Roger Glass Lecture

Building the Evidence for Rotavirus Immunization

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Bill & Melinda Gates Foundation

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Building the Evidence
For Rotavirus Immunization

1. The evidence of disease burden
2. The development of rotavirus vaccines
3. The public health impact of rotavirus vaccines
Building the Evidence 1 –

The Burden of Disease
Diarrhoeal diseases remain a major cause of Under5 child deaths

Electron microscopy identifies the major role of viruses in infantile gastroenteritis

Al Kapikian describes Norwalk virus in stools - 1972

Ruth Bishop describes rotavirus in duodenal biopsies of young children - 1973

Bishop RF, Davidson GP, Holmes IH, Ruck BJ. Lancet 1973; ii: 1281-83
Rotavirus antigen detection – the key to evidence generation and the burden of disease

- Rotavirus antigen ELISA developed in 1977
- WHO Collaborating Centre, East Birmingham Hospital, UK
- ELISA kits were constructed in the lab and mailed to developing countries

Yolken RH, Wyatt RG, Kapikian AZ. Lancet 1977; ii: 819
Rotavirus was rapidly identified as the most common cause of severe diarrhoea in young children

- Ubiquitous virus infection globally
- All children infected by the age of 2-3 years
- First infections are generally symptomatic and re-infections are common
- Peak incidence of clinical disease among children 6–18 months
- Natural immunity of ~75% is observed
- Limited strains in circulation
- Improvements in water and sanitation will not prevent infection

Linhares AH & Bresee JS. Pan Amer J Public Health 2000 8(5) 305–330
WHO study to define aetiology of diarrhoeal disease in young children <36 months of age in 5 countries

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Cases (n=3640)</th>
<th>Controls (n=3279)</th>
<th>Pathogenicity index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotavirus</td>
<td>16%</td>
<td>2%</td>
<td>8.0</td>
</tr>
<tr>
<td>ETEC</td>
<td>16%</td>
<td>5%</td>
<td>3.2</td>
</tr>
<tr>
<td><em>Shigella</em></td>
<td>11%</td>
<td>1%</td>
<td>11.0</td>
</tr>
<tr>
<td><em>C jejuni</em></td>
<td>11%</td>
<td>7%</td>
<td>1.6</td>
</tr>
<tr>
<td>EPEC</td>
<td>9%</td>
<td>6%</td>
<td>1.5</td>
</tr>
<tr>
<td>Enteric Ad</td>
<td>4%</td>
<td>2%</td>
<td>2.0</td>
</tr>
</tbody>
</table>

China, India, Mexico, Myanmar, Pakistan

Histopathology of piglet intestine infected with rotavirus shows extensive damage to gut

Normal piglet villi

Rotavirus infected showing denuded micro-villi

Villous atrophy = malabsorptive diarrhoea

Creating the Tools for Evidence Generation
WHO-coordinated Global Rotavirus Surveillance Networks

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement. ©WHO 2014. All rights reserved.

- Member State reported data but had not introduced rotavirus vaccine (n=41)
- Member State reported data and introduced rotavirus vaccine (n=24)
- Member State did not report data or not in rotavirus network
- Not applicable
Global Rotavirus Surveillance in 42 Member States 2012-2013

- Fiji n=247
- China n=1870
- Papua New Guinea n=219
- Lao People's Democratic Republic (the) n=203
- Cambodia n=943
- Mongolia n=976
- Nepal n=440
- Indonesia n=1032
- Myanmar n=608
- Azerbaijan n=613
- Georgia n=1032
- Armenia n=2096
- Tajikistan n=1432
- Republic of Moldova n=1648
- Ukraine n=1831
- Pakistan n=354
- Yemen n=1205
- Sudan (the) n=4002
- Morocco n=257
- Jordan n=221
- Syrian Arab Republic (the) n=113
- Afghanistan n=1020
- Iraq n=720
- Chile n=573
- Ecuador n=330
- Honduras n=541
- Nicaragua n=2076
- El Salvador n=1236
- Kenya n=478
- Uganda n=1236
- Ethiopia n=541
- Mauritius n=554
- Cameroon n=216
- Guinea-Bissau n=170
- Zimbabwe n=725
- Senegal n=244
- Zambia n=1350
- Nigeria n=270
- Ghana n=351
- Togo n=690

Democratic Republic of the Congo (the) n=828

Regional Median
- WPR 43%
- SEAR 43%
- EUR 41%
- EMR 40%
- AMR 24%
- AFR 38%
Rotavirus is identified as the most common cause of diarrhoeal death in young children

Where in the world is Roger?

1st Asian Rotavirus Surveillance
Bangkok 1999

Vietnamese Rotavirus Group
Hanoi 2002
Where in the world is Roger -2?

African Rotavirus Surveillance
Accra 2002

Eastern Mediterranean Rotavirus Surveillance
Cairo 2005
Understanding the Rotavirus structure and genome

Modified from B.V. Venkataram Prasad, J Infect Dis 1996; 174: S37–S46
Rotavirus G and P genotypes determined by nested multiplex RT-PCR assays

Gouvea VP7 amplicons to identify G-genotypes

Gentsch VP4 amplicons to identify P-genotypes

500bp

Rotavirus strains vary across the globe in the same time period

Brazil, 1982-94, N=130
Leite et al, 1996

Malawi, 1997-98, N=100 Cunliffe et al, 1999

Hungary, 1995-99, N=284
Banyai et al, 2004

Rotavirus strain diversity over time in South East Asia (India, Pakistan and Bangladesh)

> = 1994

- G1: 28%
- G2: 13%
- G3: 12%
- G4: 11%
- G9: 7%
- G12: 0%
- G Mixed: 14%

2000-2004

- G1: 38%
- G2: 16%
- G9: 10%
- G Mixed: 9%
- G12: 6%

1995-1999

- G1: 34%
- G2: 25%
- G3: 9%
- G4: 17%
- G9: 8%
- G Mixed: 0%

2005-2009

- G1: 34%
- G2: 29%
- G9: 25%
- G Mixed: 11%

Miles MM, Lewis KDC, Steele AD. Vaccine 2012; 202: A131-39
Evidence of the burden and the impact of vaccines is clearly demonstrated.
Rotavirus is associated with moderate-to-severe diarrhoea in young Indian children

Incidence of Moderate-to-Severe Diarrhea in Kolkata by Age and Cause

Building the Evidence 2 – Rotavirus Vaccine Development
Albert Z. Kapikian
1930 - 2014

Father of viral gastroenteritis

“His seminal basic and clinical research contributions to the study of viruses and to vaccine development have had an enormous global impact”

Anthony Fauci, Director, NIAID
Natural infection with rotavirus offers protection against the disease


Lessons learnt from early clinical development with animal rotavirus strains

- First clinical trial was conducted by Timo Vesikari with a bovine strain (RIT4237) in 1983 in Finland
- Series of clinical trials between 1984 and 1990 provided the basis of our current vaccine strategies
  - Discordant efficacy in various developing countries led to the “modified” Jennerian approach pioneered by Al Kapikian at NIH
  - Higher viral concentration had similar reactogenicity, but better immunogenicity
  - Two doses gave better immune response than one
  - Neutralizing antibody response was mostly homotypic
  - Secondary immunization – even to the same serotype – gave a broadening of the immune response
  - >50% developed serum antibody responses
  - Pre-existing ab levels correlated negatively with vaccine take

“Modified” Jennerian approach for Rhesus rotavirus reassortant vaccine

- Animal strains are naturally attenuated for humans
- Belief that homotypic protection was essential
- Designed to include the VP7 gene coding the outer capsid antigens of human rotaviruses
- Rhesus strain was developed and licensed as RotaShield

Lessons learnt from the Rhesus-human rotavirus reassortant vaccine trials

- Dehydration: 100% (US), 97% (US), 75% (Venezuela)
- Hospital admittance: 100% (US), 100% (US), 70% (Venezuela)
- MD visits: 73% (US), 69% (Finland), 71% (Venezuela)

Tetravalent Rhesus-human rotavirus reassortant rotavirus vaccines & Intussusception

- RotaShield® licensed in USA in 1998 and immediately introduced into immunization programme

- Associated with increased risk of intussusception
  - Relative risk of >30 in first week after dose 1
  - Attributable risk: 1 in 10,000 vaccinees

- ACIP recommendation for use was withdrawn and Wyeth withdrew vaccine from USA in 1999
Rhesus-human rotavirus reassortant vaccine clinical development continues...

- RotaShield® clinical trials in Africa/Asia in 1999
  - Navrongo, Ghana
  - Matlab, Bangladesh
  - Ga-Rankuwa, South Africa

- All trials were halted due to intussusception in the USA

- RRV-TV trial conducted in Ghana in 2012, using a neonatal dose schedule

Early clinical trial results led to two paradigms for Rotavirus Vaccines

Reassortant bovine-human rotavirus strains

- G1
- G2
- G3
- G4
- P[8]
- P[5]

RotaTeq™, Merck

Attenuated single human rotavirus strain

- G1P[8]

Rotarix™, GSK Bio


WHO strongly recommends the inclusion of rotavirus vaccines into national immunization systems in all regions of the world.

Countries where diarrhoeal deaths among children from diarrhoeal disease account for >10% of Under-5 mortality should prioritize rotavirus vaccine introduction.
“Modified” Jennerian Approach – Construction of NIH bovine–human reassortant rotavirus vaccine

Human Rotavirus (HRV) x Bovine RV Reassortant Hexavalent Vaccine with VP7 Serotype 1, 2, 3, 4, 8, and 9 Specificities

Serum Institute, Pune, India
Shantha Biotechnics, Hyderabad, India
Wuhan Institute, Wuhan, China
Butantan Institute, Sao Paulo, Brazil
## Live attenuated, orally administered Rotavirus Vaccine Pipeline

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Country</th>
<th>Product</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biofarma</td>
<td>Indonesia</td>
<td>Human monovalent</td>
<td>Phase 2b</td>
</tr>
<tr>
<td>Butantan Institute</td>
<td>Brazil</td>
<td>Bovine reassortant</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Serum Institute of India</td>
<td>India</td>
<td>Bovine reassortant</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Shantha Biotechnics</td>
<td>India</td>
<td>Bovine reassortant</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Wuhan Inst of Biological Products</td>
<td>China</td>
<td>Bovine reassortant</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Medica International Foundation</td>
<td>Germany</td>
<td>Rhesus reassortant</td>
<td>Phase 2b</td>
</tr>
</tbody>
</table>


10th International Rotavirus Symposium, Bangkok, September 2012
## Nationally Licensed Rotavirus Vaccines

<table>
<thead>
<tr>
<th>Manufacturer, Country</th>
<th>Product</th>
<th>Specifications</th>
<th>Date Licensed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lanzhou Institute of Biological Products China</td>
<td>Lanzhou Lamb Rotavirus (LLR) Vaccine</td>
<td>Lamb monovalent G10P[12]</td>
<td>2000 in China</td>
</tr>
<tr>
<td>Bharat Biotech International Limited India</td>
<td>ROTAVAC™</td>
<td>Monovalent, human-bovine G9P[1]</td>
<td>2014 in India</td>
</tr>
</tbody>
</table>
The US-Indo Vaccine Action Program
a successful vaccine development partnership

Visiting Bharat Biotech facility, Hyderabad

Clinical Trial team, Delhi
Non-replicating Rotavirus Vaccine Candidates: Lead candidate is P2-VP8* particle (NIH)

Considered to address the issue of improved efficacy and safety

- Developed by Taka Hoshino and Al Kapikian, NIAID
- Phase 1 safety study complete
  - Safe and well tolerated
  - Robust immune responses
- Phase 2 immunogenicity and age descending study ongoing in South Africa

Stan Cryz et al. 11th International Rotavirus Symposium, Delhi 2014
Cathy and Al Kapikian with grandson
Building the Evidence 3 –

Public Health Impact of Rotavirus Vaccines
Public Health Hero of the Americas
May, 2014

“No single person has done more to extend the benefits of immunization to people throughout the Americas”

Carissa Etienne, Director, PAHO

Polio eradication in Brazil and in Latin America
Delivered by Dr Rosario Quiroga, Vice Minister of Health, Bolivia

On behalf of 16 Latin America countries

Calling on PAHO Revolving Fund, GAVI and vaccine manufacturers to facilitate introduction

Recognize the need for rotavirus vaccines as a public good
Successful Introduction of Rotavirus Vaccines in the Americas – USA and Nicaragua in 2006

USA – impact seen between 2006 & 2008

Rotavirus vaccine introduced into Nicaragua – 2006 and many countries of Latin America

MMWR 2008; 57:697-700; Patel et al, JAMA 2009; 301: 2245-51
National Rotavirus Vaccine Introductions by Geographic Region - 69 countries*

*National introductions by geographic region as of 15 August 2014
Public health impact: Reduction in rotavirus hospitalizations

Hospitalizations: documented reductions of 50% or more in children 0-2 years old following rotavirus vaccination

- **Belgium**: 50-77% reduction in hospitalizations in children 0-2 years old following vaccination with RotaTeq & Rotarix
- **US**: 66-86% reduction in hospitalizations in children 0-2 years old following vaccination with RotaTeq
- **Bolivia**: 70% reduction in hospitalizations in children 0-2 years old following vaccination with Rotarix
- **Austria**: 74-79% reduction in hospitalizations in children 0-2 years old following vaccination with RotaTeq & Rotarix
- **Australia**: 87% reduction in hospitalizations in children 0-2 years old following vaccination with RotaTeq & Rotarix

Brazil
El Salvador
Mexico
Nicaragua
South Africa

Public health impact: Reduction in all-cause diarrhoea hospitalizations

Hospitalizations: documented reductions of nearly 20% or more in children 0-2 years old following rotavirus vaccination

- Brazil 17-48% Rotarix
- El Salvador 28-37% Rotarix
- USA 29-52% RotaTeq
- Belgium 33% RotaTeq & Rotarix
- Mexico 40% Rotarix
- Australia
- Nicaragua
- South Africa

Reduction in deaths due to diarrhoeal disease in Mexico after the introduction of rotavirus vaccine

Figure 1. Number of Diarrhea-Related Deaths among Children 59 Months of Age or Younger from July 2002 through May 2009 in Mexico, According to Age Group.

Richardson V, Pichardo JH, Solares MQ et al. NEJM; 2010: 362: 358-360
Public health impact:
Herd immunity/indirect benefits of vaccination

Hospitalizations: documented reductions of more than 50% in children eligible for vaccination

- Belgium: 65-80%
- USA: 74-85%
- Austria: 76-79%
- El Salvador: 79-86%

Hospitalizations: documented reductions of more than 20% in children NOT eligible for vaccination

- Belgium: 20-64%
- USA: 41-80%
- Austria: 35%
- El Salvador: 41-81%

How would this efficacy translate into impact on a population level?

Estimates of cumulative impact of rotavirus vaccines, 2010-2025

The Challenges Ahead for the Full Public Health Impact of Rotavirus Vaccines

- Biological Challenges of the virus and the host
- Technical Challenges of rotavirus vaccine development
- Programmatic Challenges of delivering the vaccines where they are needed most
- Funding Challenges to pay for the vaccines
- Safety Challenges of rotavirus vaccines

Courtesy: Jan Holmgren, Goteborg University
Roger Glass & Mathu Santosham

Mathu Santosham & Ciro de Quadros