Rotavirus Vaccines: Progress & Challenges

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Outline

• Burden of rotavirus
• Withdrawn Rotashield vaccine
• Current vaccines – RotaTeq and Rotarix
• Remaining issues & challenges
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• Burden of rotavirus
• Withdrawn Rotashield vaccine
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Diarrhea is a Leading Cause of Child Mortality Worldwide

- Diarrhea: 15%
- Pneumonia: 19%
- Neonatal: 37%
- Non-communicable: 7%
- Other infections: 22%

~ 700,000 deaths/year
Rotavirus is the Leading Cause Of Severe Diarrhea in Children <5 Years Globally

Developed Countries

- Rotavirus
- Unknown
- Bacterial
- Other

Developing Countries

- Rotavirus
- Unknown
- Bacterial
- Other
Rotavirus is a Major Cause of Child Mortality Worldwide -- ~200,000-250,000 Annual Deaths

1 dot = 150 deaths
Outline

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Rotashield Implemented in 1998 in US
A Setback – Rotashield Withdrawn Within 1 Year Because of Association with Intussusception

On August 31, 1998, a tetravalent rhesus-based rotavirus vaccine (RotaShield™, Wyeth Laboratories, Inc., Marietta, Pennsylvania) (RRV-TV) was licensed in the United States for vaccination of infants. The Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics, and the American Academy of Family Physicians have recommended routine use of RRV-TV for vaccination of healthy infants (1,2). During September 1, 1998–July 7, 1999, 15 cases of intussusception (a bowel obstruction in which one segment of bowel becomes enfolded within another segment) among infants who had received RRV-TV were reported to the Vaccine Adverse Event Reporting System (VAERS). This report summarizes the clinical and epidemiologic features of these cases and preliminary data from ongoing studies of intussusception and rotavirus vaccine.

1 intussusception per 10,000 vaccinated infants
Intussusception Risk Greatest in First Week After Dose 1 of Rotashield

Risk elevated >30-fold during 3-7 days after dose 1

Murphy et al. NEJM 2001; 344:564-72.
Will other oral rotavirus vaccines also cause intussusception?
Will Other Oral Rotavirus Vaccines Also Cause Intussusception?

• Unique features of the rhesus strain in Rotashield®
  – High replication and shedding (>80%)
  – Fever in >30% and some vomiting/diarrhea

• No apparent link between intussusception and natural rotavirus infection

• Not possible to confirm absence of risk without large and expensive trials (~US $1 billion)
Outline

• Burden of rotavirus disease
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• Remaining issues
Two Oral 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
<table>
<thead>
<tr>
<th>Bovine rotavirus with single human rotavirus gene substitution</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image of G1" /></td>
</tr>
<tr>
<td><img src="image3.png" alt="Image of G3" /></td>
</tr>
<tr>
<td>P[8]</td>
</tr>
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</table>

3 doses
Rotarix (GSK)

Human rotavirus

G1P[8]

2 doses
2009 – WHO Global Recommendation

WHO Recommends Global Use of Rotavirus Vaccines
Decision Could Help Protect Millions of Children in Africa and Asia from Lethal Diarrheal Disease
National RV introductions by WHO region: 55 countries*

**National introductions by WHO region as of 28 March 2014**

**Not a WHO member state**

RV = rotavirus vaccine
Rotavirus Vaccines in USA

• Feb 2006 – RotaTeq recommended
• June 2008 – Rotarix recommended
Active Rotavirus Surveillance

- Active surveillance in 3 US counties
- Enrollment of inpatients, emergency room patients, and outpatients with AGE
- Fecal specimens obtained and tested for rotavirus
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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<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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<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>
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*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

Richardson et al, NEJM 2010
Mortality decline sustained for four years post vaccine implementation in Mexico

Countrywide vaccine introduction in May 2007
Rotavirus Vaccine Experience to Date

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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
Effect of Human Rotavirus Vaccine on Severe Diarrhea in African Infants

Shabir A. Madhi, M.D., Nigel A. Cunliffe, M.B., Ch.B., Ph.D., Duncan Steele, Ph.D., Desirée Witte, M.D., Mari Kirsten, M.D., Cheryl Louw, M.D., Bagrey Ngwira, M.D., John C. Victor, Ph.D., M.P.H., Paul H. Gillard, M.D., Brigitte B. Cheuvart, Ph.D., Htay H. Han, M.B., B.S., and Kathleen M. Neuzil, M.D., M.P.H.
Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in sub-Saharan Africa: a randomised, double-blind, placebo-controlled trial

George E Armaah, Samba O Sow, Robert F Breiman, Michael J Dallas, Milagritos D Tapia, Daniel R Feikin, Fred N Binka, A Duncan Steele, Kayla F Laserson, Nana A Ansah, Myron M Levine, Kristen Lewis, Michele L Coia, Margaret Attah-Poku, Joel Owendo, Stephen B Rivers, John C Victor, Geoffrey Nyambane, Abraham Hodgson, Florian Schödel, Max Ciarlet, Kathleen M Neuzil

Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in Asia: a randomised, double-blind, placebo-controlled trial

## 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>
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<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>
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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, RV1 Prevented More Severe Rotavirus AGE in Malawi Because of Higher Burden

Efficacy  77%

Madhi et al. NEJM 2010
How well will vaccines protect against range of strains?
RotaTeq is Pentavalent & Rotarix is Monovalent

**RotaTeq**

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

*Five bovine-human rotavirus strains*

**Rotarix**

- G1P[8]

*Single human rotavirus strain*
Great Strain Diversity in African Rotarix Trial

Malawi
- G1P8: 27%
- G8P4: 24.19%
- G9P8: 24%
- G2+P4: 5%
- Other: 6%

South Africa
- G1P8: 57%
- G8P4: 17%
- G2P4: 10%
- Other: 13%

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

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?

- **2005**: P[8]G9 94%
- **2007**: P[8]G1 91%

El Salvador Rotarix, 2006 (opposite of Brazil)

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

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<th>Post-vaccine strains</th>
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<tr>
<td>Mexico</td>
<td>G9P[4]</td>
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# High Rotarix (G1P8) Effectiveness against Non-Vaccine Strains in Several Countries

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<td>Mexico</td>
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<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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Will new Rotavirus Vaccines cause Intussusception?
Why Continue to Monitor Intussusception?

• Pre-licensure trials large
  – but powered to exclude large (~10-fold) increase in risk within 30-42 days of any dose

• Further monitoring to evaluate lower risk in shorter time periods after vaccination
Post-Licensure Intussusception Data

• Low risk of intussusception in many countries
  – US, Australia, Brazil, Mexico
  – ~1-6 excess cases per 100,000 vaccinated
  – With both vaccines
How does risk compare with benefits?
# Benefits vs. Risks of Vaccination

<table>
<thead>
<tr>
<th>Country</th>
<th>Diarrhea Hospitalizations (Deaths) Prevented</th>
<th>Intussusception Cases (Deaths) Caused</th>
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<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>
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</table>
Incredible years for new rotavirus vaccines!.... And great promise for the future!!
Many Opportunities Ahead -- Rotavirus Vaccines Implemented in Africa in 2012

GHANA

RWANDA

TANZANIA

MALAWI
Acknowledgements

PATH
PAHO/WHO
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