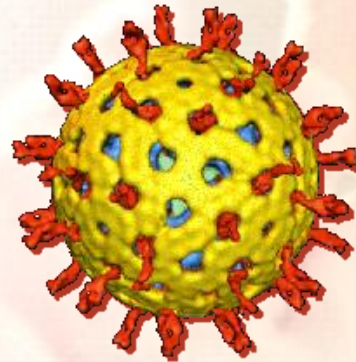


Summary of Human Rotavirus Vaccine (Rotarix™): Safety and Efficacy data



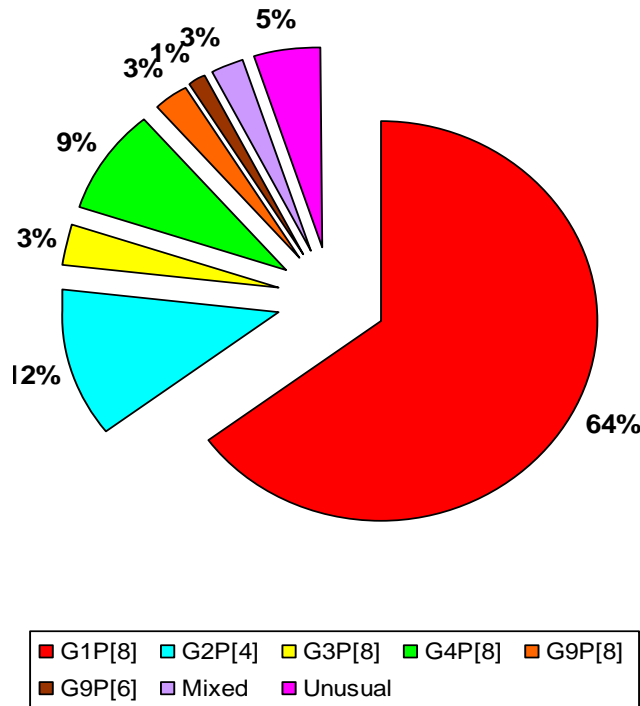
**Director Global Medical Affairs
Dr. Bernd Benninghoff**

Overview of presentation

- **Efficacy in developing and developed countries**
 - Vaccine efficacy in Europe, Latina, Asia and Africa
 - Broad protection against known and emerging strains
- **Persistent vaccine efficacy and OPV co-administration**
 - Persistent vaccine efficacy over 1st 3 years of life
 - Co-administration with Oral Polio Vaccine
- **Immunogenicity and safety profile**
 - Safety and immunogenicity in specific populations
- **Impact of 2 doses**

Global distribution of Rotavirus strains

**Distribution of human group A rotavirus P-G types (n=16474) reviewed
From 124 studies from 52 countries on five continents between 1989 & 2004**

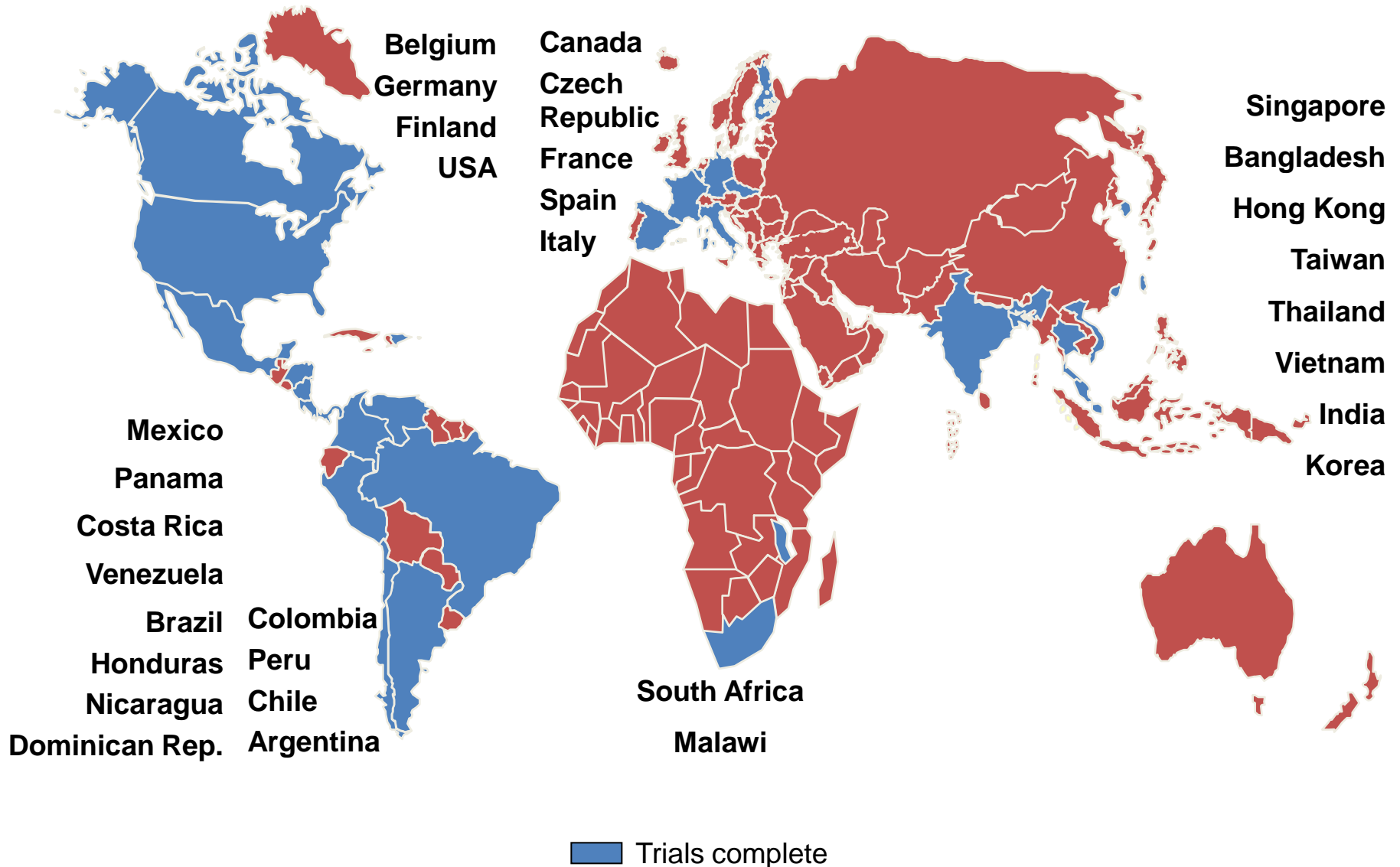


- Four commonest rotavirus strains account for 88.5% of the rotavirus diarrhoea among children worldwide¹
 - G1P[8], (64%)
 - G3P[8], (3%)
 - G4P[8], (9%)
 - G2P[4], (12%)
- G9 strains increasing recently & represent 4.1% of global rotavirus infection¹

Overview of presentation

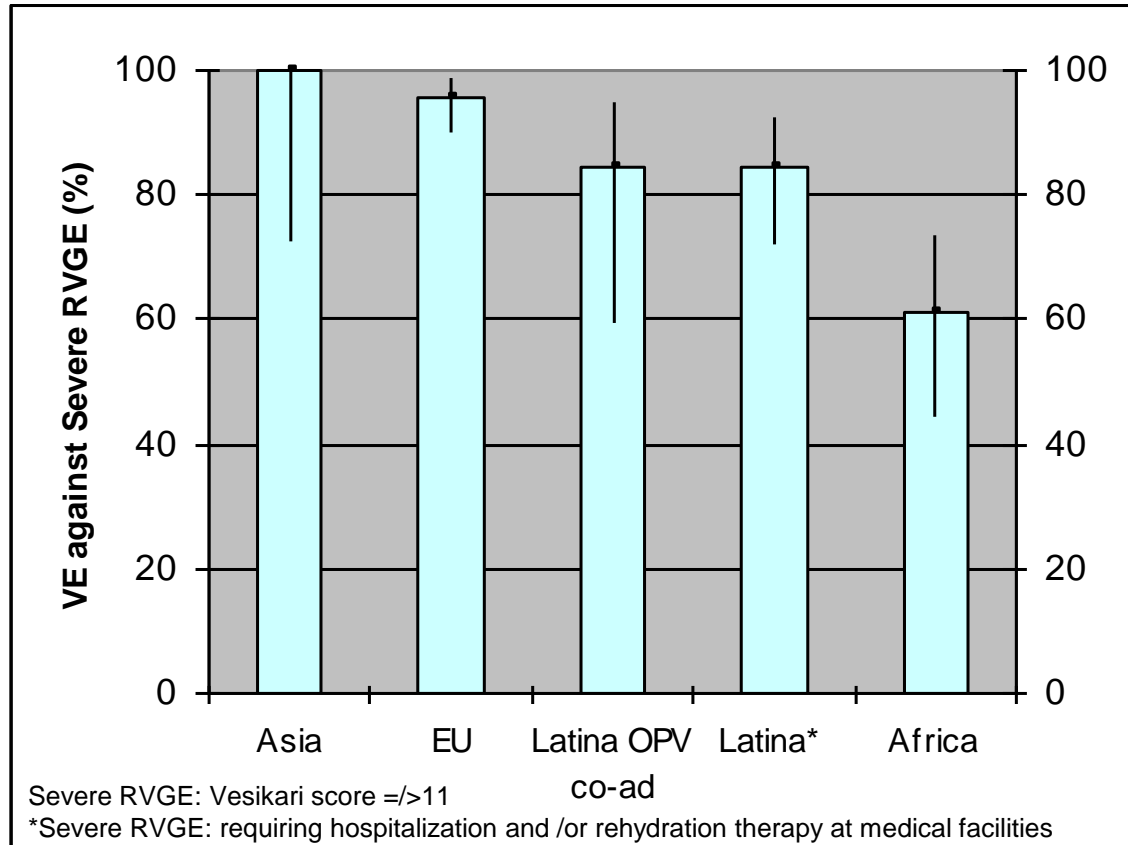
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Rotarix™: A global development program



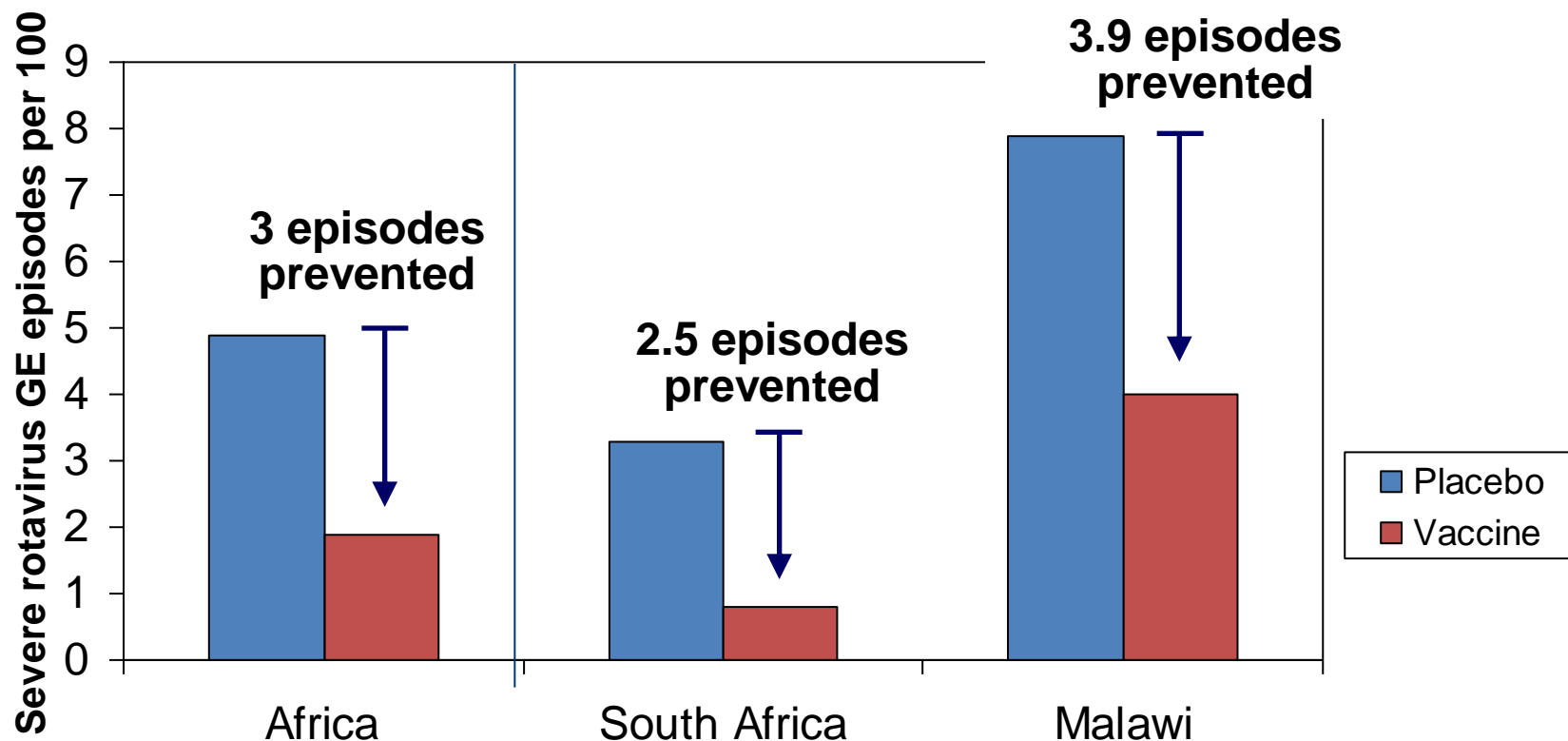
Vaccine efficacy in Europe, Latina, Asia and Africa

Efficacy follow up period: 1st RV season or till one yr of age



1. <http://www.gsk-clinicalstudyregister.com/>
2. Vesikari T et al, 2008 Lancet 370: 1757-63
3. Tregnaghi M et al, 2008, ICID Kuala Lumpur, Malaysia- June 19-22, 2008
4. Ruiz-Palacios GM et al, 2006 NEJM 354(1): 11-22
5. Cunliffe N et al, 2009, ESPID Brussels, Belgium – June 9-13, 2009, Abstract537 [<http://www.kenes.com/espид09/posters/Abstract537.htm>]

Severe rotavirus GE episodes prevented per 100 children in South Africa & Malawi



Efficacy	61.2% (44.0 – 73.2)	76.9% (56.0 – 88.5)	49.5% (19.2 – 68.3)
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1. Cunliffe N et al, 2009, ESPID Brussels, Belgium – June 9-13, 2009, Abstract537 [<http://www.kenes.com/espido9/posters/Abstract537.htm>]
2. Cunliffe N et al, 2009, VED Malaga, Spain – Sept 9-1, 2009

Protection against diverse RV types

	G1	G2	G3	G4	G8	G9	G12
VE against severe RVGE 1-yr follow up							
023 Latina	91.8 [74;98]	41 [<0;81]	87.7 [8;100]	-	-	90.6 [62;99]	-
024 Latina	100 [<0;100]	75.1 [<0;100]	-	-	-	88.3 [50;94]	-
037 Africa	64.1 [30;82]	79.2 [9;97]	83.8 [10;98]	-	64.4 [17;85]	57.0 (<0-86)	51.5 [<0;78]
036 EU	96.4 [86;100]	74.7 [<0;100]	100 [45;100]	100 [65;100]	-	94.7 [78;99]	-
VE against severe RVGE 2-yr follow up							
023 Latina	82.1 [65;92]	38.6 [<0;84]	78.9 [25;96]	61.8 [4;87]	-	86.6 [73;94]	-
028-030 Asia	100 [81;100]	100 [<0; 100]	94.5 [65;100]	-	-	91.7 [44;100]	-
036 EU	96.4 [90;99]	85.5 [24;99]	93.7 [53;100]	95.4 [68;100]	-	85.0 [72;93]	-

1. Ruiz-Palacios GM et al, 2006 NEJM 354(1): 11-22

2. Linhares et al, 2008 Lancet 371: 1181-89

3. Tregnaghi M et al, 2008, ICID Kuala Lumpur, Malaysia- June 19-22, 2008

4. Neuzil K et al, 2009, ESPID Brussels, Belgium – June 9-13, 2009, Abstract63 [http://www.kenes.com/esp09/posters/Abstract63.htm]

5. Vesikari T et al, 2008 Lancet 370: 1757-63

6. Phua KB et al, 2009, Vaccine (2009), doi:10.1016/j.vaccine.2009.07.098

Summary of presentation

- Efficacy in developing and developed countries
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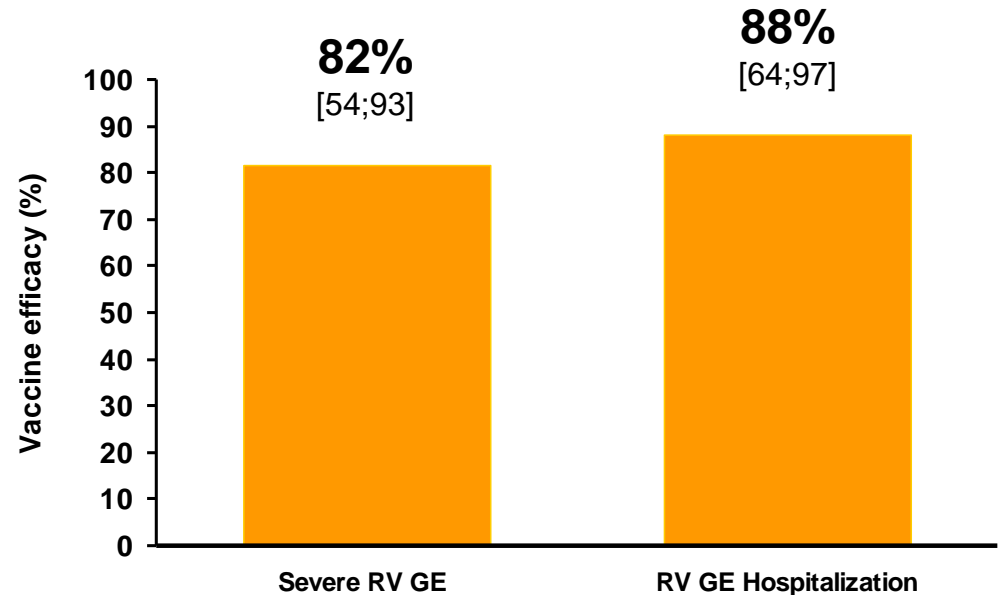
Persistent Efficacy over first 3 years of life

	n/N					Vaccine Efficacy against severe RV GE			P-Value
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	
During 1st yr follow up									
RIX4414	5263	0	0	0	0.1	100	72.2	100	<0.001
Placebo	5256	15	0.3	0.2	0.5	-	-	-	
During 2nd yr follow up									
RIX4414	5221	2	0	0	0.1	94.5	78.5	99.4	<0.001
Placebo	5194	36	0.7	0.5	1.0	-			
During 3rd yr follow up									
RIX4414	4222	0	0	0	0.1	100.0	67.5	100.0	<0.001
Placebo	4185	13	0.3	0.2	0.5	-	-	-	

1. <http://www.gsk-clinicalstudyregister.com/>
2. Phua KB et al, 2009, Vaccine (2009), doi:10.1016/j.vaccine.2009.07.098
3. Phua KB et al, 2009, ESPID Brussels, Belgium – June 9-13, 2009 [http://www.kenes.com/espido9/posters/Abstract599.htm]

Latin America (Rota 024): Co-administration of *Rotarix*TM with Oral Polio Vaccine

- Infants of 6-12 weeks
- Co-administration:
OPV + 2 doses
RIX4414 or Placebo
(n=4376) (n=2192)
- Efficacy follow-up: 7.4mo



- No impact on the efficacy of *Rotarix*TM
- In line with the high efficacy against severe RVGE of 85% demonstrated in the Latin American study with staggered OPV co-administration

Summary of presentation

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Safety and immunogenicity in HIV positive infants (S. Africa)

- **Study design**
 - A phase II, double-blind, randomized, placebocontrolled study to assess the safety, reactogenicity and immunogenicity of three doses of *Rotarix*TM when co-administered with routine childhood vaccines to HIV infected infants at 6,10 and 14 weeks of age in South Africa. (N=100)
- **Primary endpoint**
 - Occurrence of grade “2” or grade “3” fever, vomiting or diarrhoea within the 15-day solicited follow-up period after any doses.

Safety and immunogenicity in HIV positive infants (S. Africa)

Conclusions: reactogenicity/safety

- No significant difference between RIX4414 group and placebo group in terms of the incidence of grade “2” or grade “3” fever, vomiting or diarrhea within the 15-day post-vaccination period.
- The reactogenicity and safety profile of the HRV group was similar to the placebo group.
- The *Rotarix*TM 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.

Safety and immunogenicity in HIV positive infants (S. Africa)

Conclusions: immunogenicity

- *Rotarix*TM was immunogenic in HIV infected infants; the seroconversion rate 57.1% [95% CI: 34.0%; 78.2%] .
- Seroconversion was comparable to other studies in same population (Rota-037, 013, 014)
- Shedding profile not different from studies in healthy infants
- Antibody response against all concomitant vaccines was similar in both groups indicating that RIX4414 vaccine does not decrease the immune response to any of the antigens (PRP, tetanus, diphtheria, *Bordetella pertussis*, HBs, poliovirus types 1, 2 and 3) that were administered concomitantly.

Safety and immunogenicity in Preterm infants (Europe)

Study design

- A phase IIIb, double blind, randomised, placebo-controlled, multi-country, multicentre study to assess the safety, reactogenicity and immunogenicity of two doses of GlaxoSmithkline (GSK) Biologicals' oral live attenuated Human Rotavirus (HRV) Vaccine in preterm infants [born within a gestational period of 27-36 weeks.]

Primary objective

- To assess the **safety** of GSK Biologicals' HRV vaccine in terms of occurrence of serious adverse events, throughout the study period in pre-term infants receiving HRV vaccine versus pre-term infants receiving placebo.

1. F. Omenaca et. Al. 48th ICAAC/IDSA 46th annual meeting; Washington DC: October 25-28, 2008
2. <http://www.gsk-clinicalstudyregister.com/>

Safety and immunogenicity in Preterm infants

Conclusion: Safety and immunogenicity

- In preterm infants there was no statistically significant difference in terms of SAEs between the RIX4414 vaccine group and the placebo group.
- No increase in incidence of;
 - at least one unsolicited symptom after any dose during Days 0 to 30 post-vaccination in RIX4414 vaccine group as compared to placebo group.
 - each type of solicited symptoms reported within the 15 day (Days 0-14) follow-up period after each dose in RIX4414 vaccine group as compared to placebo group.
- Two doses of the RIX4414 vaccine were immunogenic in preterm infants [gestational age of 27-36 wks]:
 - the antirotavirus IgA antibody seroconversion rate of **85.7%** [95% CI: 79.0%; 90.9%]

Safety summary conclusion from clinical trial

Robust safety and tolerability profile

- SAEs occurred in 1.7% of vaccinees (N = 36,755) compared to 1.9% of placebo recipients (N = 34,454)
- No increased risk of intussusception within a 31-day period following any dose
 - In a subset of 20,169 infants followed up to 1yr 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)]
- Acceptable safety data on specific populations (preterm and HIV infants) (ESPID 2009)

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 Jan 2008; Results by 2012
- USA
 - Healthcare database study
 - Matched cohorts:
 - Rotarix*TM+ 2 control: concurrent and historical, IPV
 - 55,700 infants in *Rotarix*TM cohort; 167,100 / control cohorts
 - Outcomes: IS, Kawasaki's disease, convulsions, hospitalisations for LRTI, fatalities
 - Initiated March 2009; Results by 2012

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Official recommendations – regional



Europe¹

ESPID and ESPGHAN recommends universal mass vaccination of infants against RVGE in Europe

United States²

ACIP recommends routine RV vaccination of US infants either with *Rotarix*[™] or *RotaTeq*[™]

Australia³

PBAC recommends that the two RV vaccines (*Rotarix*[™] and *RotaTeq*[™]) be funded under the national immunization programme

1. European Society for Paediatric Infectious Diseases (ESPID) and European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Rotavirus Expert Group, 2008
2. Advisory Committee on Immunization Practices (ACIP), 2006
3. Pharmaceutical Benefits Advisory Committee (PBAC), 2007

Countries with rotavirus vaccination in childhood immunization calendar, as of 1st Sept 2009

both vaccines

Belgium
 Luxemburg
 Germany (3
 Federal States)
 Italy (Puglia
 Region)
Rotateq:
 Austria
 Finland

**USA, both
 vaccines**

Rotarix:

Brazil,
 El Salvador,
 Mexico,
 Panama,
 Venezuela,
 Ecuador,
 Peru,
 Colombia
 Bolivia (GAVI)
 Honduras (GAVI)
 Paraguay (2010)

Rotateq:

Nicaragua
 Guyana (GAVI)
 Cayman Islands

Rotarix:

Bahrain
 Qatar
 Oman

Rotarix:

- Nigeria (one
 State)
 - South Africa

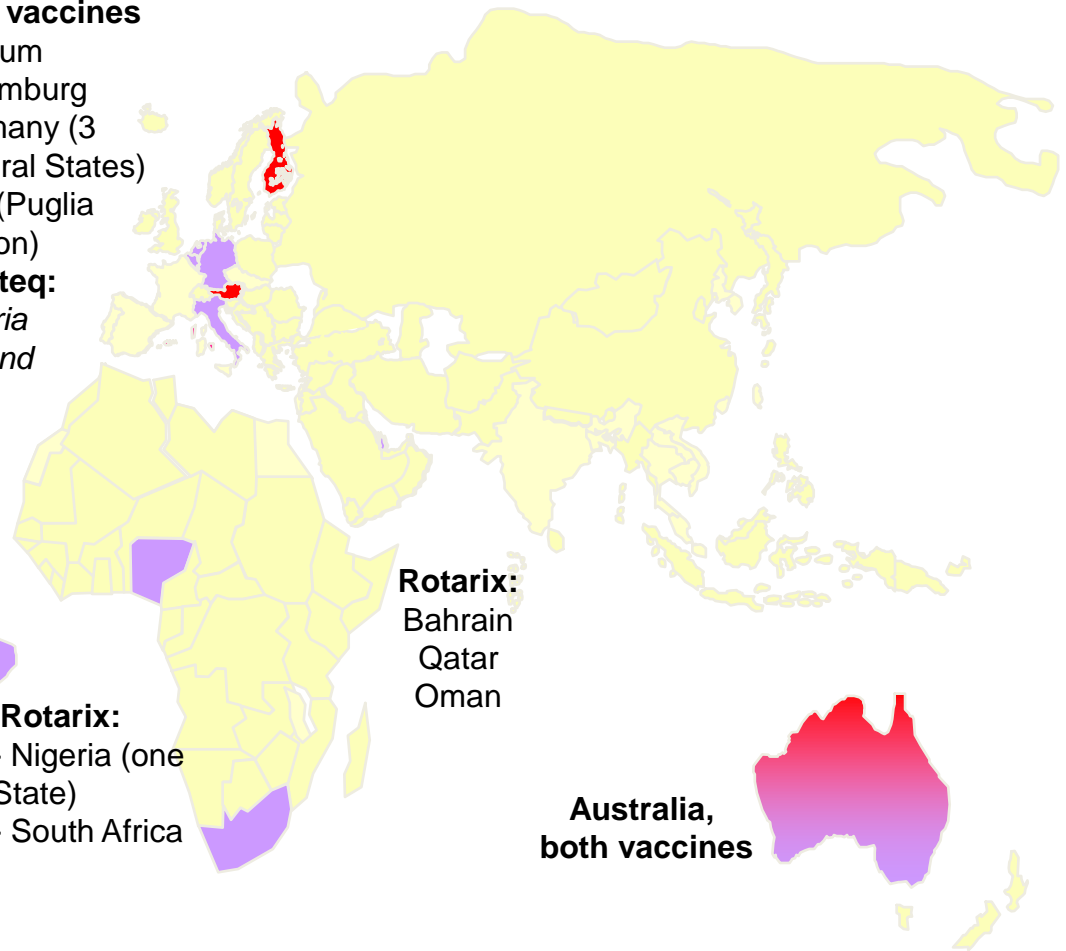
**Australia,
 both vaccines**



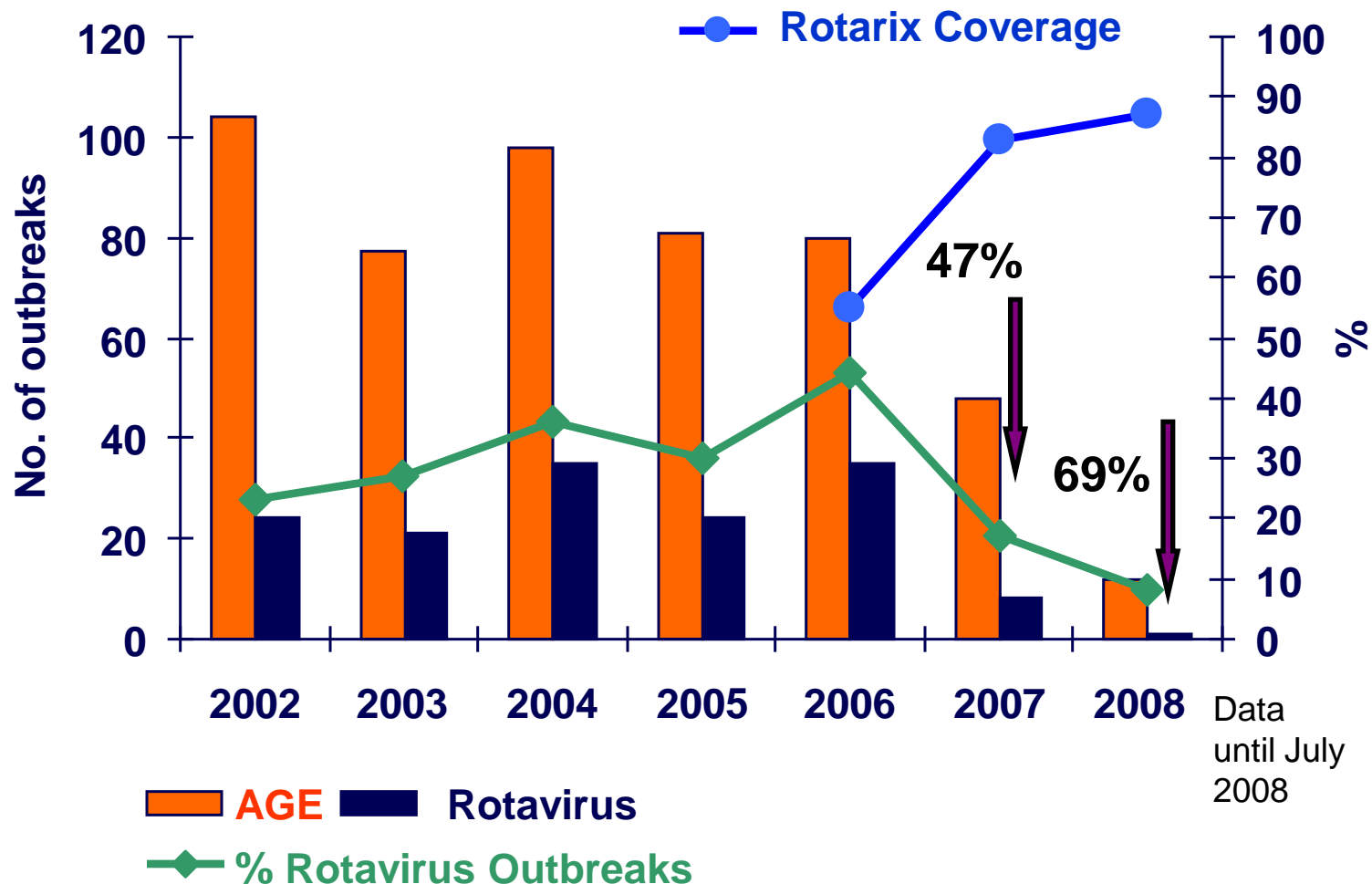
Countries with national RV immunizat.



Countries without national RV immunizat.



Outbreaks of All-Cause and of Rotavirus Specific AGE in Sao Paulo State, Brazil, Jan 2002 – Jul 2008

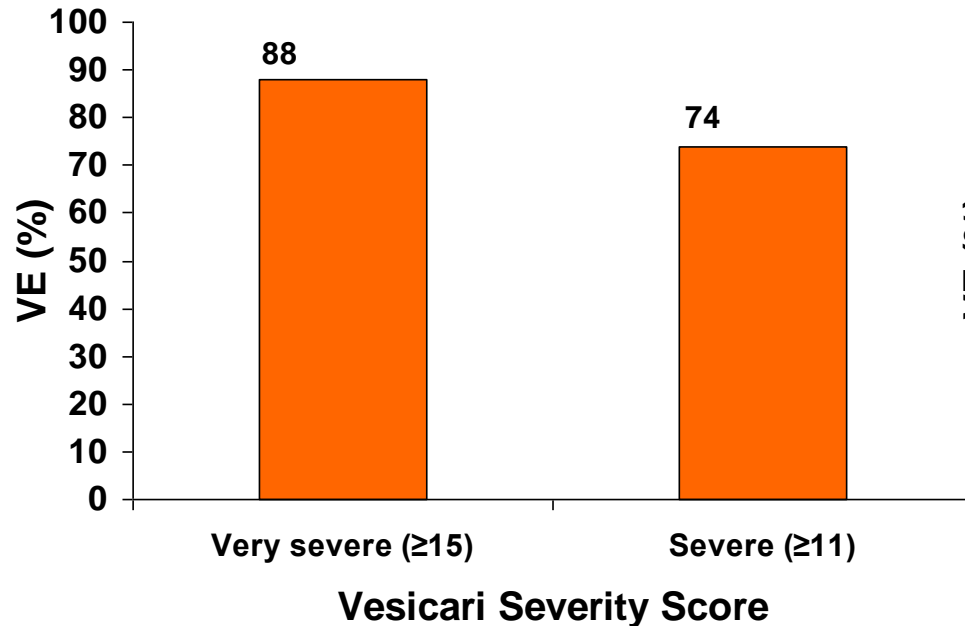


Source: Sao Paulo State Health Secretariat, available at:
http://www.cve.saude.sp.gov.br/htm/hidrica/dados/Rotavir0208_ESP.xls, last accessed on May 15th, 2009

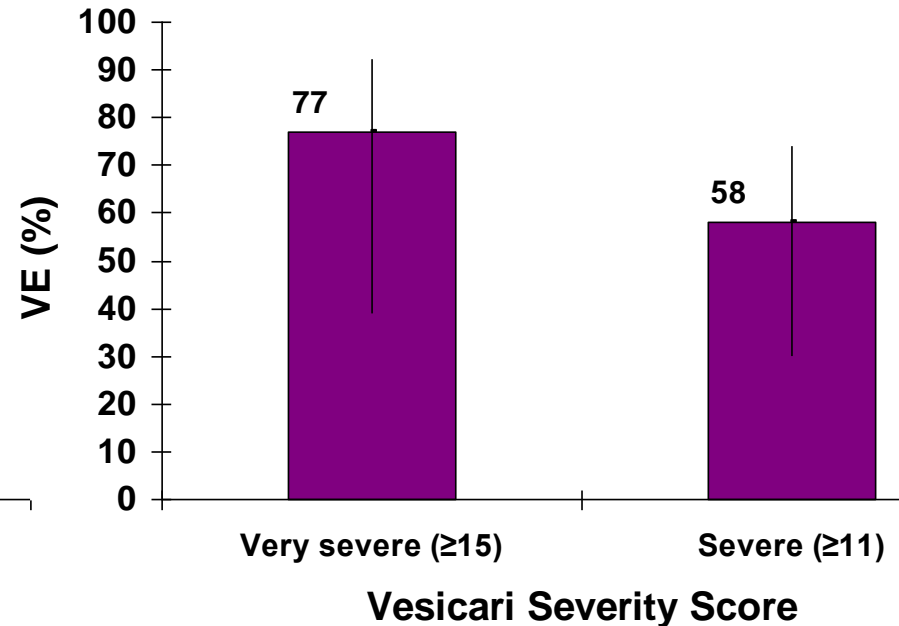
Rotavirus Vaccines Effectiveness Studies, El Salvador and Nicaragua, 2007-2008

Collaborative case-control studies from MoH/CDC/PAHO/PATH

2-Dose Effectiveness In El Salvador¹ 2007-2008



3-Dose Effectiveness in Nicaragua² 2007-2008
hospital and neighborhood

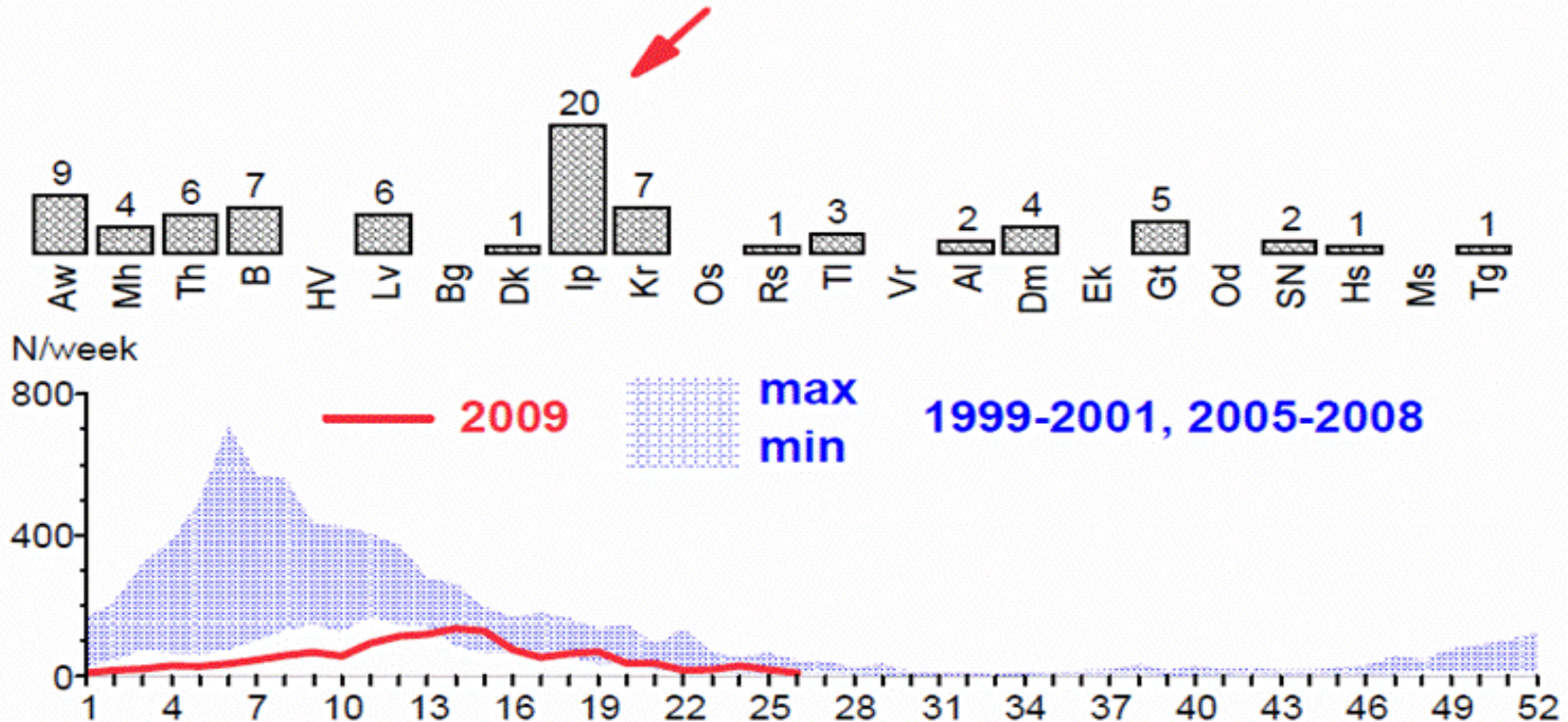


¹ WHO, *Wkly Epidemiol Rec* 2009; 84: 220-36

² Patel *et al JAMA* 2009; 301: 2243-2251

Impact of RV Vaccination: Belgium Public Health Institute, Surveillance « Laboratoires Vigies »

Rotavirus - N = 79

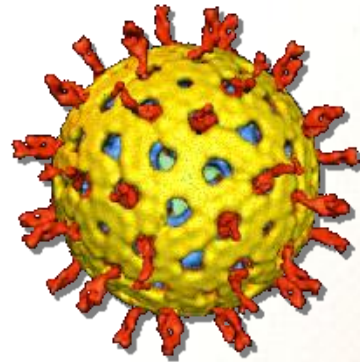


- Weekly number of RV-positive laboratory diagnoses decreased by >50% in post- vaccine period (2007-9) compared to pre-vaccine period (2005-06)
- Decline observed in all age-groups → herd protection? (data not presented)

Summary:

- Efficacy in developing and developed countries with a **two** dose schedule ✓
- Broad protection against known and emerging strains ✓
 - G1, G2, G3, G4, G8, G9, G12, P4, P6, P8
- Persistent vaccine efficacy over 1st 3 years of life ✓
- Acceptable immunogenicity and safety profile ✓
- High impact in countries which moved to UMV

Thank You



Director Global Medical Affairs
Dr. Bernd Benninghoff