Rotavirus & Rotavirus Vaccines: Fullfilling the Promise

Roger I. Glass, M.D., Ph.D.
Fogarty International Center, NIH
Viral Gastroenteritis Unit, CDC
The Rotavirus Symposia:
* A long rich history to get here!


5. 1995 CDC Atlanta, Ga

6. 2003 Mexico

7. 2005 Lisbon

8. 2008 Istambul

9. 2010 Johannesburg
Ruth Bishop receives the Prince Mahidol Award, 2011
VIRUS PARTICLES IN EPITHELIAL CELLS OF DUODENAL MUCOSA FROM CHILDREN WITH ACUTE NON-BACTERIAL GASTROENTERITIS
Ruth F. Bishop, G. P. Davidson, I. H. Holmes and B. J. Ruck

Abstract
Electron microscopy of duodenal mucosa from nine children with acute non-bacterial gastroenteritis revealed virus particles in epithelial cells from six patients. The morphology of the virus particles was identical in each of the six children. The virus belonged to the orbivirus group. No virus particles were observed in duodenal mucosa obtained from three of these children after clinical recovery. This orbivirus is believed to have been an important cause of sporadic gastroenteritis in children in Melbourne during the 3 months of the survey.
The **Promise** began! How much diarrhea was Caused by Rotavirus?……Prevention?

**Diarrhea in Children ~ 1973**

5 million deaths per year

<table>
<thead>
<tr>
<th>Etiology</th>
<th>% explained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria (Salmonella, shigella, cholera....)</td>
<td>&lt;0-6%</td>
</tr>
<tr>
<td>Parasites (Ameba, ? Giardia)</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>Foods- weanling foods</td>
<td>?</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>?</td>
</tr>
<tr>
<td>Drugs and allergies</td>
<td>?</td>
</tr>
<tr>
<td>Other conditions</td>
<td>?</td>
</tr>
<tr>
<td>“<strong>Idiopathic</strong>”</td>
<td>&gt; 85%</td>
</tr>
</tbody>
</table>
Sentinel Hospital Surveillance
Diarrhea
Vomiting
Dehydration
Shock
Death
& ORS!
Institute of Medicine
Estimates of Rotavirus Deaths--1985

High priority for Developing Countries…
“No need for an RV Vaccine for the United States”!
Diarrhea-associated hospitalizations by month & age among U.S. children < 5 years, 1979-1997
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
- ~5% of admissions in <5 yr olds
- 500,000 Outpatient visits
- 3.2 Million episodes

Cost: $400 M medical; >$1 B total
Decade of the 1980s

Harry Greenberg
Reassortment

Timo Vesikari
First successful Vaccine trial -1984

Jean Cohen & Mary Estes
Gene Coding Assignments
Rhesus Tetravalent vaccine-Rotashield

Albert Kapikian, NIH
Rotashield Licensed 1998

New vaccine may tame common childhood virus

F.D.A. Approves Vaccine for Childhood Diarrhea

By THE ASSOCIATED PRESS

Washington -- The Food and Drug Administration Monday approved the first vaccine against a leading cause of childhood diarrhea, a virus that hospitalizes 55,000 American children a year and kills one million in countries.

Vaccine offers way to prevent child diarrhea

Rotavirus Vaccine Cuts Diarrhea Hospitalizations

The New York Times

The Virginian-Pilot

Healthcare Review

Pediatric News

New Vaccine Passes Test For Disease In Children

Infectious Diseases in Children

Honour due to Kapikian

Newspaper clippings from the late 1990s highlighting the approval of the Rotashield vaccine.
### Recommended Childhood Immunization Schedule
United States, January – December 1999

<table>
<thead>
<tr>
<th>Age</th>
<th>Birth</th>
<th>1 mo</th>
<th>2 mos</th>
<th>4 mos</th>
<th>6 mos</th>
<th>12 mos</th>
<th>15 mos</th>
<th>18 mos</th>
<th>4-6 yrs</th>
<th>11-12 yrs</th>
<th>14-16 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatitis B</strong></td>
<td>Hep B</td>
<td>Hep B</td>
<td>Hep B</td>
<td>Hep B</td>
<td>DTaP</td>
<td>DTaP</td>
<td>DTaP</td>
<td>DTaP</td>
<td>DTaP</td>
<td>Hep B</td>
<td></td>
</tr>
<tr>
<td><strong>Diphtheria, Tetanus, Pertussis</strong></td>
<td>DTaP</td>
<td>DTaP</td>
<td>Hib</td>
<td>Hib</td>
<td>Hib</td>
<td>Hib</td>
<td>Hib</td>
<td>Hib</td>
<td>Hib</td>
<td></td>
<td>Td</td>
</tr>
<tr>
<td><em>H. influenzae</em> type b</td>
<td>Hib</td>
<td>Hib</td>
<td>Hib</td>
<td>Hib</td>
<td>Hib</td>
<td>Hib</td>
<td>Hib</td>
<td>Hib</td>
<td>Hib</td>
<td></td>
<td>Polio</td>
</tr>
<tr>
<td><strong>Polio</strong></td>
<td>IPV</td>
<td>IPV</td>
<td>IPV</td>
<td>IPV</td>
<td>IPV</td>
<td>IPV</td>
<td>IPV</td>
<td>IPV</td>
<td>IPV</td>
<td>Polio</td>
<td>MMR</td>
</tr>
<tr>
<td><strong>Rotavirus</strong></td>
<td><em>Rv</em></td>
<td><em>Rv</em></td>
<td><em>Rv</em></td>
<td><em>Rv</em></td>
<td><em>Rv</em></td>
<td><em>Rv</em></td>
<td><em>Rv</em></td>
<td><em>Rv</em></td>
<td><em>Rv</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Measles, Mumps, Rubella</strong></td>
<td>MMR</td>
<td>MMR</td>
<td>MMR</td>
<td>MMR</td>
<td>MMR</td>
<td>MMR</td>
<td>MMR</td>
<td>MMR</td>
<td>MMR</td>
<td>MMR</td>
<td>Var</td>
</tr>
<tr>
<td><strong>Varicella</strong></td>
<td>Var</td>
<td>Var</td>
<td>Var</td>
<td>Var</td>
<td>Var</td>
<td>Var</td>
<td>Var</td>
<td>Var</td>
<td>Var</td>
<td>Var</td>
<td></td>
</tr>
</tbody>
</table>
Estimated global distribution of the 600,000 annual deaths caused by rotavirus

85% of deaths – in low income countries

1 dot = 1000 deaths

Umesh Parashar
What is Rotavirus & why don’t I know about it?
1st Asian Rotavirus Surveillance Network Meeting, Bangkok Feb 1999

Special Thanks to Tony Nelson
Turning an idea into a regional surveillance network!

Providing data for decision makers

Training a generation of Champions in epi and lab!

Building a global network for Rota!
2nd Workshop of ARSN
Bangkok, May 2002

### Specimens screened

<table>
<thead>
<tr>
<th>Sector/Cities</th>
<th>Hospitals</th>
<th>N</th>
<th>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>Haiphong</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>
</tbody>
</table>

Total: 5768, 3247, 56

*Van Mann, et all, JID, 2001*
Rotavirus Hospitalizations in the Asian Rotavirus Surveillance Network

China: 41%
Korea: 38%
Taiwan: 41%
Vietnam: 60%
Malaysia: 56%
Indonesia: 39%

Bresee 2003 EIDJ 22
Rotavirus Surveillance:: Jan-Dec 2011
64 Countries in the WHO Network & Reporting Data

Number of Children <5 years enrolled = 45,827

sentinel sites = 185

Source: WHO/IVB New Vaccines database
Data collected from WHO Regions.

58 Member States reported clinical data

6 Member States reported genotype data only

Fatima Serhan
% positive for rotavirus among children enrolled with acute gastroenteritis who had stool specimens tested, by country and WHO region, 2009

Each point = country team in EPI, lab, Public Health Champions!

36%
We have a lot to Celebrate!

- Global recognition of importance of RV by WHO, GAVI, Gates……..
- Surveillance of RV in ~60 countries + publications
- Vaccines: 2 globally licensed (GSK, Merck)
  2 nationally licensed (China, Vietnam)
  Many candidates in the pipeline
- Evidence that vaccine can decrease RV deaths, illness, hospitalizations
- WHO recommendation for global use
- GAVI funding for Low Income Countries
- **A global RV Network – a family! A vision!**
“The Promise” : We can decrease the global burden of Diarrhea / Rotavirus with a vaccine ?
1999: The “I” word sinks Rotashield
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) (a joint committee of the Public Health Service and American Academy of Pediatrics) (1998) (1999) (2000) has recommended that RRV-TV be given intramuscularly in the left upper arm to all children aged 6 months through 19 months of age at the routine 2-month and 4-month visits. The manufacturer of RRV-TV, Wyeth Laboratories, Inc., had approved the recommendation of the ACIP that RRV-TV be given in the left upper arm using the health care provider's preferred technique.

Intussusception

The telescoping of the intestine onto itself usually at the ileal-cecal junction, leading to reversible repair or entrapment with edema, necrosis and perforation.
Interval between Vaccine and Intussusception

Murphy TV, et al, 2001
Estimates of Rotavirus Deaths: 2000
(40% decline from 1985)

Diarrheal Deaths (% of total deaths)

- 873k in 1980
- 527k in 1990
- 453k in 2000

Eternal optimist!
“What a great impact even before the vaccine!!”
Safety and Efficacy of a Pentavalent Human–Bovine (WC3) Reassortant Rotavirus Vaccine
Timo Vesikari, M.D., David O. Matson, M.D., Ph.D., Penelope Dennehy, M.D., Pierre Van Damme, M.D., Ph.D., Mathuram Santosham, M.D., M.P.H., Zoe Rodriguez, M.D., Michael J. Dallas, Ph.D., Joseph F. …..

Safety and Efficacy of an Attenuated Vaccine against Severe Rotavirus Gastroenteritis
Guillermo M. Ruiz-Palacios, M.D., Irene Pérez-Schael, M.Sc., F. Raúl Velázquez, M.D., Hector Abate, M.D., Thomas Breuer, M.D., SueAnn Costa Clemens, M.D., Brigitte Cheuvart, Ph.D., Felix Espinoza, M.D., Paul Gillard, M.D., Bruce L. Innis, M.D., Yolanda Cervantes, M.D., …,

Live oral vaccines
Tested in >60,000 infants each
Both safe & effective >85%
2 New rotavirus vaccines

GSK *Rotarix*

- Human rotavirus
- G1P[8]
- 2 doses $10^6$
- Shedding $>50\%$
- Efficacy $>85\%$
- **Trials of both $>60,000$**

Merck *RotaTeq*

- G1
- G2
- P[8]
- G3
- G4
- 3 doses $10^8$
- Shedding $<10\%$
- Efficacy $>90\%$
CDC Advisory Committee on Immunization Practices (ACIP) – Feb. 2006

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
Number of positive and total rotavirus tests from 25 continuously reporting NREVSS laboratories, by week of year, **United States**
June 2000-July 2010, 3 week moving average

Rotavirus vaccine introduced, February 2006

Tate J, 2011
Impact of Rotavirus Vaccine in the US
A Review of studies

Kansas City, MO
88% reduction
Hospitalization

Galveston, TX
94% reduction
Hospitalization or ED

Philadelphia, PA
94% reduction
Hospitalization or ED

Worcester, MA
95% reduction
Hospitalization, ED,*
Outpatient

New York State
85% reduction
Hospitalization/ED

Philadelphia, PA
87% reduction
in Community acquired
cases (Children's Hosp.)

Consequences have been enormous!
Greater than rates of immunization!
Impact of rotavirus vaccines on hospitalizations for rotavirus gastroenteritis among children <5 years old

<table>
<thead>
<tr>
<th>Country</th>
<th>Vaccine</th>
<th>Age group eligible to receive vaccine at time of study</th>
<th>Yearly reductions in hospitalizations for rotavirus gastroenteritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>RotaTeq®</td>
<td>0-1-year-olds</td>
<td>67-69%</td>
</tr>
<tr>
<td>Nationwide¹</td>
<td>RotaTeq®</td>
<td>0-2-year-olds</td>
<td>66-83%</td>
</tr>
<tr>
<td>Nationwide²</td>
<td>RotaTeq®</td>
<td>0-2-year-olds</td>
<td>86%</td>
</tr>
<tr>
<td>Nationwide³</td>
<td>RotaTeq®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>RotaTeq®, Rotarix®</td>
<td>0-1-year-olds</td>
<td>87%</td>
</tr>
<tr>
<td>Nationwide⁴</td>
<td>RotaTeq®, Rotarix®</td>
<td>0-2-year-olds</td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>RotaTeq®, Rotarix®</td>
<td>0-2-year-olds</td>
<td>50%</td>
</tr>
<tr>
<td>Nationwide⁵</td>
<td>RotaTeq®, Rotarix®</td>
<td>0-2-year-olds</td>
<td>58-77%</td>
</tr>
<tr>
<td>Nationwide⁶</td>
<td>RotaTeq®, Rotarix®</td>
<td>0-2-year-olds</td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td>RotaTeq®, Rotarix®</td>
<td>0-1-year-olds</td>
<td>74% (0-1-year-olds)</td>
</tr>
<tr>
<td>Nationwide⁷</td>
<td>RotaTeq®, Rotarix®</td>
<td>0-2-year-olds</td>
<td>76-79% (0-1-year-olds)</td>
</tr>
<tr>
<td>Nationwide⁸</td>
<td>RotaTeq®, Rotarix®</td>
<td>0-2-year-olds</td>
<td></td>
</tr>
</tbody>
</table>

Impact of rotavirus vaccines on hospitalizations for all-cause acute gastroenteritis among children <5 years old

<table>
<thead>
<tr>
<th>Country</th>
<th>Vaccine</th>
<th>Age group eligible to receive vaccine at time of study</th>
<th>Yearly reductions in hospitalizations for all-cause gastroenteritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>RotaTeq®</td>
<td>0-2-year-olds</td>
<td>45%</td>
</tr>
<tr>
<td>Nationwide¹</td>
<td></td>
<td></td>
<td>41-52%</td>
</tr>
<tr>
<td>Nationwide²</td>
<td></td>
<td></td>
<td>29-50%</td>
</tr>
<tr>
<td>Nationwide³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>Rotarix®, Rotarix®</td>
<td>0-2-year-olds</td>
<td>33% (0-2-year-olds)</td>
</tr>
<tr>
<td>Nationwide⁴</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>Rotarix®</td>
<td>0-1-year-olds</td>
<td>26-48% (0-1-year-olds)</td>
</tr>
<tr>
<td>Nationwide⁵</td>
<td></td>
<td>0-2-year-olds</td>
<td>17%</td>
</tr>
<tr>
<td>Nationwide⁶</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mexico</td>
<td>Rotarix®</td>
<td>0-2-year-olds</td>
<td>40%*</td>
</tr>
<tr>
<td>Nationwide⁷</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>El Salvador</td>
<td>Rotarix®</td>
<td>0-2-year-olds</td>
<td>28-37%</td>
</tr>
<tr>
<td>Nationwide⁸</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*During peak rotavirus season rather than whole year.

Is this a “Probe Study?”

Indirect benefits of rotavirus vaccination (herd protection)

<table>
<thead>
<tr>
<th>Location</th>
<th>Reduction in rotavirus hospital admissions among</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Children age-eligible for vaccine</td>
<td>Children not age-eligible for vaccine*</td>
</tr>
<tr>
<td>Nationwide, USA¹</td>
<td>79-81%</td>
<td>69-78%</td>
</tr>
<tr>
<td>Nationwide, USA²</td>
<td>74-85%</td>
<td>41-80%</td>
</tr>
<tr>
<td>Queensland, Australia³</td>
<td>50-70%</td>
<td>30-70%</td>
</tr>
<tr>
<td>Nationwide, Belgium⁴</td>
<td>65-80%</td>
<td>20-64%</td>
</tr>
<tr>
<td>Nationwide, Austria⁵</td>
<td>76-79%</td>
<td>35%</td>
</tr>
<tr>
<td>Sao Paulo, Brazil⁶</td>
<td>56-69%</td>
<td>24%</td>
</tr>
<tr>
<td>Nationwide, El Salvador⁷</td>
<td>79-86%</td>
<td>41-81%</td>
</tr>
</tbody>
</table>

*Typically aged 2-5 years, but age range assessed in each study differed depending on year of vaccine introduction and type assessment.

How does this happen?”

Childhood Diarrhea Deaths after Rotavirus Vaccination in Mexico

Figure 1. Number of Diarrhea-Related Deaths among Children 59 Months of Age or Younger from July 2002 through December 2010 in Mexico, According to Age Group.

Richardson V et al. NEJM 2012
WHO Recommends Global Use of Rotavirus Vaccines

5 JUNE 2009 | GENEVA/SEATTLE -- WHO has recommended that rotavirus vaccination be included in all national immunization programs to provide protection against a virus that is responsible for more than 500,000 diarrheal deaths and 2 million hospitalizations every year among children. More than 85% of these deaths occur in developing countries in Africa and Asia.

Schedule: 2 doses 6 & 10 weeks
First dose 6-15 wks; last 32 wks
Given with EPI vaccines

Recommendations extended to Rotateq ~ 12/09
What about the developing world where children die from rotavirus diarrhea?

“Can rotavirus vaccines prevent severe disease and death among children in the poorest developing countries ...and if so, how quickly can these vaccines be introduced?”
Fullfilling the Promise

Vaccine Efficacy
Finance & Supply
New approaches, vaccines,
Other concerns

Past Hurdles
Vaccines Licensed
GAVI funding
Global recognition
WHO recommendation
Safety - Intussusception, PCV...
Efficacy: Relationship between RV Vaccine Efficacy & Per Capita Income

Tony Nelson, Lancet 2010
New rotavirus vaccines behave differently in low income settings!

GSK Rotarix

- Human rotavirus
- G1P[8]
- 2 doses $10^6$
- Shedding > 50%
- Efficacy > 85%

Merck RotaTeq

- G1P[8]
- G1
- G2
- G3
- G4
- 3 doses $10^8$
- Shedding < 10
- ~50-60% Efficacy > 90%
- ~50-60%
How does the Epidemiology of RV differ by country?

<table>
<thead>
<tr>
<th></th>
<th>Industrial World</th>
<th>LMIC 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>
## Rotarix in Africa

<table>
<thead>
<tr>
<th>Location</th>
<th>Time Frame</th>
<th>Immune Response</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Africa</td>
<td>6-10 wks</td>
<td>36%</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>10-14 wks</td>
<td>60%</td>
<td>72%</td>
</tr>
<tr>
<td>Malawi</td>
<td>6-10 wks</td>
<td>??</td>
<td>???</td>
</tr>
<tr>
<td></td>
<td>10-14 wks</td>
<td>??</td>
<td>49%</td>
</tr>
</tbody>
</table>

*What role does transplacental antibody play to decrease the immune response?* Steele, AD, et al.
Loss of transplacental RV IgG in infants

T1/2 = 3-4 weeks

IgG Titer vs Months

India

US
Nicaragua: Launch National Vaccination Campaign

October 27th 2006
Antibody titers in breast milk specimens from India, Vietnam, Korea and United States

Indian women had the highest IgA and neutralizing titers against rotavirus vaccine strains

B. Jiang, PIDJ2010
Protective Effect of Natural Rotavirus Infection in an Indian Birth Cohort

Beryl P. Gladstone, Ph.D., Sasirekha Ramani, Ph.D., Indrani Mukhopadhyya, Ph.D., Jayaprakash Muliyil, M.D., Dr.P.H., Rajiv Sarkar, M.Sc., Andrea M. Rehman, Ph.D., Shabbar Jaffar, Ph.D., Miren Iturriza Gomara, F.R.C.Path., James J. Gray, F.R.C.Path., David W.G. Brown, F.R.C.Path., Ulrich Desselberger, F.R.C.Path., Sue E. Crawford, B.S., Jacob John, M.D., Sudhir Babji, M.D., Mary K. Estes, Ph.D., and Gagandeep Kang, M.D., Ph.D.

Environmental Enteropathy?

How protective is natural immunity?
How could we improve performance of current vaccines?

- **Maternal antibodies** — Change schedule -- Increase potency of vaccine
  Add booster dose (3\textsuperscript{rd} dose for Rotarix)
- **Breastfeeding** — Withhold breastfeeding for some time before/after immunization
- **Environmental Enteropathy** — Separate from OPV / ? probiotics
- **Malnutrition** — Add zinc, vit A

*Research today might improve outcomes tomorrow!*
How will the vaccine work in the field?

**Better**
- Herd protection
- Lower force of infection
- Older age of disease
- Delayed immunization = less maternal Ab
- Help the most vulnerable

**Worse**
- Delayed immunization = more early disease
- Poor coverage of most needy groups

*Research & evaluations today are needed to answer this critical question tomorrow!*
Global Distribution of Rotavirus Deaths, 2000: \( N = 500,000 \)

85% of deaths – in low income countries

1 dot = 1000 deaths

Parashar, 2005
National RV introductions: 38 countries, Sept 1, 2012

Past International RV meetings

- Not GAVI-eligible
  - Bolivia
  - Brazil
  - Cayman Islands
  - Colombia
  - Dominican Rep.
  - Ecuador
  - El Salvador
  - Guatemala
  - Guyana
  - Honduras
  - Mexico
  - Nicaragua
  - Panama
  - Paraguay
  - Peru
  - United States
  - Venezuela

- GAVI-eligible
  - Botswana
  - Ghana
  - Morocco
  - Rwanda
  - South Africa
  - Sudan
  - Bahrain
  - Iraq
  - Qatar
  - Yemen
  - Australia
  - Marshall Islands
  - Micronesia
  - Palau

C. Rosen
PATH
HEALTH: Asia fails to take up rotavirus vaccine

BANGKOK, 7 September 2012 (IRIN) - Most countries in Asia have yet to make the rotavirus vaccine part of their national immunization programme (NIP), despite a World Health Organization (WHO) recommendation to do so.

“Timely vaccination with one of the two effective rotavirus vaccines [Rotarix and Rotateq] can prevent many cases of [rotavirus] illness and hospitalizations,” WHO’s Manila office said in an email to IRIN on 7 September.

**Question** - Why is Asia the first region to have surveillance and the last to introduce vaccines?

Is Data really important...or community advocacy?
The AFRN is a collaboration between WHO, PATH, CDC & Ministries of Health funded by GAVI

The GAVI Alliance: Accelerating Africa’s access to rotavirus vaccines

Rotavirus kills more than half a million children a year. 50% are in Africa.

Rotavirus is the world’s leading cause of diarrhoeal deaths among children under five.

$4.3 Billion Refinance
Country Price $0.15-.30/dose

It can take 15-20 years for new life-saving vaccines to reach developing countries.

The first GAVI-eligible country in Africa introduced the rotavirus vaccine two years after WHO’s universal recommendation.

Rotavirus vaccine support timeline:
- WHO recommends rotavirus vaccine be included in all national immunisation programs
- GAVI approve Sudan for rotavirus vaccine support
- Sudan rolls out rotavirus vaccine
- GAVI approves 12 more African countries for rotavirus vaccine support
Drug firms cut vaccine prices to the developing world*

<table>
<thead>
<tr>
<th></th>
<th>United States</th>
<th>PAHO</th>
<th>GAVI / UNICEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK</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>Merck</td>
<td>$120 – $200/child</td>
<td>$15.45/child</td>
<td>$10.50/child [for volume over 30 M]</td>
</tr>
<tr>
<td>Bharat Biotech</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
Overall context: an increasing number of vaccine introductions in countries

Number of vaccine introductions (approved countries as of 1 Sept 2012)
Vaccine campaign to target deadly childhood diarrhoea

Programme to guard against second-biggest killer of under-fives rolls out across Africa.

BY DECLAN BUTLER

29 SEPTEMBER 2011 | VOL 477 | NATURE |
GAVI: First child being vaccinated in Sudan
April 26, 2012
Ghana
First Lady H.E. Dr. Ernestina Naadu Mills at national launch of pneumococcal and rotavirus vaccines

May 25, 2012
Rwanda
Dr. Uzziel Ndagijimana, Rwanda's Ministry of Health Permanent Secretary, administers the first rotavirus vaccine

Yemen
August 1, 2012
“Why is Rotavirus vaccine not more widely used in Spain?”

Coverage
35%

Cost
EU 100/dose
~$120
$360/child

Cost effective
???
Pipeline RV vaccines - 2012

Research -> Phase 1 -> Phase 2 -> Phase 3 -> Licensure -> Market

- CDC
- LIF
- Wuhan Institute of Biologic Products
- Shantha Biotechnics Ltd
- Bharat Biotech
- GSK
- Merck
- POLYVAC
- National Institutes of Health
- Cincinnati Children's
- BMC
- Instituto Butantan
- Serum Institute of India Ltd.
- Murdoch Child Research Institute
- International Medica Foundation
- LIBP

G Thiry, PATH
## The Next Generation- RV Vaccines

### Live oral candidates

<table>
<thead>
<tr>
<th></th>
<th>Inventor</th>
<th>Strain</th>
<th>Principle</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UK</strong></td>
<td>Kapikian</td>
<td>Bovine Reassortants</td>
<td>Like Rotateq</td>
<td>8+ licenses Serum Inst. India +</td>
</tr>
<tr>
<td><strong>116E</strong></td>
<td>Bhan/Glass/Gentsch</td>
<td>116E (G9P10)</td>
<td>Neonatal</td>
<td>Bharat India</td>
</tr>
<tr>
<td><strong>RV3</strong></td>
<td>Bishop/Barnes</td>
<td>RV3</td>
<td>Neonatal</td>
<td>Biofarma Indonesia</td>
</tr>
<tr>
<td><strong>Lanzhou</strong></td>
<td>Bai</td>
<td>LLR- Lamb</td>
<td>Jennerian</td>
<td>Lanzhou + China</td>
</tr>
<tr>
<td><strong>Rotavin</strong></td>
<td>Van Man</td>
<td>G1P8</td>
<td>Like RotaRix</td>
<td>Polyvac Vietnam</td>
</tr>
<tr>
<td><strong>Rotashield</strong></td>
<td>Kapikian/Lenard Ruiz</td>
<td>Rhesus Reassortants</td>
<td>Like Rotashield</td>
<td>----??No</td>
</tr>
</tbody>
</table>
## Non-Replicating Candidates

<table>
<thead>
<tr>
<th>Organization</th>
<th>GP</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC (USA)</td>
<td>Inactivated G1P[8], G2P[4] and G9P[6]</td>
<td>Formaldehyde or heat inactivated; POC in animals</td>
</tr>
<tr>
<td>Baylor College of Medicine (USA)</td>
<td>Virus Like Particles of vp2/6 and vp2/6/4/7</td>
<td>VLP in BCV / insect cells; POC in animals</td>
</tr>
<tr>
<td>Cincinnati Children’s Hospital Medical Center (USA)</td>
<td>VP6 subunit</td>
<td>Recombinant in E. coli; POC in mice</td>
</tr>
<tr>
<td>NIAID (USA)</td>
<td>VP8 subunit of P8, P6, P4</td>
<td>Recombinant truncated VP4 E. coli as soluble protein;</td>
</tr>
</tbody>
</table>
Other Concerns? How about......

**Intussusception**

The telescoping of the intestine onto itself usually at the ileal-cecal junction, leading to reversible repair or entrapment with edema, necrosis and perforation.
FDA News

Components of Extraneous Virus Detected in Rotarix Vaccine; No Known Safety Risk

FDA Recommends Clinicians Temporarily Suspend Use of Vaccine as Agency Learns More

FDA is recommending that healthcare practitioners temporarily suspend use of the Rotarix vaccine for rotavirus immunization in the United States while the agency learns more about components of an extraneous virus detected in the vaccine. There is no evidence at this time that this finding poses a safety risk.
Ending Preventable Child Death in a Generation

Roger I. Glass, MD, PhD
Alan E. Guttmacher, MD
Robert E. Black, MD

JAMA, July 11, 2012:308:2
The vision for the DoV is a world in which all individuals and communities enjoy lives free from vaccine-preventable diseases. Its mission is to extend, by 2020 and beyond, the full benefits of immunization to all people, regardless of where they are born, who they are, or where they live.
Fullfilling the Promise

- 38 countries have introduced RV vaccines (only 20%).
- The impact is enormous! Herd effect unanticipated!
- WHO recommendation & GAVI funding have sparked introductions in low income countries
- Evaluation of impact essential to assess lower efficacy but positive herd effects
- Research essential - to improve existing vaccines, develop less expensive & more effective alternatives
- Vaccine finance remains a challenge to make programs sustainable
Fullfilling the Promise

- **Its all about people, networks, partnerships!**
- We have the ability to decrease diarrheal diseases in children substantially and prevent deaths from rotavirus completely through the global use of vaccines.
- We have the knowledge, financial support, motivation and incredible people – you!
- While many challenges remain – in research, implementation, financing, advocacy, the goal is clear, compelling and achievable in a decade!
Core Partners

Mathuram Santosham
Johns Hopkins Bloomberg School of Public Health, USA

Ciro A. de Quadros
Sabin Vaccine Institute, USA

Umesh Parashar
US Centers for Disease Control and Prevention, USA

Kathy Neuzil
PATH, USA

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Institute of Virology, Uzbekistan

Tony Nelson
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Vesta Richardson
Ministry of Health, Mexico

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Bill & Melinda Gates Foundation, USA

Oyewale Tomori
Redeemer’s University, Nigeria

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Aga Khan University, Pakistan
The Organizing Committee

Piyanit, Thai MoH

Duncan Steele Gates

Ciro deQuadros Sabin

Kathy Neuzil Path

Umesh Parashar CDC

Mathu Santosham Johns Hopkins
The Viral Gastroenteritis Section

Jon Gentsch
Umesh Parashar

Manish Patel
Jackie Tate
Daniel Payne

Baoming Jiang
Margaret Cortese
Ben Lopman
We have a lot to Celebrate!

But don’t forget the Promise!
All children should be protected from RV with a safe, effective & affordable RV vaccine soon!

We still have a lot more to do…….