador

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

De Palma, BMJ, 2010
Herd Protection: Reduction in Rotavirus among UNVACCINATED Age Groups in El Salvador

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<tr>
<td>&lt; 1 year</td>
<td>84% (80 to 88)</td>
<td>76%</td>
</tr>
<tr>
<td>1 year</td>
<td>86% (82 to 89)</td>
<td>84%</td>
</tr>
<tr>
<td>2 years</td>
<td>65% (50 to 75)</td>
<td>0</td>
</tr>
<tr>
<td>3 years</td>
<td>41% (-7 to 68)</td>
<td>0</td>
</tr>
<tr>
<td>4 years</td>
<td>68% (29 to 85)</td>
<td>0</td>
</tr>
</tbody>
</table>

These age cohorts were ineligible to receive rotavirus vaccine

Yen et al, PIDJ 2011
First evidence of impact of vaccine on diarrhea mortality in Mexico
Effect of Rotavirus Vaccination on Death from Childhood Diarrhea in Mexico

Vaccine Introduced (May 2007)

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
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>
</tr>
<tr>
<td>Rotarix</td>
<td>Africa</td>
<td>South Africa, Malawi</td>
<td>62% (44%-73%)</td>
</tr>
</tbody>
</table>

Armah et al. Lancet 2010  
Zaman et al. Lancet 2010  
Madhi et al NEJM 2010
What does 50% efficacy mean?

Would you rather have 99% of my salary or 1% of Bill Gates’?
Despite lower efficacy, rotavirus vaccines prevent more disease in high burden settings.

Madhi, NEJM 2010
GAVI-supported RV introductions, 35 countries

**Americas**
- Bolivia (2008)
- Guyana (2010)
- Haiti (2013)
- Honduras (2009)
- Nicaragua (2006)

**Europe**
- Armenia (2012)
- Georgia (2013)
- Moldova (2012)

**Middle East**
- Tajikistan (2015)
- Uzbekistan (2014)
- Yemen (2012)

**Africa**
- Angola (2014)
- Burkina Faso (2013)
- Burundi (2013)
- Cameroon (2014)
- Djibouti (2014)
- Eritrea (2014)
- Ethiopia (2013)
- The Gambia (2013)
- Ghana (2012)
- Guinea-Bissau
- Kenya (2014)
- Liberia
- Madagascar (2014)
- Malawi (2012)
- Mali (2014)
- Mauritania (2014)
- Mozambique
- Niger (2014)
- Rwanda (2012)
- Senegal (2014)
- Sierra Leone (2014)
- Sudan (2011)
- Tanzania (2012)
- Togo (2014)
- Zambia (2013)
- Zimbabwe (2014)
Rwanda

- Introduced RotaTeq (RV5) in May 2012
- 3 doses given at 6, 10, and 14 weeks of age
Decline in childhood diarrhea hospitalizations at 27 district hospitals in Rwanda after rotavirus vaccine introduction.
Decline in proportion of childhood hospitalizations caused by diarrhea in Rwanda

- Decline in proportion of childhood hospitalizations caused by diarrhea in Rwanda.

Graph showing:
- Total Hospital Admissions
- AGE Admissions
- % of Admissions Due to AGE

Key highlights:
- 2009: 19% of Admissions
- 2010: 20% of Admissions
- 2011: 19% of Admissions
- 2012: 19% of Admissions
- 2013: 12% of Admissions
- 2014: 13% of Admissions

VACCINE intervention noted in 2010-2011.
Ghana

• Introduced Rotarix (RV1) in April 2012
• 2 doses given at 6 and 10 weeks of age
Decline in rotavirus hospitalizations after vaccine implementation in Ghana

Armah et al CID 2016
How well will vaccines protect against range of strains?
RotaTeq is Pentavalent & Rotarix is Monovalent

**RotaTeq**

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

Five bovine-human rotavirus strains

**Rotarix**

G1P[8]

Single human rotavirus strain
Rotarix (G1P8) Efficacy Similar Against Vaccine & Non-Vaccine Strains in African Trial

Madhi et al. NEJM 2010
Increase in G2P4 Prevalence after Use of Rotarix (G1P8) in Brazil Raises Concern


*Gurgel et al, EID, 13(10), 2007

RAPID COMMUNICATION

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

*Nakagomi et al, Arch Vir 153(3); 2008
Is increasing prevalence of G2P[4] in Brazil caused by vaccine pressure or is it just natural variation?

El Salvador Rotarix, 2006 (opposite of Brazil)

Guatemala (no vaccine)

Honduras (no vaccine)

Patel et al. EID 2009
High Rotarix (G1P8) Effectiveness against Non-Vaccine Strains in Several Countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Post-vaccine strains</th>
<th>Vaccine Effectiveness (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>G2P[4]</td>
<td>85% (54, 95)</td>
</tr>
<tr>
<td>Mexico</td>
<td>G9P[4]</td>
<td>94% (16, 100)</td>
</tr>
<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>
</tr>
</tbody>
</table>
Will new Rotavirus Vaccines cause Intussusception?
Post-Licensure Intussusception Data

• Mexico, Brazil, US, and Australia have reported a low risk of intussusception
  – ~1-6 cases per 100,000 vaccinated
  – With both vaccines

• **Key Question** – How does the risk compare with benefits of vaccination?
## Benefits vs. Risks of Vaccination

<table>
<thead>
<tr>
<th>Country</th>
<th>Diarrhea Hospitalizations (Deaths) Prevented</th>
<th>Intussusception Cases (Deaths) Caused</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mexico</td>
<td>11,600 (663)</td>
<td>41 (2)</td>
</tr>
<tr>
<td>Brazil</td>
<td>69,600 (640)</td>
<td>55 (3)</td>
</tr>
<tr>
<td>Australia</td>
<td>7,000 (0)</td>
<td>6 (0)</td>
</tr>
<tr>
<td>US</td>
<td>53,000 (16)</td>
<td>48 (0)</td>
</tr>
</tbody>
</table>

*
Key Messages

✓ Marked impact of rotavirus vaccines in affluent countries
  ▪ Indirect benefits to unvaccinated groups
  ▪ Reduction of diarrhea mortality

✓ Efficacy lower in low income settings
  ▪ But impact greater because of high burden
  ▪ Early data from African countries promising

✓ Both vaccines show broad protection against strains included and not included in vaccine

✓ Low risk of intussusception seen with both vaccines
  ▪ Outweighed by benefits of vaccination
Norovirus Vaccines
Norovirus is the leading cause of outbreaks of AGE.
Norovirus is now the leading cause of severe gastroenteritis in US children

- 21% of severe AGE episodes caused by norovirus
- ~1 million annual pediatric medical care visits
  - $273 million in health care costs
Norovirus causes severe disease in both young children & the elderly
GI.1 intranasal

Norovirus Vaccine against Experimental Human Norwalk Virus Illness


GI.1/GII.4 intramuscular

Norovirus Vaccine Against Experimental Human GII.4 Virus Illness: A Challenge Study in Healthy Adults

# IM bivalent (GI.1, GII.4) vaccine efficacy

<table>
<thead>
<tr>
<th>Illness Severity Infected</th>
<th>Vaccine (N=50)</th>
<th>Placebo (N=48)</th>
<th>% Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>20.0%</td>
<td>37.5%</td>
<td>47% (-4%, 73%)</td>
</tr>
<tr>
<td>Mod-severe</td>
<td>6.0%</td>
<td>18.8%</td>
<td>68% (-11%, 91%)</td>
</tr>
<tr>
<td>Severe</td>
<td>0%</td>
<td>8.3%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Bernstein 2015 JID
Challenges for a norovirus vaccine

- **Target** groups?
  - Infants
  - Elderly
  - Travelers
  - Foodhandlers

- **Duration** of protection?

- Protection against multiple **genotypes**?

- Need to be updated to keep up with viral **evolution**?

Acknowledgements

PATH
PAHO/WHO
Ministries of Health
GAVI Alliance
BMGF