From 1999 – 2009: Over 5 Million Children Died from Rotavirus Disease

Global annual rotavirus deaths: 527,000—predominantly in developing countries


Global mortality figure: WHO. Weekly Epidemiological Record. 82(32).
Rotavirus is the Most Common Cause of Severe, Dehydrating Diarrhea among Children Worldwide

Each year it causes:

- Over 500,000 deaths
- 111 million cases of diarrhea
- 25 million outpatient visits
- 2 million hospitalizations

Global surveillance shows that 40% of diarrheal hospitalizations in young children are due to rotavirus.

Source: WHO. Weekly Epidemiological Record. 2008;83(47).
Objectives
To Share Information Describing:

- WHO recommendations on use of rotavirus vaccines
- WHO surveillance strategy
- Preliminary 2009 global surveillance data
- Activities to improve surveillance data quality
### Currently Available Rotavirus Vaccines

<table>
<thead>
<tr>
<th></th>
<th>Rotarix® (GSK Bio)</th>
<th>RotaTeq® (Merck)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Origin</strong></td>
<td>Human monovalent</td>
<td>Bovine pentavalent</td>
</tr>
<tr>
<td><strong>Strain</strong></td>
<td>G1, P[8]</td>
<td>G1, G2, G3, G4, P[8], G6P[7]</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>Lyophilized, reconstituted or liquid</td>
<td>Liquid</td>
</tr>
<tr>
<td><strong>Vaccine course</strong></td>
<td>2 doses – oral</td>
<td>3 doses - oral</td>
</tr>
<tr>
<td><strong>Schedule</strong></td>
<td>With DTP1 and DTP2</td>
<td>With DTP1, DTP2, and DTP3</td>
</tr>
<tr>
<td><strong>Intussusception risk</strong></td>
<td>No association observed</td>
<td>No association observed</td>
</tr>
<tr>
<td><strong>Age restrictions</strong></td>
<td>First dose at 6-15 weeks of age. Maximum age for last dose of either vaccine is 32 weeks of age.</td>
<td></td>
</tr>
<tr>
<td><strong>WHO Pre-qualification</strong></td>
<td>Yes, in 2007</td>
<td>Yes, in 2008</td>
</tr>
</tbody>
</table>
Evolution of WHO Recommendations: Administration of Rotavirus Vaccines

2007

- Included in immunization programmes in regions where efficacy data suggested public health impact
  - Americas & Europe
- Additional effectiveness & safety data required prior to recommendation for global vaccination
  - Especially Asia & Africa

2007 – 2009

- Accumulating data from vaccine trials & post licensure monitoring data
  1. Vaccine efficacy
  2. Safety
Vaccine Efficacy Estimates Generally Correlate with Mortality Quartiles

<table>
<thead>
<tr>
<th>WHO mortality strata</th>
<th>Under-5 Child Mortality</th>
<th>Vaccine Efficacy</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGH</td>
<td>Highest (top 25%)</td>
<td>50-64%</td>
<td>Ghana, Kenya, Malawi, Mali</td>
</tr>
<tr>
<td>INTERMEDIATE</td>
<td>High mid (next 25%)</td>
<td>46-72%</td>
<td>Bangladesh, South Africa</td>
</tr>
<tr>
<td></td>
<td>Low mid (next 25%)</td>
<td>72 - 85%</td>
<td>Viet Nam, Region of the Americas</td>
</tr>
<tr>
<td>LOW</td>
<td>Least (lowest 25%)</td>
<td>85 – 100%</td>
<td>Region of the Americas, Europe, Western Pacific</td>
</tr>
</tbody>
</table>

Global Advisory Committee on Vaccine Safety, December 2008 and June 2009

- **December 2008, reviewed:**
  - Safety data: Phase III efficacy studies (Rotarix™ & RotaTeq®)
  - Post-marketing safety data: US, Australia, & Latin America.

- **Concluded:**
  - No increased risk of intussusception: within confines of the clinical trials
  - Can rule out with confidence intussusception risk of the order of Rotashield®
  - However, available post-marketing surveillance data too few to rule out risk of substantially lower magnitude

- **June 2009:**
  - No data directly support hypothesis that administration of rotavirus vaccine outside of age range 6–15 weeks for 1st dose & 32 weeks for 2nd dose is associated with an increased risk of intussusception

NIH Photo: X-ray of intussusception

Rotavirus vaccines: an update

Rotaviruses are the most common cause of severe diarrhoeal disease in young children throughout the world. According to 2004 estimates by WHO, 527,000 children aged <5 years die each year from vaccine-preventable rotavirus infections; most of these children live in low-income countries. Two oral, live, attenuated rotavirus vaccines, Rotarix (GlaxoSmithKline Biologicals, Rixensart, Belgium) and RotaTeq

Le point sur les vaccins antirotavirus

Les rotavirus sont la cause la plus fréquente de maladie diarrhéique grave chez le jeune enfant partout dans le monde. Selon les estimations effectuées par l’OMS en 2004, 527,000 enfants âgés de <5 ans meurent chaque année d’une infection à rotavirus évitable par la vaccination; la plupart de ces enfants vivent dans des pays à faible revenu. Deux vaccins antirotavirus vivants atténués pour voie orale, le Rotarix (GlaxoSmithKline Biologicals, Rixen-
2009 WHO Recommendations for Rotavirus Vaccine Administration

- Rotavirus vaccine for infants should be included in all national immunization programmes.
- In countries where diarrhoeal deaths account for ≥10% of mortality among children aged <5 years, the introduction of the vaccine is strongly recommended.
- WHO recommends that the first dose of either RotaTeq® or Rotarix™ be administered at age 6–15 weeks.
- The maximum age for administering the last dose of either vaccine should be 32 weeks.
- Recommends that 2 doses of Rotarix™ be administered with 1st and 2nd doses of DTP rather than with second and third doses. This ensures maximum immunization coverage and reduces potential for late administration beyond approved age window.
Rotavirus Vaccines Included in a Coordinated Approach to Diarrhoeal Disease Control

http://www.who.int/wer/2009/wer8451_52
Rotavirus Vaccines and Porcine Circoviruses

- Unexpectedly, porcine circovirus (PCV) detected in both vaccines
  - Circoviruses: circular, single-stranded DNA, infect birds & pigs

- PCV1 identified in Rotarix; PCV1 and PCV2 in RotaTeq
  - PCV 1 & 2 infect pigs. PCV1 not known to cause disease in any animals; PCV2 can cause disease in pigs

- WHO Global Advisory Committee on Vaccine Safety reviewed Rotarix safety data. 26 March 2010: 'benefits of vaccination far outweighed any currently known risk' associated with Rotarix

- WHO Strategic Advisory Group of Experts on Immunization reviewed Rotarix data. 13-15 April 2010 meeting. In absence of any known risk, 'strongly recommended the continued use' of Rotarix for immunization programmes
WHO Surveillance Strategy
Surveillance for Rotavirus and new VPDs
When and why?

- **Before vaccine introduction**
  - Demonstrate disease burden
  - Justification to introduce vaccine
  - Establish system to measure vaccine impact
  - Identify circulating strains

- **After vaccine introduction**
  - Monitor vaccination program impact, when combined with
    - Epidemiological studies (case-control, modelling)
  - Monitor any change in circulating strains: needs strong laboratory support
  - Platform to evaluate safety
Surveillance for Rotavirus and New VPDs: How, Where and Who?

Data Collection

Sentinel surveillance

Hospital based

Children <5 years of age

• Admitted to the hospital:
  • For treatment of acute gastroenteritis - diarrhoea
  • Strong laboratory capacity (syndrome)

• Seek to coordinate with other surveillance activities: invasive bacterial diseases

Photos: Patan Hospital, Nepal
Sentinel vs. National Surveillance

1. Sentinel:
   - Children's Hospital

   • Easier, cheaper
   • Likely good lab
   • Better quality data (active vs. passive)
   • Monitor trends over time
   • More severe cases, so not representative of all disease

2. National:
   - Every HCF, Every Case

   • More expensive, harder, more labour intensive
   • Transport samples to lab
   • All disease in the country (mild, severe)
   • Monitor trends over time
   • Identify outbreaks, epidemics

Netherlands
Spain
Complementary Reporting Structure
Layered Approach to Rotavirus Surveillance

- **Core sentinel sites**
  - Hospitals
  - Combined rotavirus and meningitis surveillance
  - 1 per country, larger countries up to 3

- **Population-based sites**: generate incidence estimates
  - 1 one site per region (6 WHO Regions + 3 WHO African sub-regions)

- **Centers of excellence**
  - Specialized epidemiologic studies, complement surveillance
Global New Vaccines Surveillance

Preliminary 2009 Data
Recent Transition of RotaADIP Surveillance to WHO coordination

- **Transition phase:**
  - July 2008 through July 2010
  - 14.9 million USD funding through GAVI

- **Past 2 years of activities:**
  - WHO regional offices coordinate with Ministry of Health
  - Technical support from WHO and partners
  - Selection of sites to be transitioned to WHO / GAVI
  - Data standardization
  - Define and standardize layered structure
Global Rotavirus Information and Surveillance Bulletin
Volume 1: December 2009
Reports on this Bulletin are welcome.
Please email Dr. Carsten Mandel (mandel@who.int)

This is the first biennial WHO Global Rotavirus Surveillance Bulletin to describe sentinel surveillance for rotavirus infection among hospitalized children under five years of age and to summarize collated surveillance data for 2008. This bulletin is the culmination of years of effort by many partners to provide such routine and standardized information.

Rotavirus Disease Burden on Children and Rotavirus Vaccination
Rotavirus diseases account for 17% of the 10.4 million deaths among children <5 years of age globally.1 Among children aged <5 years, rotavirus infection is the leading cause of severe acute diarrheal disease, accounting for an estimated 527,000 deaths annually, and is a leading cause of hospitalizations for diarrhoea2, reflecting a significant cost in health resources.3 Rotavirus was first isolated in 1973, and vaccine development has been a priority to prevent the large burden of disease. With the licensure of two new rotavirus vaccines in 2006, the global health community now has the tools to prevent a major contributor to childhood death and severe illness.

The WHO Rotavirus Surveillance Network
The main purpose of the WHO rotavirus surveillance system is to provide data to decision makers regarding the introduction of rotavirus vaccine and to monitor the impact of vaccination. The system focuses on hospitalized children and provides information on the proportion of hospitalized diarrhoea caused by rotavirus. Prior to 2006, rotavirus surveillance networks in the WHO regions of the Americas, Europe, Africa and Eastern Mediterranean were coordinated by the respective WHO Regional Offices with funding through the polio programme and technical support from the Centers for Disease Control and Prevention, Atlanta (CDC). Surveillance in Asia was conducted by the Asian Rotavirus Surveillance Network (ARSN) supported by CDC. In 2006, the coordination of the ARSN was transferred to the WHO, and regional offices in the South-East Asia and Western Pacific Regions. Thus all the regional surveillance networks are now coordinated by WHO Regional Offices, using standard definitions, core dataset and laboratory methods, with financial support provided to Global Alliance for Vaccines and Immunization (GAVI) eligible countries. In the coming years, global surveillance will continue to strengthen as more countries join the WHO network. During 2008, 44 WHO Member States were part of the network (Figure 1).

Figure 1. Countries Participating in the WHO Network, 2008


Figure 1: Countries Participating in the WHO Network, 2008

9th International Rotavirus Symposium, 2-3 August 2010
Rotavirus Surveillance
Preliminary Data, 2009

Photo: Dr. Duncan Steele
Rotavirus Surveillance
Countries Participating in the WHO Network and Reporting Data for 2009

Data collected from WHO Regions.

Yes (55 Member States or 28% of Member States)

Slide date: 2 August 2010
Rotavirus Global and Regional Laboratory Network Structure, 2010

- WHO Global Reference Laboratory
- WHO Regional Reference Laboratories

CDC
National Public Health Institute of Rio de Janeiro
Christian Medical College
Republican Research and Practical Centre for Epi and Microbiology
Korea CDC
NAMRU-3
Noguchi Memorial Institute for Medical Research
University of Limpopo (Medunsa Campus)
Murdoch Children's Research Institute
<table>
<thead>
<tr>
<th>Region</th>
<th># of Reporting Countries</th>
<th># Enrolled with Case Report Form and Stool Collected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2008</td>
<td>2009</td>
</tr>
<tr>
<td>African</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Americas</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>European</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>South East Asian</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
<td>55</td>
</tr>
<tr>
<td>% Increase 2008 to 2009</td>
<td>20%</td>
<td></td>
</tr>
</tbody>
</table>
### WHO Coordinated Rotavirus Surveillance
### % Rotavirus Positive by WHO Region, 2009 Preliminary Data

<table>
<thead>
<tr>
<th>WHO Region</th>
<th>Number of Specimens Tested</th>
<th>% Rotavirus Positive *</th>
</tr>
</thead>
<tbody>
<tr>
<td>African</td>
<td>5,071</td>
<td>33</td>
</tr>
<tr>
<td>Americas**</td>
<td>13,085</td>
<td>25</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>10,910</td>
<td>42</td>
</tr>
<tr>
<td>European</td>
<td>6,330</td>
<td>37</td>
</tr>
<tr>
<td>South East Asian</td>
<td>2,596</td>
<td>37</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>4,977</td>
<td>46</td>
</tr>
</tbody>
</table>

* % positive = median of %ages of all reporting countries in the Region

**Includes countries administering rotavirus vaccine
### Rotavirus Surveillance

**% of Enrolled that Tested Positive by Month, Selected Countries, Preliminary 2009 Data**

<table>
<thead>
<tr>
<th>Country/Site</th>
<th>Year of introduction of the vaccine in the infant national immunization schedule</th>
<th>January % +ve</th>
<th>February % +ve</th>
<th>March % +ve</th>
<th>April % +ve</th>
<th>May % +ve</th>
<th>June % +ve</th>
<th>July % +ve</th>
<th>August % +ve</th>
<th>September % +ve</th>
<th>October % +ve</th>
<th>November % +ve</th>
<th>December % +ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Democratic Republic of Congo</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Ecuador</td>
<td>2007</td>
<td>14</td>
<td>17</td>
<td>17</td>
<td>13</td>
<td>14</td>
<td>26</td>
<td>27</td>
<td>28</td>
<td>15</td>
<td>15</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Syrian Arab Republic</td>
<td></td>
<td>71</td>
<td>29</td>
<td>54</td>
<td>52</td>
<td>34</td>
<td>22</td>
<td>45</td>
<td>33</td>
<td>52</td>
<td>68</td>
<td>53</td>
<td>58</td>
</tr>
<tr>
<td>Ukraine</td>
<td></td>
<td>79</td>
<td>78</td>
<td>78</td>
<td>80</td>
<td>54</td>
<td>31</td>
<td>42</td>
<td>28</td>
<td>21</td>
<td>32</td>
<td>28</td>
<td>51</td>
</tr>
<tr>
<td>Myanmar</td>
<td></td>
<td>68</td>
<td>71</td>
<td>33</td>
<td>25</td>
<td>22</td>
<td>17</td>
<td>9</td>
<td>24</td>
<td>27</td>
<td>39</td>
<td>52</td>
<td>59</td>
</tr>
<tr>
<td>Viet Nam</td>
<td></td>
<td>87</td>
<td>83</td>
<td>57</td>
<td>58</td>
<td>60</td>
<td>59</td>
<td>91</td>
<td>85</td>
<td>51</td>
<td>54</td>
<td>57</td>
<td>65</td>
</tr>
</tbody>
</table>

*Percent positive breakdown:

- **Brown**: >= 40% of tested samples were positive for Rotavirus
- **Red**: >=30% and <40% of tested samples were positive for Rotavirus
- **Orange**: >=20% and <30% of tested samples were positive for Rotavirus
- **Yellow**: >=10% and <20% of tested samples were positive for Rotavirus
- **Green**: <10% of tested samples were positive for Rotavirus
- **ND**: No data available
Comparison of Distribution of Rotavirus Strains Globally with 2009 Preliminary Data

**Global**

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

**2009 Surveillance**

- **G1P[8]**: 32%
- **G4P[8]**: 4%
- **G3P[8]**: 15%
- **G2P[8]**: 5%
- **G9P[8]**: 4%
- **G4P[8]**: 4%
- **G3P[8]**: 15%
- **G2P[8]**: 5%
- **G1P[8]**: 32%
- **untypeable**: 12%
- **mixed**: 16%
- **uncommon**: 12%

Gentsch et al. J Infect Dis 2005
Improving Quality
New and Underutilized Vaccines Meeting
Surveillance Data Quality

- **Data Availability & Quality Limited by** perception of surveillance as special project, lack of adherence to guidelines
- **Data Could be Used More by** sentinel sites, MoH internal use (GAVI applications, monitoring performance indicators) & MoH 'external' use (MoF, WHO, paediatrics & medical societies)

MoH ownership critical for sustainability & high data quality

**Next Steps:**
- WHO & partners engage MoH to 'own' and use data
- MoH regular supervision of sites; possibly integrated with other activities
- WHO consider development of advocacy tools & further refinement of & finalization of guidelines