Rotavirus & Rotavirus Vaccines: Where are we now & where are we going?

8th International Rotavirus Symposium
Istanbul, June 2-4, 2008
Roger Glass, Fogarty Center, NIH
Essentials of Rotavirus

- Most common cause of severe diarrhea in children
- All children infected by age 5
- “Democratic” virus
- First infections symptomatic
- Natural immunity
- Limited strains in circulation
- Improvements in sanitation won’t prevent infection
1979-WHO Control of Diarrheal Diseases Program

“The world needs a rotavirus vaccine”
Estimated global distribution of the >500,000 annual deaths caused by rotavirus

1 dot = 1000 deaths

Parashar, 2005
The value of a rotavirus vaccine differs by the income level of the country!
Burden of Rotavirus in the US

Risk

- 1 : 10^6
- 1 : 80
- 1 : 7
- 1 : 0.9

Events

- 20-40 Deaths
- 60-70,000 Hospitalizations
- 500,000 Outpatient visits
- 3.2 Million episodes

Cost: $400 M medical; >$1 B total
Burden of Rotavirus in the US

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1 : 7
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Value of vaccine depends on direct vs. indirect costs
WHO’s Generic Protocol

Generic Protocol for rotavirus surveillance and disease burden estimation in developing countries

WHO

- Sentinel Hospital Surveillance
- Simple data collection
- Outcomes: Rates of rotavirus hospitalizations and/or % Rv positive
- Allows for strain characterization
- Foundation for surveying other outcomes (outpatient, costs, intussusception)

J. Bresee, et al.

<table>
<thead>
<tr>
<th>Sector/Cities</th>
<th>Hospitals</th>
<th>Specimens screened N</th>
<th>Rotavirus positives N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>North</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hanoi</td>
<td>National Children’s Hospital</td>
<td>1233</td>
<td>657</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>St. Paul’s Children’s Hospital</td>
<td>390</td>
<td>185</td>
<td>47</td>
</tr>
<tr>
<td><strong>Haiphong</strong></td>
<td>Children’s Hospital</td>
<td>886</td>
<td>531</td>
<td>60</td>
</tr>
<tr>
<td><strong>South</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Khanh Hoa</td>
<td>General Hospital</td>
<td>589</td>
<td>348</td>
<td>59</td>
</tr>
<tr>
<td>Ho Chi Minh City</td>
<td>General Pediatrics N. 1</td>
<td>1724</td>
<td>982</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>General Pediatrics N. 2</td>
<td>946</td>
<td>544</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>5768</strong></td>
<td><strong>3247</strong></td>
<td><strong>56</strong></td>
</tr>
</tbody>
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Van Mann, et all, JID, 2001
Rotavirus Hospitalizations in the Asian Rotavirus Surveillance Network

China: 41%
Korea
Taiwan: 41%
Vietnam: 60%
Hong Kong: 29%
Malaysia: 56%
Indonesia: 39%
Myanmar: 56%

Bresee 2003 EIDJ
Rotavirus Surveillance

In 1997, no countries had systemic surveillance for rotavirus or timely data on burden of disease

• In 2008, > 50 countries have established routine surveillance for rotavirus including assessment of strains
<table>
<thead>
<tr>
<th></th>
<th>Industrial World</th>
<th>Low income Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Seasonality</strong></td>
<td>Winter</td>
<td>Year round</td>
</tr>
<tr>
<td><strong>Age (% &lt; 1 yr)</strong></td>
<td>40%</td>
<td>80%</td>
</tr>
<tr>
<td><strong>Serotypes</strong></td>
<td>5 common</td>
<td>Mostly common</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Some additional</td>
</tr>
<tr>
<td><strong>Mixed infections</strong></td>
<td>Rare</td>
<td>common</td>
</tr>
<tr>
<td><strong>Case fatality</strong></td>
<td>Low</td>
<td>high</td>
</tr>
</tbody>
</table>
1998 – Rotashield licenced in the US
Intussusception Among Recipients of Rotavirus Vaccine — United States, 1998–1999

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.
Interval between Vaccine and Intussusception

Murphy TV, et al, 2001
Incidence Rates and Numbers of Hospitalized Cases of Intussusception by Age (months) VSD, 1991-1997

80% of the IS were in the 50% of infants >90 days when vaccinated
The next generation of rotavirus vaccines

- **GSK**
  - Rotarix
  - Human rotavirus
    - G1P[8]

- **Merck**
  - RotaTeq
  - Bovine rotavirus with single human rotavirus gene substitution
    - G1
    - P[8]
    - G2
    - G3
    - G4
CDC Advisory Committee on Immunization Practices (ACIP) – Feb. 2006

Draft -- Recommendations for Pentavalent Bovine-Human Rotavirus Vaccine (PRV)

- Routine immunization of infants with 3 doses of PRV at 2, 4, and 6 months of age
- Three doses at 2, 4, and 6 months of age
- Dose 1 between 6-12 weeks of age
- All doses by 32 weeks of age
- 4-10 week interval between doses
Rotarix introduced in Brazil, Mexico, Panama, El Salvador, and Venezuela (Mar-Oct 2006)

First rotavirus immunizations in Panama by President Martin Torrijos, March 14, 2006
Current Status

• Rotavirus immunization is routine in the US, Austria, Belgium, Luxemburg, Australia

• Latin America- Brazil, Panama, Nicaragua, Guyana, El Salvador, Venezuela, Bolivia, *Mexico

• Evaluations that are currently ongoing!
What more is needed?

For economics?
For efficacy?
For safety?
For introduction?
Vaccine Finance

Cost-effectiveness vs. cost of vaccine

Range of prices—$7.50 vs. $100 +/dose

Direct vs. indirect costs

What price is affordable for low, middle & high income countries & how do we get there?
The biggest challenge for Rotavirus vaccines today is

Will they work well in low income countries?

Preliminary data suggests that they might not. We will need to figure this out soon!
1997- WHO Consensus Meeting

- Wyeth requested global recommendation following single Venezuelan trial. No trials had been conducted in other sites

WHO Recommended

- Must demonstrate efficacy in at least one low income country of Asia and Africa
- Should encourage “simultaneous” testing in low income countries

What is different about these children? And where do we get funds to study them?
Rotavirus Vaccine Program – 2003-2008
First priority

• “To demonstrate the efficacy of vaccines from the multinational manufacturers- Merck and GSK- in low income countries of Asia and Africa“

• Data is essential to make the business case and for decision making

• $30 Million for 5 years to address this question!
Will the new vaccines work equally well in low income countries?

*Immune responses to the GSK vaccine in infants*

- Finland: >90%
- Latin America: ~70%
- S. Africa: ~44-51%
- Bangladesh: ~55%

*Why is there a gradient in response?*

*Will this correlate with efficacy?*

*What can we do to anticipate/prevent this?*

*What if the vaccines are only 50% effective?*
Live oral vaccines – problems in the developing world

- **OPV** Less immunogenic/more doses needed for children in India (not Africa) (*T. Jacob Johns*)
- **Cholera (Oral chol)** Less immunogenic/higher titer needed in Thai/Indonesian studies (*Mike Levine*)
- **Typhoid** Oral vaccine gave variable results in different settings (*Mike Levine*)
- **Oral RV**
  - RIT Failed in Africa/Peru
  - WC3 Failed in Africa
  - RRV Lower efficacy in Peru/Brazil
  - GSK Being tested in S.Africa/Bangladesh
Hurdles to Immunization for a Live Oral Rotavirus Vaccine

Factors that lower viral titer

• Breast milk
• Stomach acid
• Maternal antibodies

Factors that impair immune response

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

• Do they inhibit the immune response to vaccine?
• Are maternal antibody titers higher among children in less developed countries (LDCs)?
Geometric Mean Concentration of Transplacental RV IgG among vaccine recipients in Finland

<table>
<thead>
<tr>
<th>Status</th>
<th>N</th>
<th>GMC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder*</td>
<td>164</td>
<td>92.5 (76.8 – 111.4)</td>
</tr>
<tr>
<td>Non-Responder</td>
<td>40</td>
<td>218.6 (148.4 – 321.9)</td>
</tr>
</tbody>
</table>

*Responder: Positive for Rotavirus IgA (≥ 20 units/ml) after second dose of vaccine

R. Ward; Unpublished
<table>
<thead>
<tr>
<th>Site</th>
<th>Age at Enrollment</th>
<th>N</th>
<th>GMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td>2 months</td>
<td>204</td>
<td>109 (92.2 – 130.2)</td>
</tr>
<tr>
<td>Mexico</td>
<td>2 months</td>
<td>154</td>
<td>231 (200.5 – 267.0)</td>
</tr>
<tr>
<td>South Africa</td>
<td>6 weeks</td>
<td>84</td>
<td>352 (251.7 – 494.7)</td>
</tr>
<tr>
<td>(before 2002 season)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Africa</td>
<td>10 weeks</td>
<td>53</td>
<td>539 (402.1 – 721.9)</td>
</tr>
<tr>
<td>(after 2002 season)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bangladesh</td>
<td>6 weeks</td>
<td>232</td>
<td>282 (252.8 – 312.5)</td>
</tr>
</tbody>
</table>

Presented by Dick Ward, September 2004, RAPID meeting
Breastfeeding Questions

- Are the neutralizing titers of breast milk different among women from the US and other less developed countries?
- What is the interval between breastfeeding and administration of oral vaccines?
30% of breast milks neutralize 2 logs of virus!
Interfering Microbes

The human microbiome

The gut has 10 times more bacteria than the body has cells. 97% of these organisms have never been identified.

- Viruses (e.g. Enteroviruses, noroviruses, astrovirus, adenovirus)
- Vaccine viruses (OPV, polyvalent RV vaccines)
- Bacteria (bacterial overgrowth; helicobacter)

Many can interfere with viral adherence, entry & immune response!
Other issues of concern

- Underlying protoplasm –
  - Malnutrition, zinc deficiency, diarrheal illness, HIV, malaria, TB, other debilitating illnesses

- Rotavirus problems –
  - Strain diversity
  - Co-infections with other rotaviruses
  - Inoculum size (given mixed infections) & other modes of transmission


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.
Could we improve the “take” of live oral vaccines?

- Maternal antibodies — Delay immunization and increase potency of vaccine, dose; change buffer
- Breastfeeding — Withhold breastfeeding before/after immunization
- Microbes — Separate from OPV / probiotics
- Stomach acidity — Experiment with different buffers or raise titer of vaccine
- Malnutrition — Add zinc, vit A,

Research today might improve outcomes tomorrow!
Trials are ongoing

• GSK vaccine
  In S. Africa*
  Malawi
  Results Q3-4, 2008

Bangladesh –
In discussion

*middle income

• Merck Vaccine
  Bangladesh
  Vietnam
  Kenya
  Mali
  Ghana

Results 2009-2010?

Rotavirus Vaccine Program
GSK Trial – S Africa

• Results in June 2008
• Design – 3 cells  2 doses (10/14 wks)
  3 doses (6/10/14 wks)
  placebo

– *Late dose & 3rd dose (14 weeks) diminish impact of maternal antibody*

*Changes in timing have already being made!*
Soweto, S. Africa
- Per capita >$5000
- Electricity > 90%
- Water > 90
- Sewage > 80
- Seasonal disease
- 40-50% in year 1

Kibera, Kenya
- Per capita ~500
- Electricity low
- Water low
- Sewage low
- Year round disease
- >70% in year 1

Can results from S. Africa predict results elsewhere?
What should we do now?

1. Wait and pray for success

2. Try to improve immune response with research now!

3. Consider alternative vaccines - as an insurance policy
   - Neonatal strains
   - Parenteral vaccines
     - Subunit
     - Killed vaccines
Neonatal Strains

- RV3 (Australia) and 116E (India- Bharat)
- Each grow in newborns
- Immunogenic & protective in natural infection
- Both in development as vaccines
- Benefit: Could avoid problems of poor immune response in the presence of maternal antibody + lower cost
Inactivated Rotavirus Vaccines
A low hanging fruit

1. Greater efficacy in developing countries
2. Greater safety (or perception) – Age of administration not an issue
3. Easier administration - not oral
4. Lower cost to develop, manufacture, (smaller trials, existing methods)
5. Practical for combination vaccines
Who Will Supply inexpensive Rotavirus Vaccines to the World?

Big Pharma
- Merck

Emerging Manufactures
- Brazil
- Indonesia
- China
- Germany
- India
UK-Bovine Reassortant vaccine

- Developed by Kapikian, NIH
- Demonstrated efficacy in Finland
- Licensed to 8 companies
- Gates-PATH grant to support development in China (Wuhan) and India (Shanta)
- Early development phase

Likelihood of success may be predicted from results of trials of Merck vaccine now ongoing
Summary

Where are we now?

• Rotavirus surveillance in >50 countries
• Disease burden appreciated
• Global vaccine priority – GAVI, WHO, Gates
• 2 vaccines licensed; others in development
• ~ 8 Countries with national programs

The train has left the station!
Summary

Where are we going?

• Efficacy of live oral vaccines remains to be established in low income countries
• New countries coming on board
• Vaccine price remains an issue in middle and high income countries
• Effectiveness evaluations ongoing
• Emerging manufacturers on board
• Impact on mortality will still require time
We have come a long way with surveillance & introduction into middle/high income countries

Questions of efficacy in low income countries and finance remain critical
Question: What data would you need to consider rotavirus introduction in your country?

- Is rotavirus perceived to be a problem?
- Is data on burden of disease available?
- For low income countries, has the vaccine been proven effective in your setting?
- What is the cost or cost-effectiveness?
  - GSK $7/dose in Brazil -~$200/dose Austria
  - Merck $? “Competitive” for Latin America ~ $60/dose for US
- Would a WHO recommendation affect your decision?
Special thanks to Albert Sabin and his institute

The father of live oral vaccines and OPV, the vaccine most widely used in the world today!

(a former Fogarty Fellow!)

And to Ciro and the Staff of the SVI
Thanks to the Viral Gastroenteritis Section, CDC

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