Impact of Rotarix™ on the burden of severe rotavirus disease and new challenges

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Director Global Medical Affairs
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ROT-2010-021
Overview

• **Efficacy in developing and developed countries**
  - Broad protection against circulating strains
  - Natural early RV exposure impacts on measurement of vaccine efficacy

• **Safety profile**
  - IS
  - PCV 1

• **Vaccine Impact**
  - Vaccine effectiveness (Brazil)
  - Mortality (Mexico)
  - Routine vaccination in Belgium
A pivotal study on rotavirus infection and severity of disease

- Two natural infections provide 100% protection against subsequent moderate/severe disease
- Natural RV infection attenuates severity of subsequent infections, regardless of serotype

Rotarix™ global efficacy against severe RVGE

Central and South America

11 countries severe RVGE\(^1,2\)
- 1\(^{st}\) year FU: 84.7% (71.7–92.4)
- 2\(^{nd}\) year FU: 80.5% (71.3–87.1)

OPV co-ad (six countries) severe RVGE\(^4\)
- 1\(^{st}\) year FU: 81.6% (54.4–93.5)

Africa

Two countries severe RVGE\(^8\)
- 1\(^{st}\) year FU: 61.2% (44.0–73.2)

Europe

Six countries severe RVGE\(^3\)
- 1\(^{st}\) year FU: 95.8% (89.6–98.7)
- 2\(^{nd}\) year FU: 90.4% (85.1–94.1)

South East Asia

Three countries severe RVGE\(^5,7\)
- 1\(^{st}\) year FU: 100% (72.2–100)
- 2\(^{nd}\) year FU: 96.1% (85.1–99.5)
- 3\(^{rd}\) year FU: 100% (67.5–100.0)

Co-ad, co-administration; FU, follow-up

5. Phua KB, et al. APCP. 2009
7. Phua KB, et al. ESPID. 2009
*Rotarix™ protects against G1 and several non-G1 rotavirus strains*

<table>
<thead>
<tr>
<th>Source</th>
<th>Region</th>
<th>VE [95%CI] against severe RVGE 1-year follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruiz-Palacios et al. 2006¹</td>
<td>Latin America</td>
<td>G1: 90.8 [70–98], G2: 45.4 [-81–86], *G3: 86.9 [63–97], *G4: 86.9 [63–97], G9: *86.9 [63–97], G12: -</td>
</tr>
<tr>
<td>Neuzil et al. 2009³</td>
<td>Africa</td>
<td>G1: 64.1 [30–82], G2: 79.2 [9–97], G3: 83.8 [10–98], G4: - , G8: 64.4 [17–85], G9: - , G12: 51.5 [&lt;0–78]</td>
</tr>
<tr>
<td>Vesikari et al. 2007⁴</td>
<td>Europe</td>
<td>G1: 96.4 [86–100], G2: 74.7 [&lt;0–100], G3: 100 [45–100], G4: 100 [65–100], G9: - , G12: 94.7 [78–99]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source</th>
<th>Region</th>
<th>VE [95%CI] against severe RVGE 2-year follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linhares et al. 2008⁵</td>
<td>Latin America</td>
<td>G1: 82.1 [64–92], G2: 38.6 [&lt;0–84], G3: - , G4: - , G8: - , G9: - , G12: -</td>
</tr>
<tr>
<td>Phua et al. 2009⁶</td>
<td>Asia</td>
<td>G1: 100 [81–100], G2: 100 [&lt;0–100], G3: 94.5 [65–100], G4: - , G8: - , G9: 91.7 [44–100], G12: -</td>
</tr>
<tr>
<td>Vesikari et al. 2007⁴</td>
<td>Europe</td>
<td>G1: 96.4 [90–99], G2: 85.5 [24–99], G3: 93.7 [53–100], G4: 95.4 [68–100], G8: - , G9: 85.0 [72–93], G12: -</td>
</tr>
</tbody>
</table>

*Pooled data for G3, G4 and G9.

## Efficacy of rotavirus vaccines by mortality stratum and country

<table>
<thead>
<tr>
<th>Mortality rate defined by WHO</th>
<th>RV vaccine efficacy estimates</th>
<th>Countries where studies were performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGH</td>
<td>50–64%</td>
<td>Ghana, Kenya, Malawi, Mali</td>
</tr>
<tr>
<td>INTERMEDIATE</td>
<td>46–72%</td>
<td>Bangladesh, South Africa</td>
</tr>
<tr>
<td>72–85%</td>
<td></td>
<td>Vietnam, countries in the Region of the Americas</td>
</tr>
<tr>
<td>LOW</td>
<td>85–100%</td>
<td>Countries in the Region of the Americas, Europe, Western Pacific</td>
</tr>
</tbody>
</table>

Adapted from WHO. Wkly Epidemiol Rec 2009;84:533-40
Severe RVGE episodes per 100 infants prevented in South Africa & Malawi

N = 4939 infants. Randomised, placebo-controlled trial. First year follow-up. Rotarix™ was coadministered with OPV and other EPI vaccines. HIV-positive infants were not excluded and breastfeeding was not restricted.

Despite the lower efficacy, the number of severe RVGE cases prevented was greater in Malawi than in South Africa (6.7 vs 4.2/100 infants)
Rotavirus seroconversion in developing countries

Seroconversion rates for antirotavirus IgA in Malawi and South Africa vs age at dose 2/last dose of Rotarix™ or placebo

Malawi

- Rotarix™ Dose 2: 47.2%
- Placebo: 40.4%

Mean age +/- SD (weeks):
- 11.7±1.21
- 11.6±1.16
- 11.1±1.23
- 11.1±1.28

South Africa

- Rotarix™ Dose 2: 57.1%
- Placebo: 16.7%

Time between Dose 2/last dose of placebo and post-vaccination blood draw: 1 month

High level of early exposure in these countries

1. Han HH WSPID. 2009
Accumulated immunity estimates over time for Rotarix™ versus no rotavirus vaccination

The estimates for Vaccine Efficacy seem to be different in various regions of the world; probably due to the high level of exposure early during the first months in developing countries.

Early protection in UMV is important to help reduce the number of infections.

Adapted from Standaert B et al., ESPID. 2010
Overview

• **Efficacy in developing and developed countries**
  - Broad protection against circulating strains
  - Natural early RV exposure impacts on measurement of vaccine efficacy

• **Safety profile**
  - IS
  - PCV 1

• **Vaccine Impact**
  - Vaccine effectiveness (Brazil)
  - Mortality (Mexico)
  - Routine vaccination in Belgium
Clinically acceptable safety profile

• No increased risk of intussusception in clinical trials leading to registration within a 31-day period following any dose

• In a subset of 20,169 infants followed up to 1 year after dose 1 (10,159 vaccinees and 10,010 placebo): 4 cases in vaccinees compared with 14 cases with placebo [Relative Risk: 0.28 (95% CI: 0.10, 0.81)]

• Clinically acceptable safety data on specific populations (preterm and HIV positive infants)

**Rotarix™ pharmacovigilance: analysis of observed vs expected IS incidence**

### O/E analysis for day 30 period by dose 1

(64.4 WW million doses – Jan 2010)

<table>
<thead>
<tr>
<th>Region</th>
<th>N Doses</th>
<th>Observed</th>
<th>Expected (range)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worldwide</td>
<td>34,201,432</td>
<td>123</td>
<td>261.4-4,821.6</td>
<td>0.20</td>
</tr>
<tr>
<td>Europe</td>
<td>1,376,093</td>
<td>41</td>
<td>13.9-48.1</td>
<td>1.88</td>
</tr>
<tr>
<td>US</td>
<td>993,710</td>
<td>5</td>
<td>22.7-37.2</td>
<td>0.21</td>
</tr>
</tbody>
</table>

### O/E analysis for day 7 period by dose 1

<table>
<thead>
<tr>
<th>Region</th>
<th>N Doses</th>
<th>Observed</th>
<th>Expected (range)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worldwide</td>
<td>34,201,432</td>
<td>78</td>
<td>61.0-1,125.0</td>
<td>0.56</td>
</tr>
<tr>
<td>Europe</td>
<td>1,376,093</td>
<td>29</td>
<td>3.3-11.2</td>
<td>5.27</td>
</tr>
<tr>
<td>US</td>
<td>993,710</td>
<td>2</td>
<td>5.3-8.7</td>
<td>0.36</td>
</tr>
</tbody>
</table>

**Limitations of analysis**

- Background incidence rate of IS varies by region
  - Europe: 40-100/100,000 per year
- Under-reporting of IS; reporting bias
- Age distribution of vaccination

Data Lock Point: 11 Jan 2010 Periodic Safety Update Report; Analysis shared with EMEA, FDA, WHO/GACVS, TGA
Rotarix™ and Rotateq® Active Surveillance in Australia

- **Australia**
  - Active surveillance for IS
  - 2 active surveillance mechanisms:
    - hospital-based case finding
    - monthly reports from paediatricians
  - No overall increase in IS following rotavirus vaccine
  - Evidence suggestive of an elevated risk within 21 days following the first dose only

<table>
<thead>
<tr>
<th>IS cases following Dose 1 in infants 1 to ≤ 3 months</th>
<th>Rotarix™</th>
<th>RotaTeq®</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-7 days relative risk [RR]</td>
<td>3.7 (95%CI 0.8, 10.8)</td>
<td>4.8 (95%CI 1.0, 14.1)</td>
</tr>
<tr>
<td>1-21 days RR</td>
<td>1.7 (95%CI 0.5, 4.2)</td>
<td>3.2 (95%CI 1.2, 7.0)</td>
</tr>
</tbody>
</table>

**Rotarix™ Post-Authorization Safety Studies (PASS): Ongoing**

- **Mexico**
  - Active surveillance for IS
  - Self-controlled case series analysis
  - Birth cohort: 575,000 with UMV
  - Primary outcome: Intussusception
  - Initiated January 2008; End of study by 2012

- **USA**
  - Healthcare database study
  - Matched cohorts: Rotarix™ + 2 control: concurrent and historical, IPV
    55,700 infants in Rotarix™ cohort; 167,100 / control cohorts
  - Outcomes: IS, Kawasaki’s disease, convulsions, hospitalisations for LRTI, fatalities
  - Initiated April 2009; End of study by 2010

Rotarix™ safety label updates from recent clinical and surveillance data

• Intussusception: Warnings and precautions
  – “Although no causal relationship has been established between vaccination with Rotarix™ and intussusception, as a precaution, healthcare professionals should follow-up on any symptoms indicative of intussusception ... Parents/guardians should be advised to promptly report such symptoms.”
  – “In post-marketing experience, cases of intussusception have been reported in temporal association with Rotarix™. Most cases were reported within seven days following the first dose”

• HIV+ subjects: contraindication for immunocompromised removed, wording in warnings & precautions
  – “Asymptomatic and mildly symptomatic HIV infections are not expected to affect the safety or efficacy of Rotarix™. A clinical study in a limited number of asymptomatic or mildly symptomatic HIV positive infants showed no apparent safety problems. Administration of Rotarix™ to infants who have known or suspected immunodeficiency should be based on careful consideration of potential benefits and risks.”

• Premature babies: Posology section updated
  – “Rotarix™ may be given with the same posology to preterm infants born after at least 27 weeks of gestational age.” (safety & immuno data)

The safety profile of Rotarix™ is based on the following:

- Extensive clinical data in more than 90,000 participants worldwide
- Testing confirms the presence of material from PCV-1 in all clinical trials
- Therefore, any potential impact on the safety of the vaccine through the presence of material from PCV-1 has been extensively studied in infants

GSK and regulatory agencies worldwide have robust surveillance systems in place to carefully monitor the safety of RV vaccines.

- GSK has reviewed all the clinical and post-marketing safety experience and has concluded that the benefit/risk profile of Rotarix™ remains positive
- Rotarix™ safety data has been analyzed by FDA, EMA and also by the WHO
- EMA confirms positive benefit-risk balance of Rotarix™
- WHO and FDA also communicated that there is no current evidence that the presence of PCV-1 materials in Rotarix™ could pose a safety risk

GSK continues to carefully monitor any safety issues and will continue to regularly update regulatory authorities worldwide.

GSK is currently investigating processes to manufacture the vaccine free of the virus.

No current evidence that PCV1 in Rotarix™ poses a risk to Public Health

Websites accessed 27th July 2010:
http://www.who.int/vaccine_safety/topics/rotavirus/rotarix_statement_march_2010/en/
http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm211101.htm
Summary: Safety profile
Safety and effectiveness will continue to be monitored

• An overall increase in IS after RV vaccination was not observed, but results suggested an elevated risk for IS following the first dose

• There are no current evidence that PCV1 in Rotarix™ poses a risk to Public Health
  – EMA confirms positive benefit-risk balance of Rotarix™
  – WHO and FDA also communicated that there is no current evidence that the presence of PCV1 materials in Rotarix™ could pose a safety risk

• To date, the benefit-risk ratio with Rotarix™ remains positive and supports rotavirus vaccination
Overview

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Rotavirus test results, pre- and post-introduction of Rotarix™, in children <5 years evaluated at a São Paulo hospital, 2004–2008

Reduction of 66.3% (p < 0.001) in the positivity rate for rotavirus
A significant decline in diarrhoea-related deaths was seen for children aged <5 years after introduction of RV vaccination in Mexico*

Number of diarrhoea-related deaths among children 59 months of age or younger from July 2002 to May 2009 in Mexico, according to age group

A decrease of acute GE deaths in children ≤11 months was observed in 2008 (41%), and a decrease of 66% (cf baseline) in 2009

* Introduction of Rotarix™ in the Mexican immunisation program

Monthly distribution of the number of RV positive tests per year in 9 Belgian hospitals: All hospitalised subjects

Impact on RV-positive stool samples in hospitalised children:
Approximately 60% reduction in the number of RV-positive tests in the 1\textsuperscript{st} year, and a further reduction towards over 75% in the 2\textsuperscript{nd} year

* RV vaccination with both Rotarix™ and Rotateq®. Rotarix™ is the most employed vaccine in Belgium.

Adapted from Raes et al. ESPID. 2010
Summary: Rotarix™

- Efficacy in developing and developed countries with a two dose schedule
  - Broad protection against G1 and several non-G1 strains
  - High level of early exposure may have an impact on vaccine efficacy
  - Early protection in UMV is important to help reduce the number of infections

- Safety and effectiveness data continue to be monitored
  - To date, the benefit-risk ratio with Rotarix™ remains positive and supports rotavirus vaccination

- Implementation of routine RV vaccination globally is expected to have a positive impact on public health, especially in Africa where the disease burden is high
Thank You
### Incidence rates of Intussusception, 1st year of life

#### Selected studies

<table>
<thead>
<tr>
<th>Country</th>
<th>Population &amp; methods</th>
<th>Rate / 100,000 per year</th>
<th>Reference or data source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>Single hospital, 2002-2004</td>
<td>71</td>
<td>Bines et al. 2006</td>
</tr>
<tr>
<td>Austria</td>
<td>2005-2006</td>
<td>56.2</td>
<td>Karl Zwiauer, personal communication</td>
</tr>
<tr>
<td>Austria</td>
<td>2006</td>
<td>43.6</td>
<td>Karl Zwiauer, personal communication</td>
</tr>
<tr>
<td>Belgium</td>
<td>Health Insurance, whole country 2000-2006</td>
<td>82</td>
<td>Hospital discharges per year (Pers Comm.)</td>
</tr>
<tr>
<td>Denmark</td>
<td>Complete birth cohort + hospital discharge 1980-2001</td>
<td>78.2</td>
<td>Fischer et al. 2004; table 2</td>
</tr>
<tr>
<td>Germany</td>
<td>BavariPro; OPS code only</td>
<td>37.4</td>
<td>Study report</td>
</tr>
<tr>
<td>Germany</td>
<td>BavariPro; ICD-10 or OPS code</td>
<td>72</td>
<td>Study report</td>
</tr>
<tr>
<td>Germany</td>
<td>ESPED</td>
<td>72.2</td>
<td>Study report; Adjusted for underreporting</td>
</tr>
<tr>
<td>Germany</td>
<td>Federal Health statistics, whole country, 2000-2005</td>
<td>96.7</td>
<td>Eva-Christina Schnabel, pers comm</td>
</tr>
<tr>
<td>Japan</td>
<td>Hospital records, 1978-2002</td>
<td>185</td>
<td>Nakagomi et al. 2006</td>
</tr>
<tr>
<td>Latin America</td>
<td>2003-2005 (12 countries)</td>
<td>40.4</td>
<td>GSK study 204; Saez-Llorens, Velazquez et al, MS.</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Surveillance network + capture-recapture adj., 2003-2006</td>
<td>49.3</td>
<td>Buettcher et al. 2007</td>
</tr>
<tr>
<td>USA</td>
<td>Hospitalisations, Claims db, 1993-2004</td>
<td>35</td>
<td>Tate et al. 2008</td>
</tr>
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