Challenges for Rotavirus Vaccines

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29 April 2015
Diarrhoea is the second leading cause of death in young children between 1 month and 5 years

~700,000 deaths / year
~11% of under 5 mortality
Deaths concentrated in South Asia and Sub-Saharan Africa

Rotavirus associated with ~ 200-250,000 deaths / year

GEMS – a large diarrhoea study in >20,000 children in 4 African and 3 Asian countries, funded by the foundation

A single episode of moderate-to-severe diarrhoea increased the risk of death of young children by 8.5 fold at approx. 60 days after diarrhoea episode

Where: 44% of cases died at a medical facility; 56% of cases died at home or outside a medical facility

Lesson: Without the single 60-day follow-up visit, many deaths would have been missed

Kotloff K et al. Lancet 2013; 382(9888): 209-22
Global Enteric Microbiology Study (GEMS)  
Linear Growth Data

**Impact on Growth:** Height-for-age (HAZ scores - measure of stunting) declined between enrollment and follow up for all children; and the decline was significantly greater in diarrhea cases compared to control children without diarrhea.

**Relationship to Mortality:** Stunting was observed to be a risk factor for fatal cases of moderate-to-severe diarrhea in all age groups.

- **0 – 11 months:** HR = 0.62 (95% CI 0.54 – 0.72)
- **12 – 23 months:** HR = 0.74 (95% CI 0.63 – 0.87)
- **24 – 59 months:** HR = 0.47 (95% CI 0.38 – 0.57)

*Kotloff K et al. Lancet 2013; 382(9888): 209-22*
GEMS study identifies major pathogens associated with moderate-to-severe diarrhoea in young children

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

Kotloff K et al. Lancet 2013; 382(9888): 209-22
“Environmental enteropathy”?

- Interrupts absorptive and barrier gut functions
- Contributes to under-nutrition (along with nutritional intake)
- Is responsible for 30-50% of the stunting of young children
- Stunting increased by 5% with each diarrheal episode

Under-nutrition leads to vulnerability to infectious diseases including diarrhoea. Diarrhoea reduces the absorptive ability of the gut, leading to under-nutrition.

Background on Presentation “Challenges for Rotavirus Vaccines”

1. Pathogen – rotavirus is successful enteric pathogen of young of all species

2. Host – young children <24 months of age

3. Vaccine – live, attenuated, orally delivered vaccine

4. Immunization program – complexities and issues in programmatic delivery

5. Financing vaccine programs – increasing costs for countries
1/ Rotavirus – the pathogen

Electron micrograph of rotavirus particles from stool

Ruth Bishop, Tom Flewett, Al Kapikian

Ruth Bishop describes rotavirus in duodenal biopsies of young children - 1973
Tom Flewett names rotavirus after the Latin word for wheel - 1974
Al Kapikian pioneers vaccine development and the modified Jennerian approach – 1980s-2013
Rotavirus characteristics important for vaccine development

Electron micrograph of rotavirus particles found in the stool

Modified from B.V. Venkataram Prasad, J Infect Dis 1996 174 S37–S46
Gambling with Antigens
Betting on the most common combinations
Rotavirus strain diversity

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>G-types</td>
<td>Wa</td>
<td>Au64</td>
<td>M37</td>
<td>K8</td>
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<td>P</td>
<td>107E1B</td>
<td>McN13</td>
<td>AU-1</td>
<td>HCR3</td>
<td>157C</td>
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<td>MW333</td>
<td>MW023</td>
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<td>69M</td>
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<td>PA169</td>
<td>HAL1166</td>
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<td>7</td>
<td>WI61</td>
<td>US1205</td>
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<td>116E</td>
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<td></td>
<td></td>
<td>Mc323</td>
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<tr>
<td>8</td>
<td>L26</td>
<td>US585</td>
<td></td>
<td>1321</td>
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</tr>
</tbody>
</table>

- **Yellow**: Globally common strains
- **Green**: Uncommon strains
- **Gray**: Regionally common strains
- **Light Blue**: Neonatal strains

Genstch J et al. J Infect Dis 2005; 192: 146-159
Distribution of rotavirus strains globally

N=21,256

G1P[8] 52.2%
G4P[8] 7.5%
G2P[4] 11.5%
G3P[8] 2.8%
other 18.2%
G9P[6]
G9P[8] 2.3%

Gentsch et al. J Infect Dis 2005
Rotavirus strains differ regionally during same time period

Brazil, 1982-94, N=130

Malawi, 1997-98, N=100

Hungary, 1995-99, N=284

Banyai et al, 2004; Cunliffe et al, 1999; Gentsch, 2005; Leite et al, 1996
Wide diversity of different rotavirus strains in West Africa (2008 – 2010)

**Nigeria**

- G3P[?] 17%
- G8P[8] 12%
- G3P[8] 4%
- G3P[6] 2%
- G1P[MIX] 8%
- G1P[8] 5%
- G9P[8] 4%
- G9P[4] 0%
- G9P[8] 0%
- GmixP[?] 0%

**Ghana**

- G1P[8] 35%
- G1P[6] 12%
- G2P[8] 1%
- G2P[6] 9%
- G4P[4] 7%
- G3P[6] 3%
- G4P[4] 3%
- G9P[4] 1%
- G10P[4] 6%
- G10P[6] 1%
- G1P[4] 1%
- G1P[6] 5%

*Courtesy of George Armah, Regional Rotavirus Laboratory, Noguchi, Ghana*
Distribution of rotavirus G types, Malawi (1997 – 2007)

N = 1130

Courtesy of Nigel Cunliffe, University of Liverpool and Malawi College of Medicine
Natural infection with rotavirus offers protection against disease


2/ The young child as Host

- Most common cause of severe diarrhoea in infants and young children
- 95% of all children infected by age 1-3 years of age
- First infections are symptomatic and re-infections common
- Peak incidence of clinical illness among children 6-18 months of age
- Natural immunity of ~75% after first symptomatic infection

Improvements in water and sanitation will not prevent infection

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2 Linhares and Bresee, Pan Amer J Public Health 2000 8(5) 305–330
Pathogenesis of Rotavirus

Villous enterocytes

Villous Atrophy

Mononuclear cell infiltration

Small Intestine
Pathogenesis of Rotavirus

**Normal Villi** – (microscopic tentacles that line the wall of the small intestine)

**Villous atrophy** (erosion of tentacles)

= malabsorptive diarrhoea
Treatment of rotavirus infection

- The only treatment is oral rehydration solution (ORS), which will keep the child alive with fluids and electrolytes, but cannot prevent the damage caused by the infection.

- No antibiotics are available, as this is a viral infection.
Repeated episodes of Rotavirus infection are common in the first 2 years of life.

Rotavirus is the most common cause of diarrhoeal death in young children

Tate JE, Burton AH, Boscho-Pinto C et al. Lancet Infect Dis 2010

10 countries account for ~85% of rotavirus associated mortality
There are currently two vaccines commercially available internationally. Both are considered highly effective.

**Rotarix™, GSK Biologicals**
(derived from a single common strain of human rotavirus) G1P8

**RotaTeq, Merck Research**
(Reassorted bovine-human rotavirus)
Genetically engineered vaccine consisting of 5 different strains to protect against the 5 most common
Rotavirus Vaccine Paradigms

**Human monovalent vaccines**
- Natural infection offers protection
- High replication in the host - attenuated by TC passage
- Broad immunity is acquired through various immune effector mechanisms
- Heterotypic protection is gained through broad immune response

**Animal reassortant vaccines**
- Naturally attenuated strains in humans – lower replication
- Higher titres required
- Expectation that neutralizing antibody in the gut lumen is required
- Reassortant vaccine constructs to include the common human rotavirus antigens
The Paradigms for Rotavirus Vaccine Development

RotaTeq™, Merck

Five bovine-human rotavirus strains

Rotarix™, GSK Bio

Single human rotavirus strain

Rotavirus Vaccine Efficacy (Pre-licensure studies) was different in high and low income countries

<table>
<thead>
<tr>
<th>Region</th>
<th>Vaccine</th>
<th>Efficacy (%)</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>US/Finland/Other</td>
<td>RotaTeq</td>
<td>98%</td>
<td>(88.3, 100)</td>
</tr>
<tr>
<td>Latin America/Finland</td>
<td>Rotarix</td>
<td>84.7%</td>
<td>(71.7, 92.4)</td>
</tr>
<tr>
<td>India</td>
<td>Rotavac</td>
<td>56.3%</td>
<td>(12.8, 73.3)</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>RotaTeq</td>
<td>51.0%</td>
<td>(12.8, 73.3)</td>
</tr>
<tr>
<td>Africa</td>
<td>RotaTeq</td>
<td>64.2%</td>
<td>(40.2, 79.4)</td>
</tr>
<tr>
<td></td>
<td>Rotarix</td>
<td>61.7%</td>
<td>(44.0, 73.2)</td>
</tr>
</tbody>
</table>

Efficacy against severe disease in first year of life

Vesikari T, Matson DO, Dennehy P et al. NEJM 2006; 354:23-33
Madhi SA, Cunliffe NA, Steele AD et al. NEJM 2010; 362: 346-357
WHO recommends rotavirus vaccine trials in Africa and Asia

- Kenya
- South Africa
- Malawi
- Ghana
- Mali

GSK-RVP partnership
Merck-RVP partnership
WHO Meeting to review efficacy data of Rotavirus Vaccines

WHO arranged an international consultative meeting before the developing country efficacy data were completed to review how to interpret the data

- Public health benefit of the vaccines should be utilized rather than a point estimate of efficacy
- Understanding local epidemiology and burden of disease was important to estimate potential cost benefits of the vaccine
- Research on the programmatic limitations of the vaccines would help elucidate better uptake and overall impact
<table>
<thead>
<tr>
<th>Region</th>
<th>Vaccine</th>
<th>Countries</th>
<th>Vaccine Efficacy</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>Rotarix™</td>
<td>Malawi, South Africa</td>
<td>61.7</td>
<td>44.0, 73.2</td>
</tr>
<tr>
<td>Africa</td>
<td>RotaTeq®</td>
<td>Ghana, Kenya, Mali</td>
<td>64.2</td>
<td>40.2, 79.4</td>
</tr>
<tr>
<td>Asia</td>
<td>RotaTeq®</td>
<td>Bangladesh, Vietnam</td>
<td>51.0</td>
<td>12.8, 73.3</td>
</tr>
</tbody>
</table>

Madhi SA, Cunliffe NA, Steele AD et al. NEJM 2010; 362: 346-357
Severe rotavirus gastroenteritis episodes prevented per 100 children vaccinated, Rotarix™

- Africa: 3 episodes prevented (Efficacy 61.2% (44.0 – 73.2))
- South Africa: 2.5 episodes prevented (Efficacy 76.9% (56.0 – 88.5))
- Malawi: 3.9 episodes prevented (Efficacy 49.5% (19.2 – 68.3))

Madhi SA & Cunliffe NA, et al. NEJM 2010; 362: 346-357
Globally, rotavirus causes ~ 40% of all severe gastroenteritis

Vaccine efficacy against severe rotavirus GE: 50-60%

Vaccine efficacy against all cause severe GE: 30% (Rotarix™) and 23% (RotaTeq®)
Monovalent Rotarix™ (G1P[8])
Good protection against non-G1 strains in Africa

Malawi (87%: non-G1)

South Africa (43%: non-G1)

Madhi SA, Cunliffe NA, Steele AD et al. NEJM 2010; 362: 346-358
Steele AD, Neuzil KM, Cunliffe NA et al. BMC Infect Dis 2012; 12: 213
Vaccine efficacy against severe rotavirus gastroenteritis due to different serotypes

Madhi SA, Cunliffe NA, Steele AD et al. NEJM 2010; 362: 346-358
Steele AD, Neuzil KM, Cunliffe NA et al. BMC Infect Dis 2012; 12: 213
**Rotarix™ in HIV-positive infants in South Africa**

- Seroconversion rate in the ATP cohort for immunogenicity: 57.1% [95% CI: 34.0%; 78.2%] in the HRV group.
  - Seroconversion was comparable to other studies in same population (Rota-014 and -013).

- The reactogenicity and safety profile of the HRV group was similar to the placebo group
  - Shedding profile not different from studies in healthy infants.

- The HRV vaccine did not increase the immune suppression in subjects in terms of CD4 count and viral load as similar results were observed in the placebo group

*Steele AD, Madhi SA, Tumbo J et al.; P Infect Dis J 2010*
## Immunogenicity of rotavirus vaccine is lower at younger ages

<table>
<thead>
<tr>
<th>Countries</th>
<th>Rotarix Schedule</th>
<th>Anti-rotavirus IgA antibody Seropositivity Rates</th>
</tr>
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<tbody>
<tr>
<td>Vietnam</td>
<td>9, 13*</td>
<td>62.5 (54; 71)</td>
</tr>
<tr>
<td></td>
<td>13, 17*</td>
<td>81.1 (73; 88)</td>
</tr>
<tr>
<td>Philippines</td>
<td>6, 10</td>
<td>61.4 (53; 69)</td>
</tr>
<tr>
<td></td>
<td>10, 14</td>
<td>72.9 (65; 80)</td>
</tr>
<tr>
<td>South Africa</td>
<td>6, 10</td>
<td>35.8** (23; 50)</td>
</tr>
<tr>
<td></td>
<td>10, 14</td>
<td>60.5** (43; 76)</td>
</tr>
</tbody>
</table>

*median age **sero-conversion
Rotavirus vaccines should be part of a comprehensive strategy to control diarrheal diseases with the scaling up of both prevention (promotion of early and exclusive breastfeeding, hand washing with soap, improved water and sanitation) and treatment packages (including low-osmolarity Oral Rehydration Salts and zinc).

WHO recommends Rotavirus Vaccine be included in all national immunization programs

WHO recommends that the first dose of either vaccine be administered as soon as possible after 6 weeks of age, along with DTP vaccination

WHO also recommends removing the age restriction for the administration of rotavirus vaccine
National Rotavirus Vaccine Introductions by Geographic Region - 77 countries*

*As of April 1, 2015
**Not a WHO member state
RV = rotavirus vaccine
Public health benefits of rotavirus vaccination

Ghana’s First Lady, Dr Ernestina Mills, vaccinates a child with Rotarix™ – 27 April 2012

Permanent Secretary to the Rwanda MOH, Dr Uzziel Ndagijimana, vaccinates a child with RotaTeq® - 25 May 2012
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, with vaccines RotaTeq & Rotarix
- **Bolivia**: 70% reduction in hospitalizations, with vaccine RotaTeq
- **Austria**: 74-79% reduction in hospitalizations, with vaccines RotaTeq & Rotarix
- **US**: 66-86% reduction in hospitalizations, with vaccine RotaTeq
- **Australia**: 87% reduction in hospitalizations, with vaccines RotaTeq & Rotarix

Impact of rotavirus vaccine on rotavirus disease in the USA

CDC data. MMWR 2009 (58)41: 1146-49
Reduction in rotavirus cases among children <5yrs old, in seven hospitals, El Salvador

79% reduction in hospitalized rotavirus diarrhoea children <5 yrs

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

Since introduction of the rotavirus vaccine:

- 40-50% reduction in diarrhoea hospitalizations among children
- 60-70% reduction in rotavirus-associated hospitalizations among vaccinated children

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%

Reduction in diarrhoeal deaths 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
4/ Programmatic Challenges

Infant receiving rotavirus vaccination in The Sudan, 2011
1 in every 5 children remain unimmunized with traditional vaccines (2014)

- African, 8.45
- American, 1.16
- Eastern Mediterranean, 2.31
- European, 0.61
- South East Asian, 9
- Western Pacific, 0.89

21.8 million not receiving their DTP3 vaccination
Lack of immunization happens everywhere – maybe for different reasons!

“If you connect the measles it spells out ‘My parents are idiots.’”
**Rotavirus vaccination coverage: Example from the Americas**

Countries and territories with the rotavirus vaccine in the EPI schedule, Region of the Americas, September, 2012.

### Countries

- Brazil
- Colombia
- Ecuador
- El Salvador
- Guatemala
- Guyana
- Honduras
- Mexico
- Nicaragua
- Panama
- Paraguay
- Peru
- Venezuela

### DTP3+Hib3 Rotavirus

- Brazil: 100, 87
- Colombia: 85, 78
- Ecuador: 100, 100
- El Salvador: 89, 90
- Guatemala: 85, 54
- Guyana: 93, 77
- Honduras: 100, 100
- Mexico: 97, 98
- Nicaragua: 100, 98
- Panama: 87, 95
- Paraguay: 76, 72
- Peru: 91, 84
- Venezuela: 78, 66

Lucia Helena D'Oliveira, PAHO
Updated DTP rates:
24% children vaccinated late in Africa and Asia

Colin Sanderson, LSTMH
Programmatic challenges in the field

Vaccine delivery

Vaccine packaging and presentation

Maintaining the vaccine cold chain

Vaccine waste
Impact of high-volume vaccines on cold chain capacity in developing countries

Vaccine volume per dose

**Polio**: 2.5 cm³/dose (10-dose vial)*
**Measles**: 1.5 cm³/dose (20-dose vial)*

**Rotarix**
- Contents include vaccine, diluent, applicator, connector:
  111.6 cm³/dose
- Vaccine only: 11.4 cm³/dose

*Source: WHO. Guidelines on the international packaging and shipping of vaccines. 2002; WHO/V&B/01.05.

2500 doses – measles
1600 doses - OPV

625 doses - Rotarix
A risk of country coping mechanisms: using cold chain storage space beyond prudent levels

Serge Ganivet, WHO, Harare
And national government health budgets may not be able to expand sufficiently to pay for new vaccines.
Vaccine Security

Vaccine Security Principles set by UNICEF:

- A healthy industry (ie. multiple manufacturers) is vital to ensure an uninterrupted and sustainable supply of vaccines
- Procurement from manufacturers in industrialized and developing countries
- Long-term accurate forecasting from UNICEF and accurate production plans from manufacturers
- Option to quote tiered pricing should be given to manufacturers—in accordance with World Bank (wealth) classification
Vaccine Security – healthy vaccine market and competitive prices

**Hepatitis B**

- **Average UNICEF price per dose**
  - 0.49
- **PAHO price per dose**
  - 0.52
- **Yearly Manufacturering**
  - 2001: 3
  - 2002: 3
  - 2003: 2
  - 2004: 1
  - 2005: 1
  - 2006: 1
  - 2007: 1
  - 2008: 1
  - 2009: 1
  - 2010: 1
  - 2011: 1

**Graph Details**
- Industrialised Manufacturers
- Emerging Manufacturers

**Price in Us$**
- 2001: 0.55
- 2002: 0.55
- 2003: 0.55
- 2004: 0.55
- 2005: 0.55
- 2006: 0.55
- 2007: 0.55
- 2008: 0.55
- 2009: 0.55
- 2010: 0.55
- 2011: 0.55
“The primary focus of the Gates Foundation has been to explore ways to reduce common diseases such as malaria and rotavirus that affect the world’s poor.”

~ Bill Gates

In interview with Charlie Rose, an American Journalist, Dec 22, 2008
## Rotavirus Vaccine Pipeline Overview

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Country</th>
<th>Product</th>
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<tbody>
<tr>
<td>Bharat Biotech International Ltd.</td>
<td>India</td>
<td>Human 116E strain *</td>
</tr>
<tr>
<td>Biofarma (Murdoch Childrens)</td>
<td>Indonesia</td>
<td>Human RV3 strain</td>
</tr>
<tr>
<td>Serum Institute of India</td>
<td>India</td>
<td>Bovine reassortant *</td>
</tr>
<tr>
<td>Shantha Biotechnics</td>
<td>India</td>
<td>Bovine reassortant *</td>
</tr>
<tr>
<td>Butantan Institute</td>
<td>Brazil</td>
<td>Bovine reassortant *</td>
</tr>
<tr>
<td>Wuhan Inst of Biological Products</td>
<td>China</td>
<td>Bovine reassortant *</td>
</tr>
<tr>
<td>Lanzhou Institute</td>
<td>China</td>
<td>Lamb monovalent</td>
</tr>
<tr>
<td>Medica International Foundation</td>
<td>Germany</td>
<td>Rhesus reassortant *</td>
</tr>
<tr>
<td>PolyVac</td>
<td>Vietnam</td>
<td>Human monovalent</td>
</tr>
</tbody>
</table>

**Sources:** [http://www.gavialliance.org/resources/DOC_11e_AVI_Progress_Report.pdf](http://www.gavialliance.org/resources/DOC_11e_AVI_Progress_Report.pdf)

*10th International Rotavirus Symposium, Bangkok, September 2012*

Costing of Immunization

- Human Resources: 40.7%
- Service Delivery: 62.8%
- Supply Chain & Logistics: 37.2%
- Cold Chain Equip’t & Overheads: 23.1%
- Vehicles & Transport: 9.3%
- Training & Capacity Building: 1.7%
- Social Mobilization, IEC, & Advocacy: 1.7%
- Programme Management: 14.7%
- Disease Surveillance: 4.1%
Resources required for immunization programs

- Building, electricity, water, and Overhead
- Staff training and outreach
- Social Mobilization
- Staff Salaries
- Vaccine transport
- Cold chain capabilities
- Vaccine
Share of secure routine immunization program financing, by funding source

- GAVI and local governments provide most of the funding

- The size of this “pie” has increased substantially over the past 10 years

Impact of New Vaccine Introduction
South Africa

EPI programme had to triple the transport logistics when Rotavirus vaccine was introduced.

Refurbish cold chain at Central Deport and District level depots.

- Pneumococcal
- Rotavirus
- DTP-IPV-Hib
- DTP-Hib
- BCG, OPV, Measles, HepB
Challenges to controlling rotavirus –

The work we do is complicated
The reasons we do it are not
Hurdles to Immunization for a Live Oral Rotavirus Vaccine

Factors that lower viral titre
- Breast milk
- Stomach acid
- Maternal antibodies

Factors that impair immune response
- Malnutrition - Zn, VitA
- Interfering microbes - viruses and bacteria
- Other infections - HIV, malaria, TB, diarrhea

Factors to improve vaccine response
- Multiple doses
- Increased titre
- OPV co-administration

Epidemiology of the virus
- Age of infection
- Multiple diverse strains
- Epidemiology