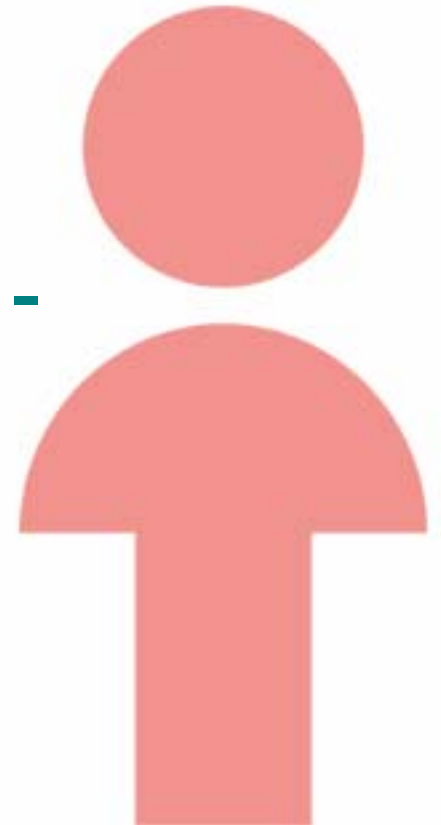


Rotarix™

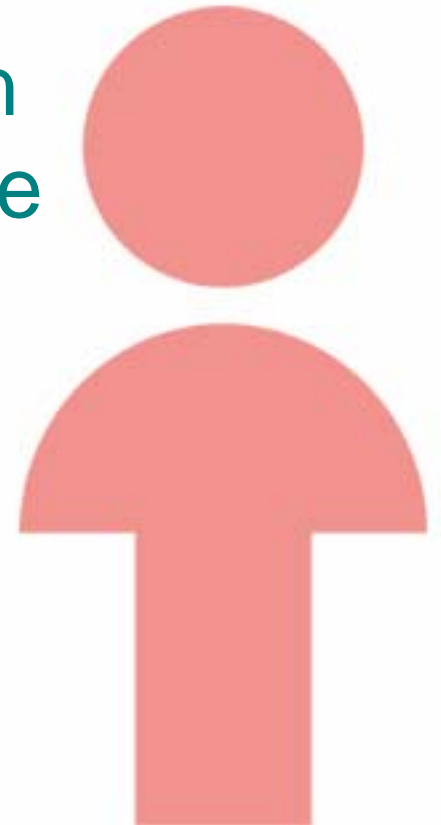
Rota-037: Interim Results -
Africa



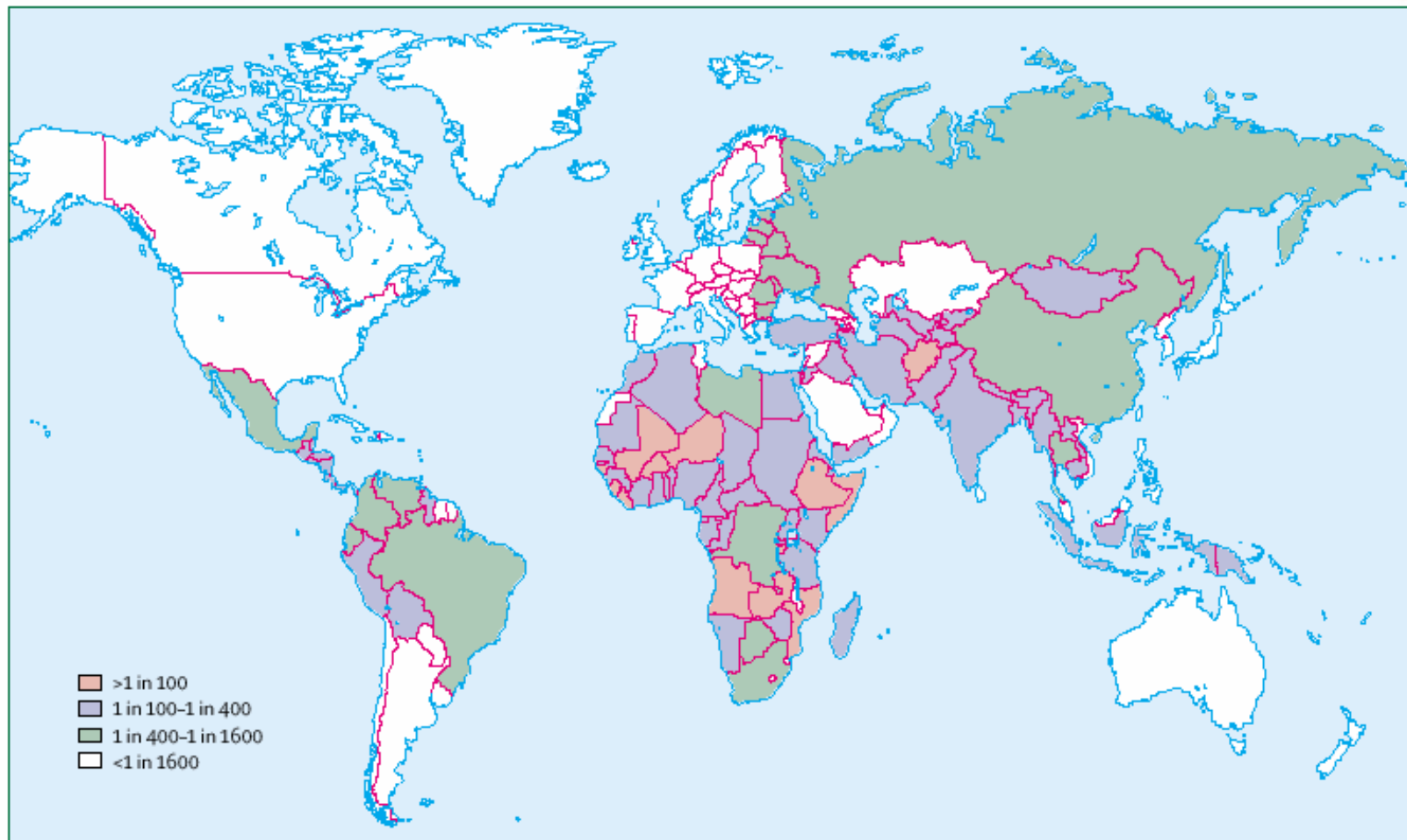


Efficacy of Human Rotavirus
Vaccine RIX4414 (*Rotarix*™) in
South African Infants During the
First Year of Life
– an Interim Report

Rotarix

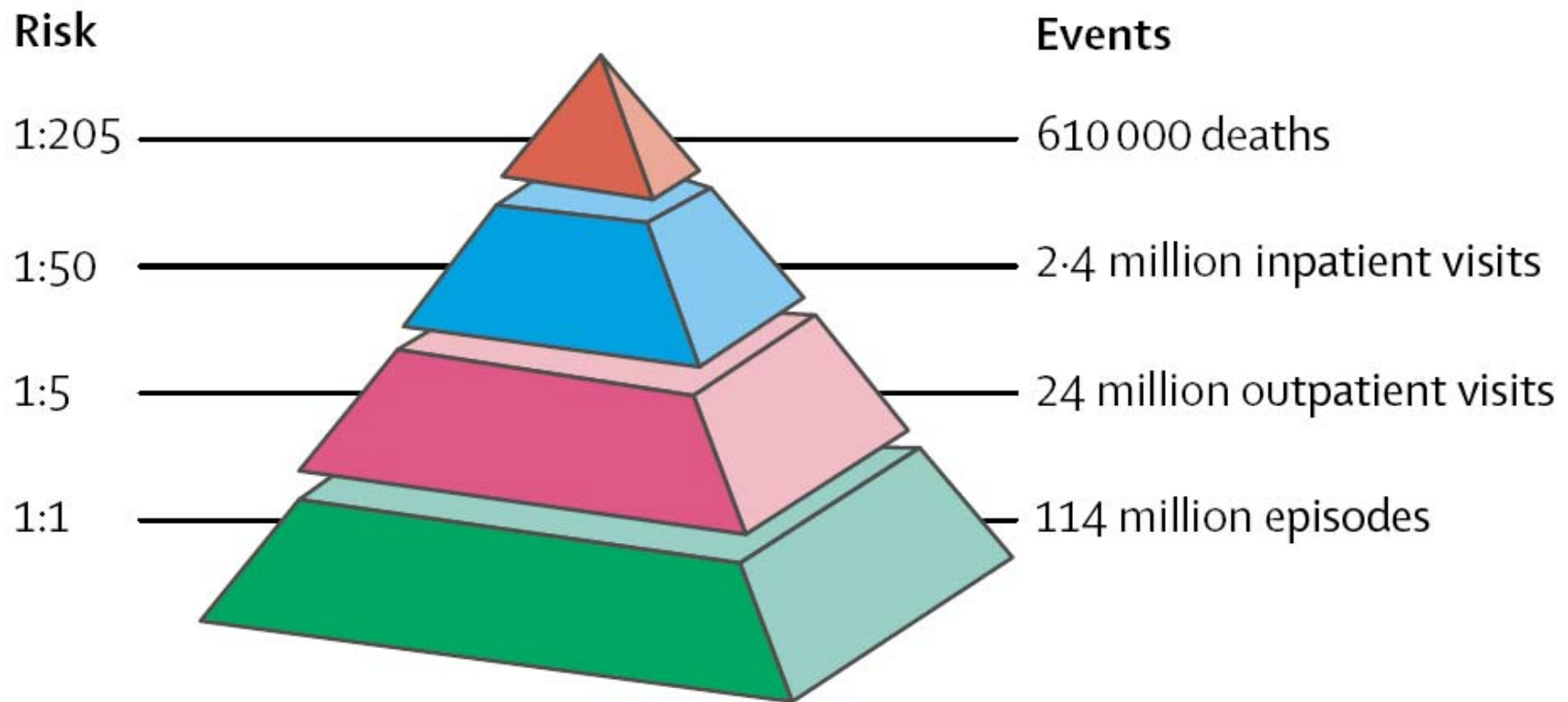


Contribution Of Gastroenteritis To Global Child Mortality per year



Estimated mortality from rotavirus diarrhoea
(risk of death per child by 5 yrs of age)

Global rotavirus Disease Burden and risk per year



Background

- **South Africa** *Steele et al. Vaccine 2003, 21(5-6):354-360*
 - Rotavirus accounts for 24 % of diarrhoeal cases.
 - Rotavirus cause ~25% of hospitalisations due to diarrhoeal diseases in children < 5 years.
 - Seasonal with a clear peak in autumn winter season.
- **Malawi** *Cunliffe et al. Lancet 2001, 358(9281):550-555*
 - Rotavirus is responsible for a third of outpatient attendances and hospital admissions for acute GE among children < 5 years.
 - Rotavirus is identified throughout the year.

Background - Global

- Rotavirus vaccine efficacy established in Europe and Latin America: 90-100% protection against severe rotavirus GE and 74-85% protection against rotavirus GE of any severity.

Linhares et al. Lancet 2008; Vesikari et al. Lancet 2007; Ruiz-Palacios et al. NEJM 2006

- RV disease is a global burden and any effective vaccination concept must prove its global reach, bringing a new vaccine to both developed and developing nations, especially in Africa and some Asia countries where it is most needed.
- Data from the Rota-037 African study.

Current WHO Position

- WHO recommends rotavirus vaccination in areas where vaccine efficacy is established, however awaiting vaccine efficacy (VE) data from Africa and Asia to make a global recommendation.

WHO, Weekly Epidemiological Record. Vol.82; 32:285-296; 10th Aug 2007.

Rota-037 Interim Analysis of RIX4414 (*Rotarix*TM) Efficacy Trial in South Africa

Site features:

- High prevalence of paediatric HIV:
30% of newborns are HIV-exposed
5-6% of birth cohort are HIV infected
- 40% un-employment rate in study-communities in an Urban area.
- Despite free access to Public Health Care, only 37% of children with GE receive ORT*.



* Oral Dehydration Therapy
Countdown 2008 Equity Analysis group: *Lancet* 2008; 371

Rota-037 Study Objectives RIX4414 (*Rotarix*TM) Efficacy Study In South Africa And Malawi

- **Primary Objective:** Efficacy against severe wild-type rotavirus gastro-enteritis (RV GE) [≥ 11 Vesikari scores] from 2 weeks post last dose until one year of age (pooled RIX4414 groups).
- **Secondary objective:** To assess the efficacy RIX4414 (*Rotarix*TM) vaccine (pooled RIX4414 groups) to prevent any RV GE caused by the circulating wild-type RV strains during the period from 2 weeks post last dose until one year of age.

Madhi, S. , Oral presentation, 8th international Rotavirus Symposium, Istanbul, Turkey, June 3-4, 2008

Rota-037 clinical trial details: <http://clinicaltrial.gov/ct2/show/NCT00598468?term=rota&rank=2>



Rotarix

Rota-037 Interim Analysis: Methods – Study Design

Phase III, double-blind, randomized (1:1:1), placebo-controlled and multi-centre trial in South Africa and Malawi.

- Study enrolment in South Africa

Treatment group	Number	Dose1 (6 wks)	Dose2 (10 wks)	Dose3 (14 wks)
RIX4414 – 3d	2 115	RIX4414	RIX4414	RIX4414
RIX4414 – 2d		placebo	RIX4414	RIX4414
Placebo	1 052	placebo	placebo	placebo

- Routine EPI* vaccines including oral polio vaccine (OPV) co-administered.
- Surveillance period: 2 weeks after last dose of RIX4414 / placebo until one year of age or 31 August 2007 (mean duration: 7 months)

* EPI vaccines: DTPw-Hep B/Hib and OPV

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Rota-037 clinical trial details: <http://clinicaltrial.gov/ct2/show/NCT00598468?term=rota&rank=2>

Rota-037 Interim Analysis: Methods Continued

- Gastroenteritis: Diarrhea (3 or more, loose stools/24 hours) with or without vomiting.
- Severity of GE graded on 20-point Vesikari scale (severe ≥ 11).
- Stools analyzed for rotavirus by **ELISA (*RotaClone*TM)**. Rotavirus positive samples tested by **RT-PCR** followed by **Reverse Hybridization assay** to determine the G and P types.
- Total vaccinated cohort (TVC) included in the interim analysis: 1952 vaccinees (RIX4414 pooled) and 976 Placebo recipients.

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Rota-037 clinical trial details: <http://clinicaltrial.gov/ct2/show/NCT00598468?term=rota&rank=2>

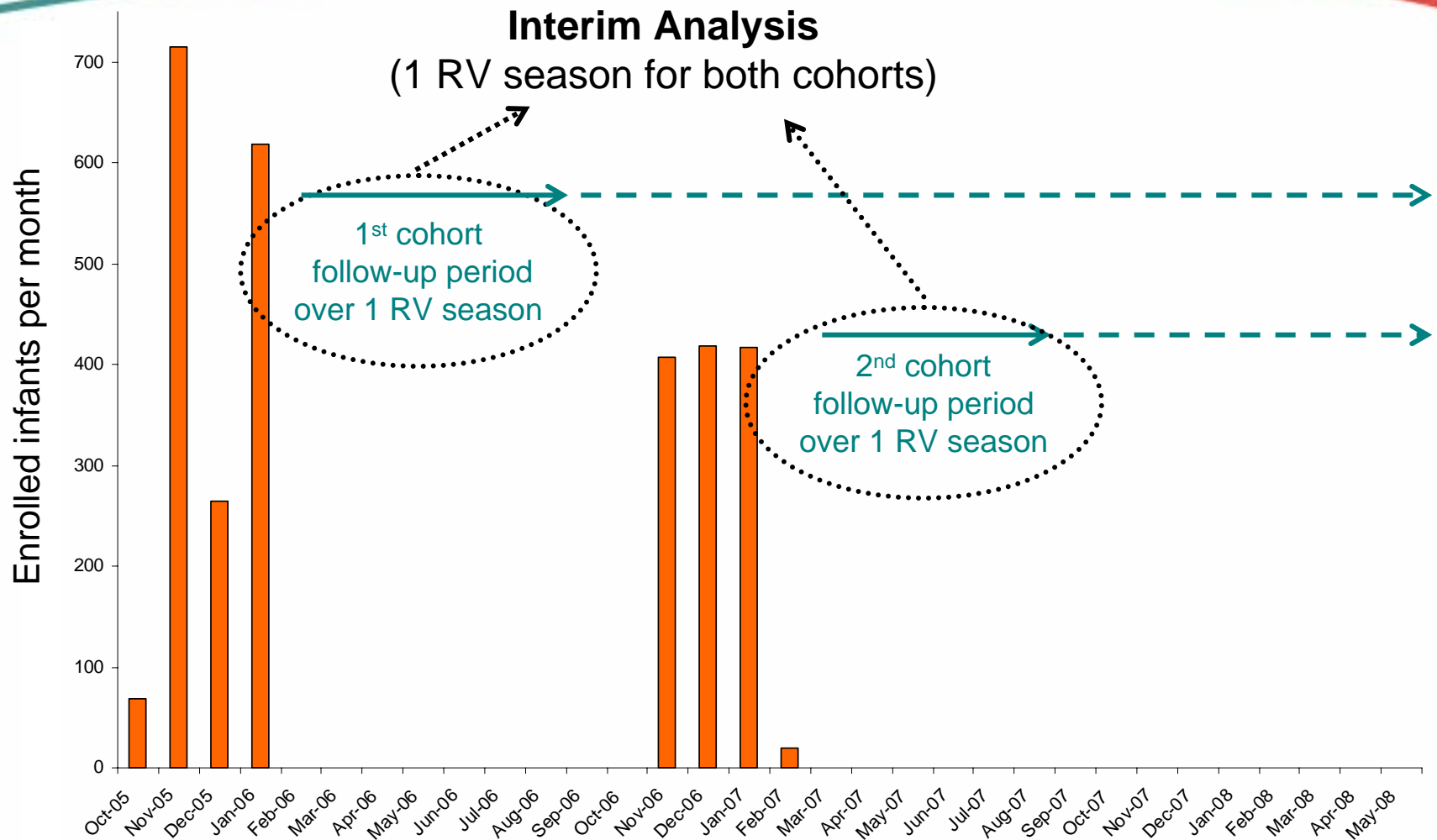
Rota-037: Scope Of Interim Analysis

- An interim analysis on vaccine efficacy against both severe and any RV GE was performed on the efficacy data collected from infants enrolled in South Africa.
- The interim analysis was conducted by the independent data centre supporting the Independent Data Monitoring Committee in order to maintain blinding.
- The duration of follow up is 7 months (mean duration) from 2 weeks after last dose of HRV vaccine or placebo.

Madhi, S. , Oral presentation, 8th international Rotavirus Symposium, Istanbul, Turkey, June 3-4, 2008

Rota-037 clinical trial details: <http://clinicaltrial.gov/ct2/show/NCT00598468?term=rota&rank=2>

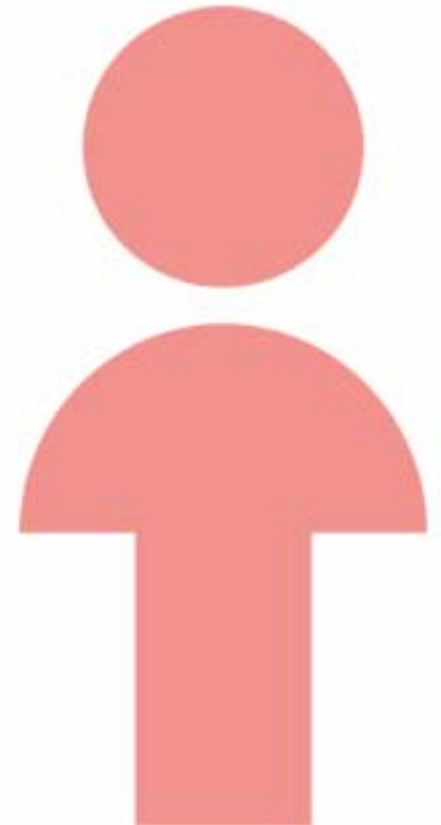
Rota-037 Interim analysis: Follow-up of Infants Enrolled per Month in South Africa





Results

Rotarix

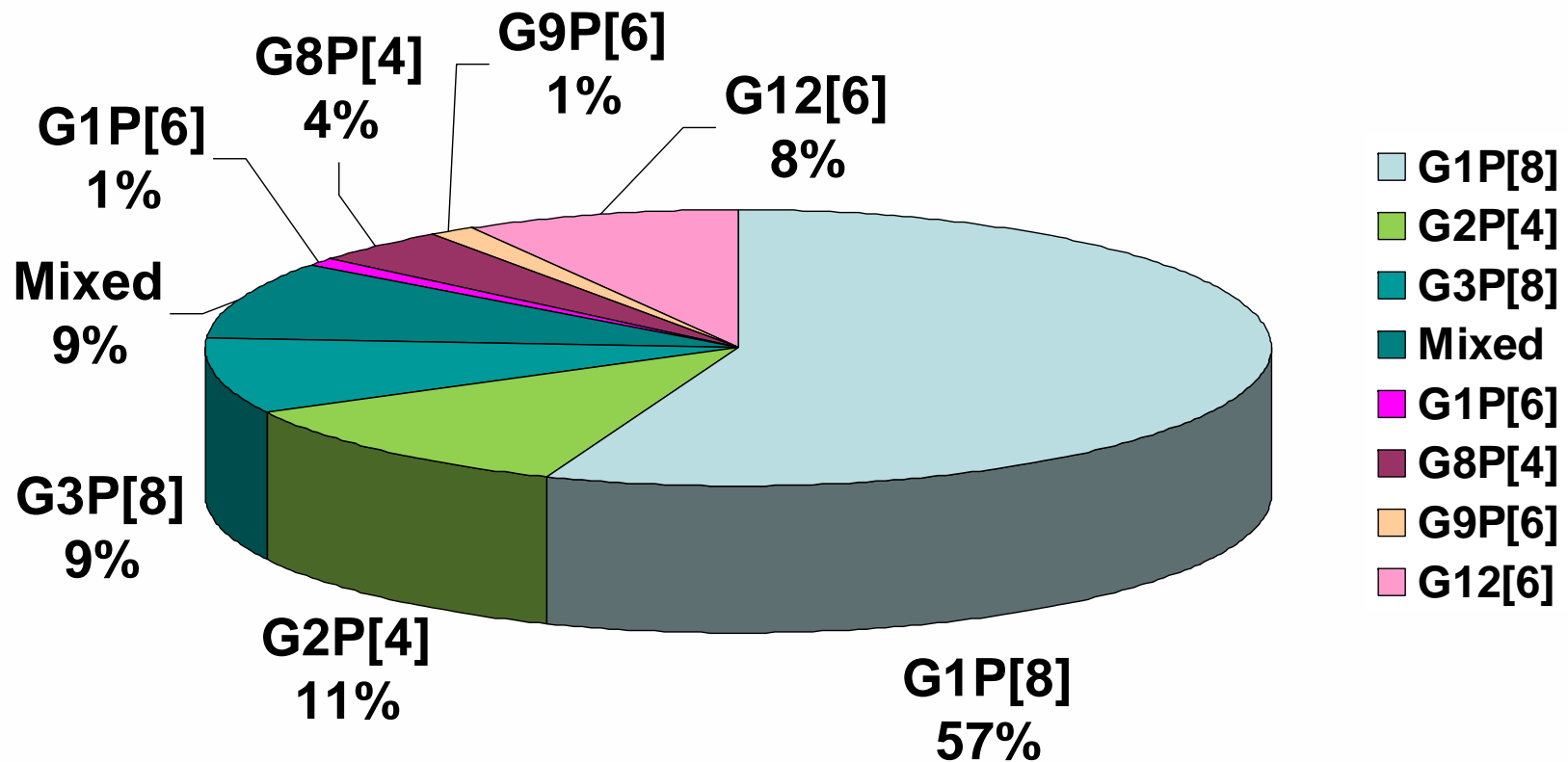


Rota-037 Interim analysis: Demographic Characteristics

Mean	RIX4414 (pooled) n=1952	Placebo n=976
Age at dose 1 (weeks)	6.3 (3-11)	6.3 (2-10)
Age at dose 2 (weeks)	11.1 (8-20)	11.1 (9-19)
Age at dose 3 (weeks)	16.0 (12-25)	16.0 (12-25)
Male %	49.6	51.9
African %	95.3	95.0
White Caucasian/European %	0.3	0.1
Other %	4.5	4.9

Rota-037 Interim Analysis (1 RV season): Serotype Distribution of RV Confirmed Episodes of GE

(from 2 weeks post-last dose of RIX4414/placebo until one year of age /
31 Aug 2007: TVC cohort)



Mixed types: G1+G2+G3+P[4]+P[8]; G1+G2+P[4]; G1+G2+P[4]+P[8]; G1+G3+P[8]; G2+G8+P[4]; G3+G8+P[8]

Rota-037 Interim Analysis (1 RV season): Vaccine Efficacy Against RV GE Of Any Severity

(from 2 weeks post-last dose of RIX4414/placebo until one year of age /
31 Aug 2007: TVC cohort)

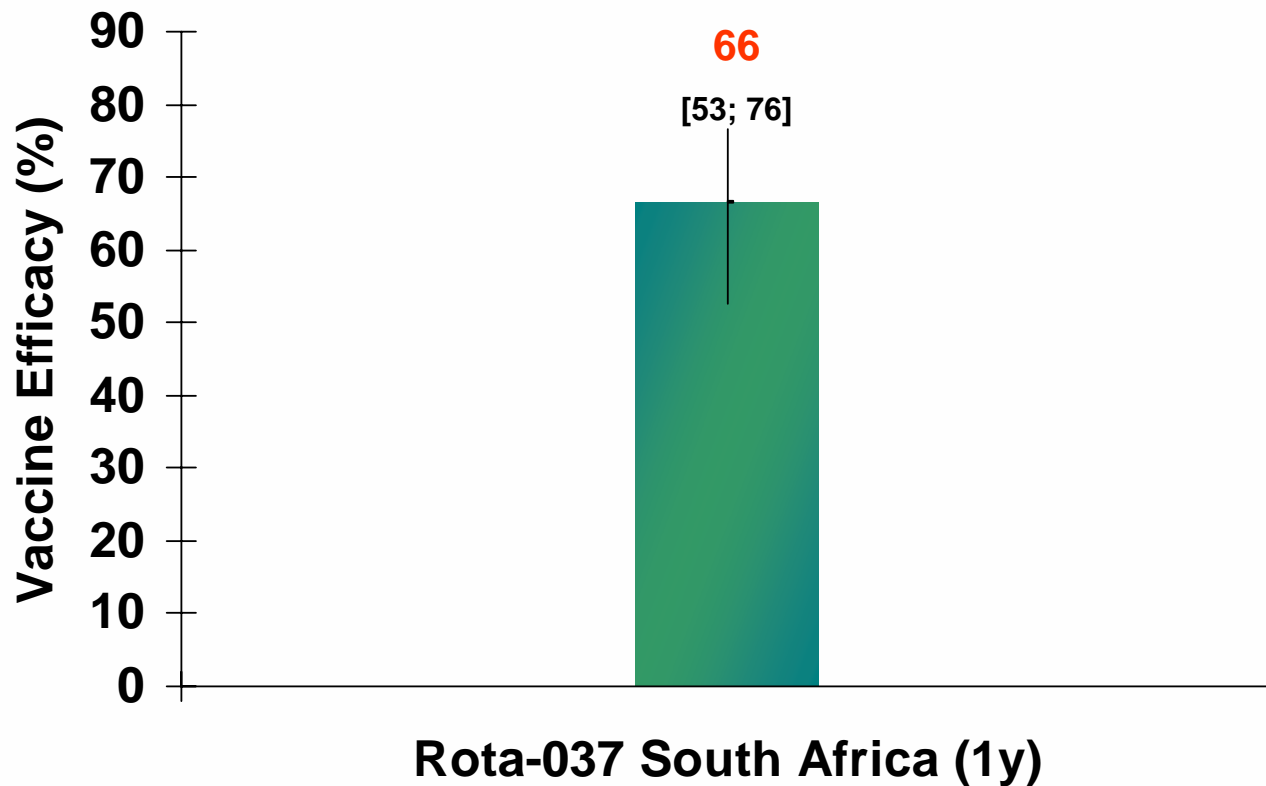
	RIX4414 N = 1952 (%)	Placebo N = 976 (%)	Vaccine efficacy [95% CI]	P-value
Any RV GE	57 (2.9)	85 (8.7)	66.5 [52.6; 76.5]	<0.001

Madhi, S. , Oral presentation, 8th international Rotavirus Symposium, Istanbul, Turkey, June 3-4, 2008

<http://www.rotavirus2008.com>

Rota-037 Interim Analysis (1 RV season): Vaccine Efficacy Against RV GE Of Any Severity

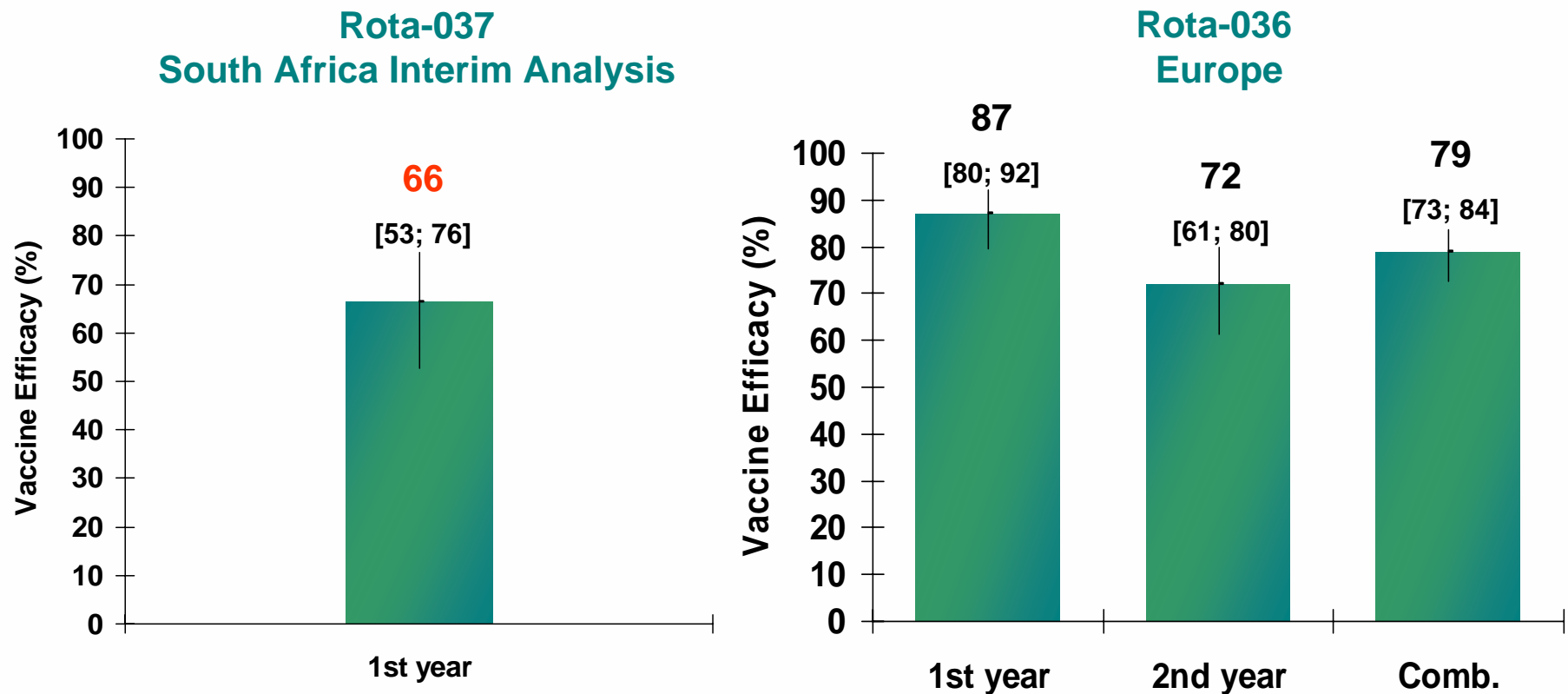
(from 2 weeks post-last dose of RIX4414/placebo until one year of age /
31 Aug 2007: TVC cohort)



Madhi, S. , Oral presentation, 8th international Rotavirus Symposium, Istanbul, Turkey, June 3-4, 2008

<http://www.rotavirus2008.com>

Vaccine Efficacy Against RV GE Of Any Severity, South Africa (Interim Analysis) and Europe



Madhi, S. , Oral presentation, 8th international Rotavirus Symposium, Istanbul, Turkey, June 3-4, 2008

Vesikari T, et al. Lancet 2007 Nov 24;370(9601):1757-63.

Rota-037 Interim Analysis (1 RV season): Vaccine Efficacy Against Severe RV- GE

(from 2 weeks post-last dose of RIX4414/placebo until one year of age /
31 Aug 2007: TVC cohort)

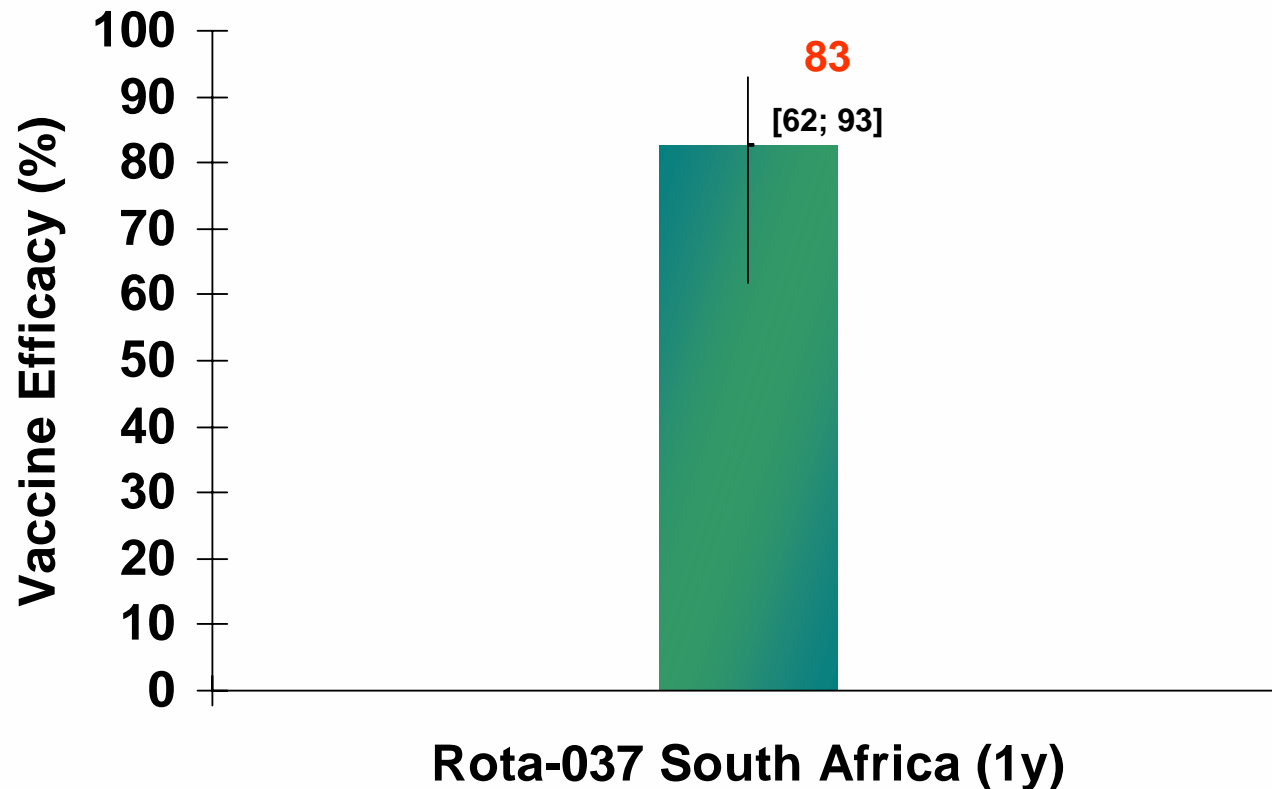
	RIX4414 N = 1952 (%)	Placebo N = 976 (%)	Vaccine efficacy [95% CI]	P-value
Severe RVGE	9 (0.5)	26 (2.7)	82.7 [61.9; 92.9]	<0.001

Madhi, S. , Oral presentation, 8th international Rotavirus Symposium, Istanbul, Turkey, June 3-4, 2008

<http://www.rotavirus2008.com>

Rota-037 Interim Analysis (1 RV season): Vaccine Efficacy Against Severe RV- GE

(from 2 weeks post-last dose of RIX4414/placebo until one year of age /
31 Aug 2007: TVC cohort)

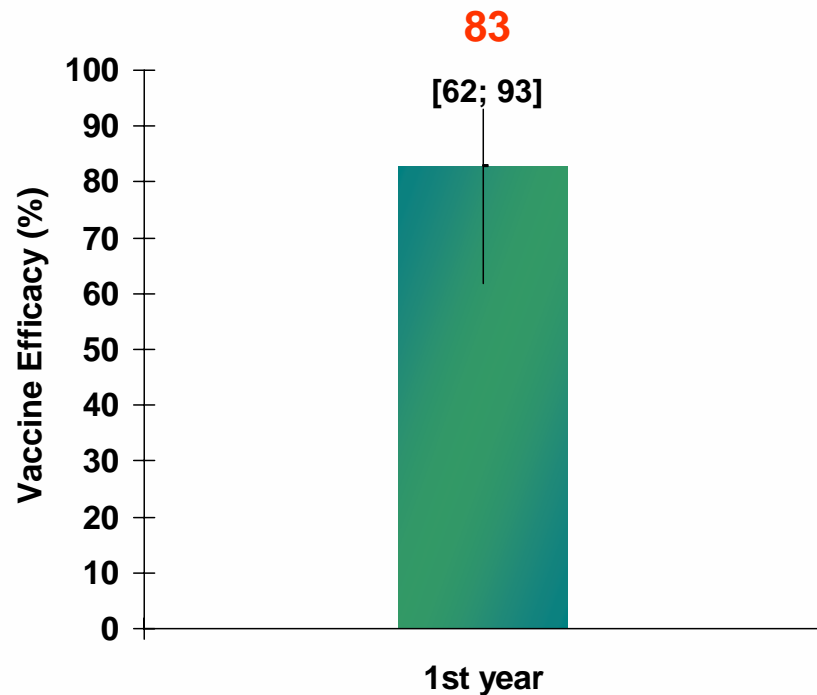


Madhi, S. , Oral presentation, 8th international Rotavirus Symposium, Istanbul, Turkey, June 3-4, 2008

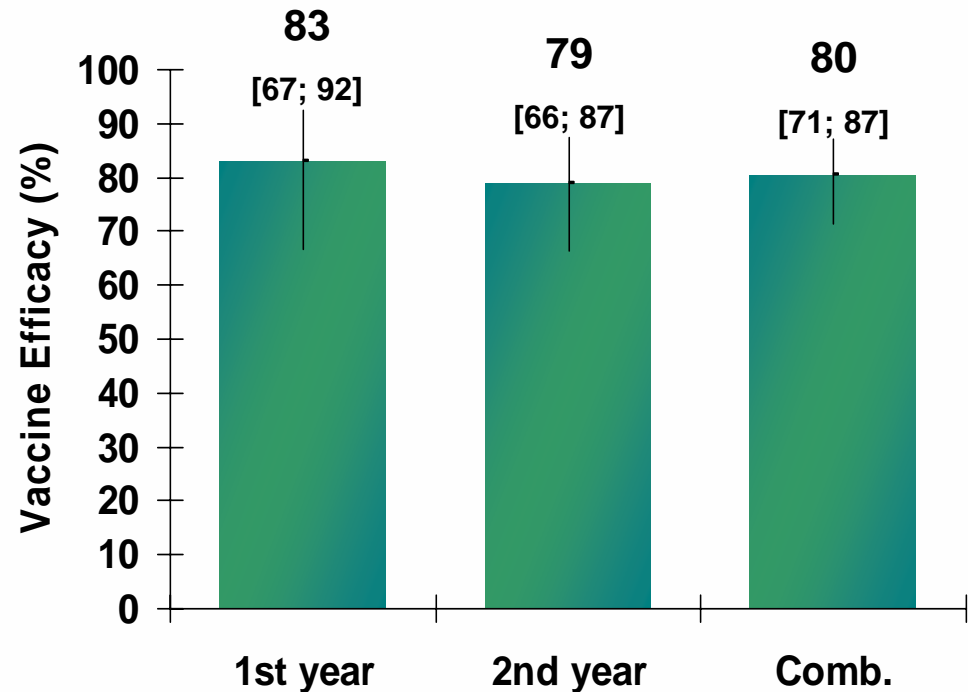
<http://www.rotavirus2008.com>

Vaccine Efficacy Against Severe RV- GE , South Africa (I. A.) and Latin America

Rota-037
South Africa Interim Analysis

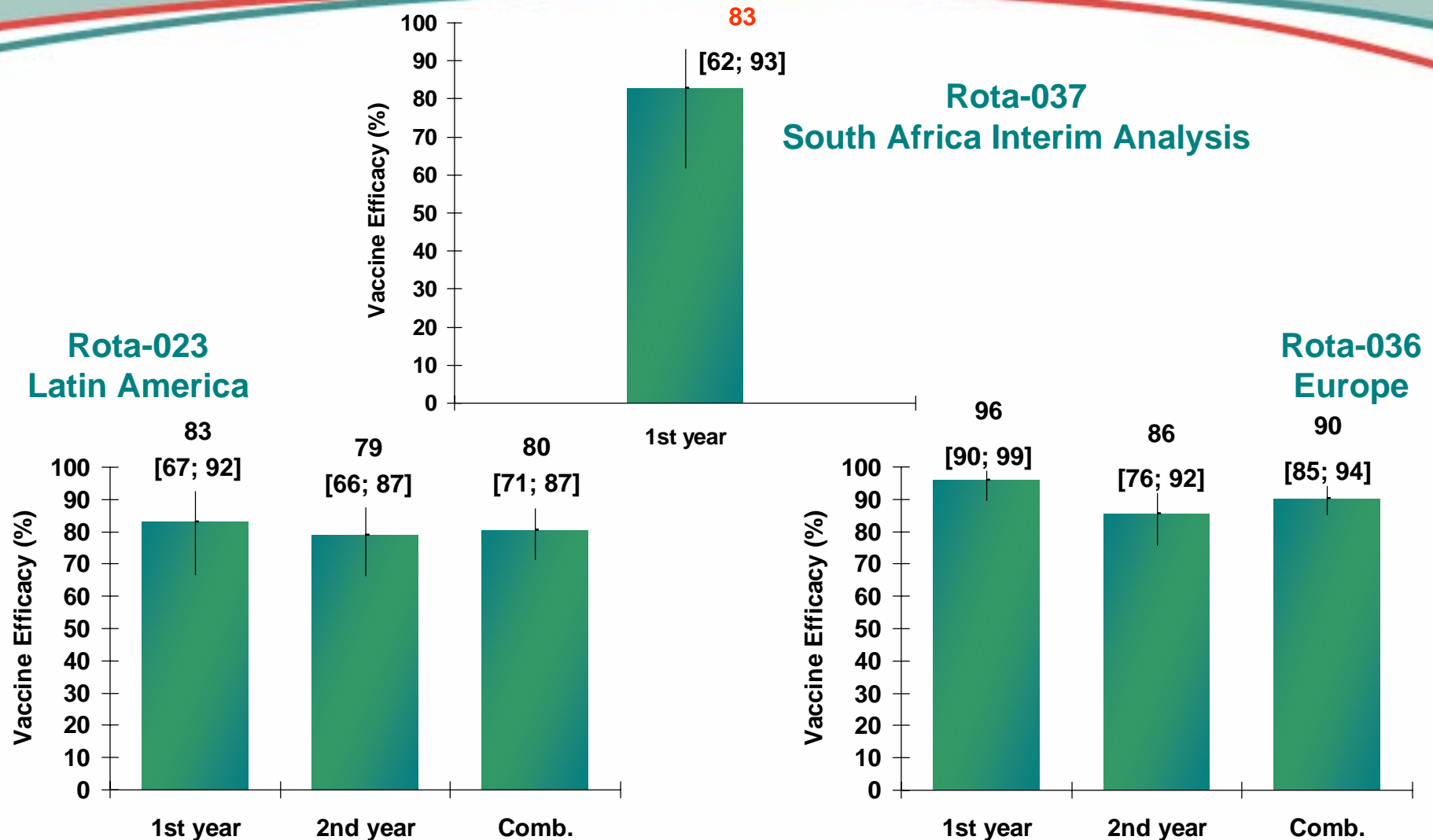


Rota-023
Latin America



Madhi, S. , Oral presentation, 8th international Rotavirus Symposium, Istanbul, Turkey, June 3-4, 2008
Linhares A.C. et al., Lancet, 2008, 371(9619):1181-1189

Vaccine Efficacy Against Severe RV- GE , South Africa (I. A.), Latin America and Europe



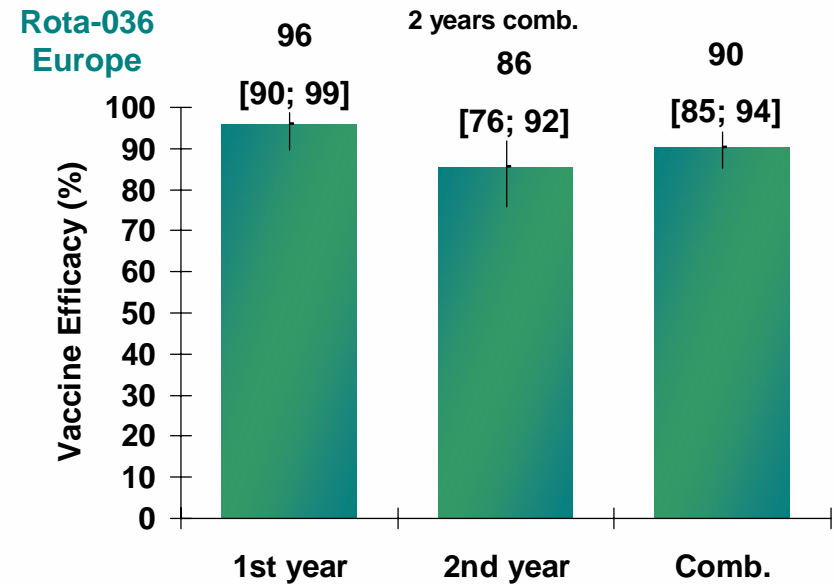
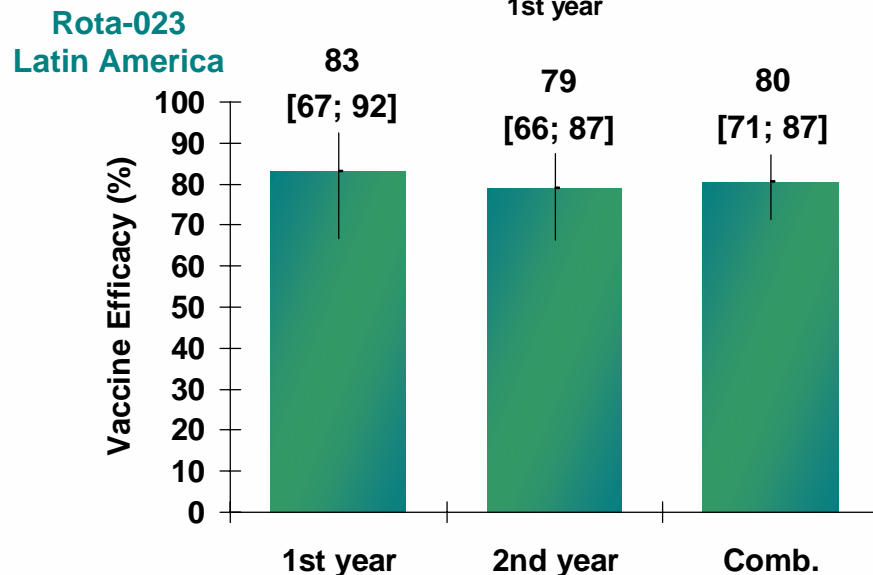
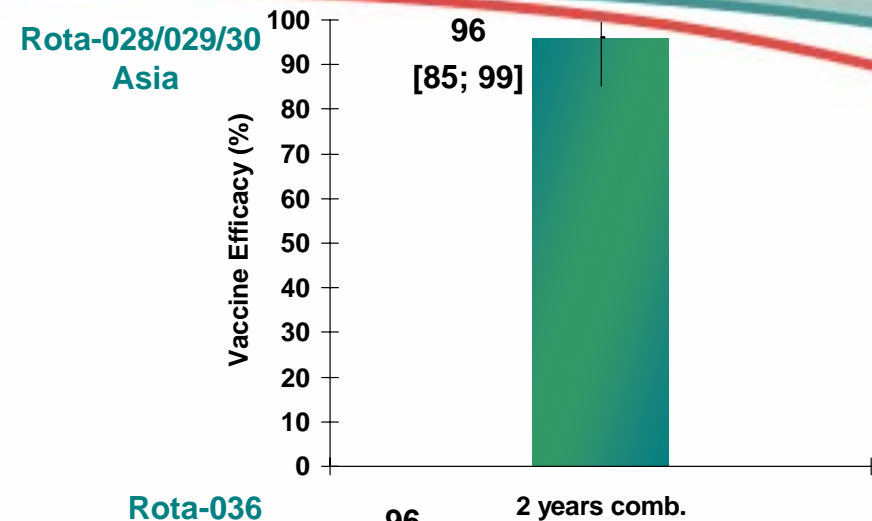
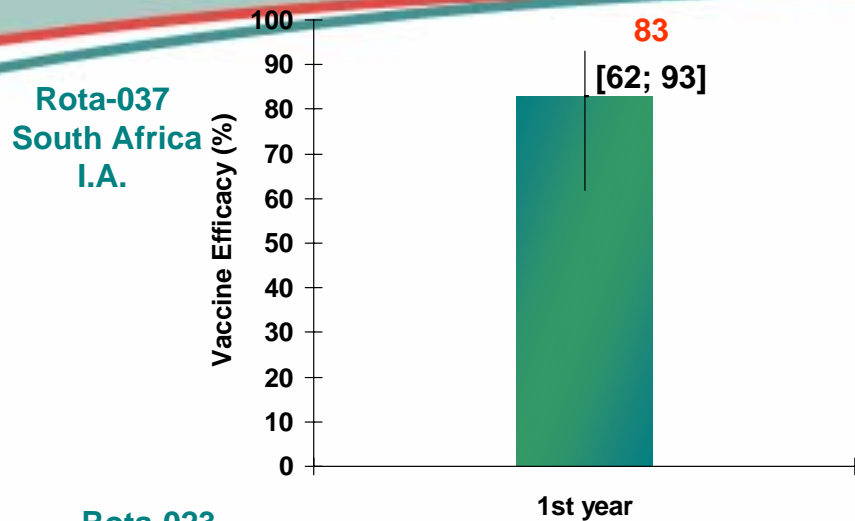
Madhi, S. , Oral presentation, 8th international Rotavirus Symposium, Istanbul, Turkey, June 3-4, 2008

Vesikari T, et al. Lancet 2007 Nov 24;370(9601):1757-63.

Linhares A.C. et al., Lancet, 2008, 371(9619):1181-1189



Vaccine Efficacy Against Severe RV- GE , South Africa (I. A.), Asia, Latin America and Europe



Madhi, S. , Oral presentation, 8th international Rotavirus Symposium, Istanbul, Turkey, June 3-4, 2008
 Vesikari T, et al. Lancet 2007 Nov 24;370(9601):1757-63.
 Linhares A.C. et al., Lancet, 2008, 371(9619):1181-1189
 Phua, K.B. et al., Abstract, 13th ICID Kuala Lumpur, Malaysia- June 19-22, 2008



Conclusions

- RIX4414 (*Rotarix*[™]) offers **high and sustained protection** against severe RV-GE during the first year of life in South African infants
- Infants are from communities that also have high prevalence of HIV infection.
- Protection occurred in a setting where multiple G-types circulate (G1 and non-G1 RV types).
- Results can be considered to update the WHO recommendation regarding the role of RV vaccination in Africa.
- The full analysis of this study will include data from Malawi, and will address the full range of trial endpoints.

Final Analysis (South Africa & Malawi)

Efficacy and safety

Results: Serotype Distribution of RVGE Episodes in Study sites during Trial Period

(serotype distribution in the placebo group used as a proxy)
(from 2 weeks post-last dose of placebo until one year of age)

Serotype	South Africa		Malawi		Pooled countries	
	n	%	n	%	n	%
Any	114	100.0	62	100.0	176	100.00
G1WT+P8WT	65	57.02	8	12.90	73	41.48
G1WT+P4	1	0.88	0	0.00	1	0.57
G1WT+P6	1	0.88	1	1.61	2	1.14
G2+P4	19	16.67	3	4.84	22	12.5
G3+P8WT	6	5.26	0	0.00	6	3.41
G8+P4	4	3.51	15	24.19	19	10.80
G9+P8WT	0	0.00	15	24.19	15	8.52
G12+P6	11	9.65	17	27.42	28	15.91
G12+P8WT	0	0.00	3	4.84	3	1.70
G1WT+G2+P4+P8WT	1	0.88	0	0.00	1	0.57
G1WT+G3+P8WT	2	1.75	0	0.00	2	1.14
G2+G8+P4	1	0.88	0	0.00	1	0.57
G3+G8+P8WT	3	2.63	0	0.00	3	1.70

Primary Objective: Vaccine Efficacy Against Severe RV GE

(from 2 weeks post-last dose of RIX4414/placebo until one year of age : ATP cohort for efficacy)

	RIX4414 N = 2974 n(%)	Placebo N = 1443 n(%)	Vaccine efficacy % [95% CI]	P-value
Severe RV GE	56 (1.9)	70 (4.9)	61.2 [44.0; 73.2]	<0.0001

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

The primary objective was met because the lower limit of the of the 95% CI on vaccine efficacy is >0%.

Efficacy Conclusions

- RIX4414 (*Rotarix*[™]) offers high protection against severe RV GE during the first year of life in African infants [VE = 61.2%]
 - Infants are coming from communities that have high prevalence of HIV infection
 - WHO EPI vaccination schedule was used
 - All routine childhood vaccines including OPV were co-administered
 - No restriction on breast feeding
- Overall public health impact is anticipated to be similar to other geographical settings
 - overall efficacy against severe GE of **any cause** 30%
- No **significant** difference in vaccine efficacy between 2-dose and 3-dose schedules.
- Differences in vaccine efficacy across different study sites might be due to differences in circulating RV types rather than study population effect. Interpretation should be done with caution (post-hoc analysis).

Study Vaccine

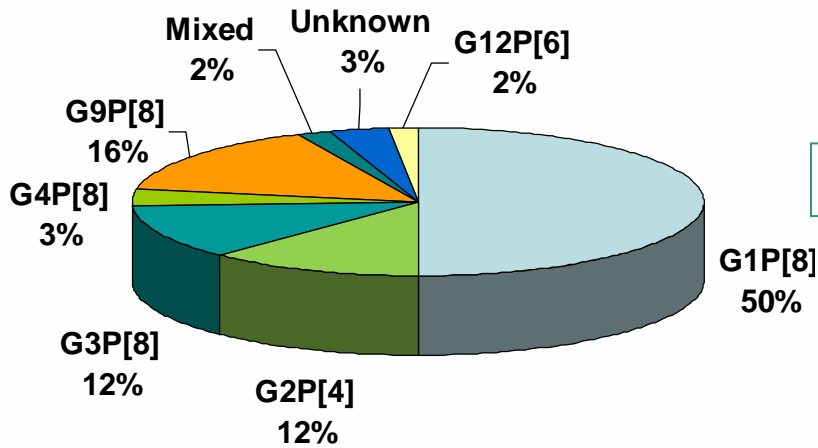
- Live attenuated human rotavirus vaccine, RIX4414 (*Rotarix*[™])
 - G1P[8] strain RIX4414
 - Derived from parent strain 89-12¹ by cloning and passaging.
 - Vaccine dose: 10⁶ median Cell Culture Infective Dose (CCID₅₀)
 - Highly attenuated, satisfactory safety profile
 - Licensed in more than 100 countries world-wide

Bernstein et al. Lancet 1998

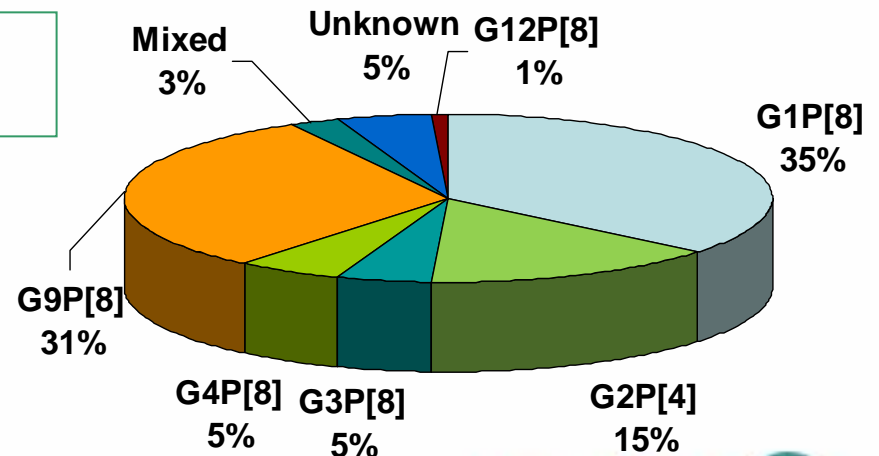
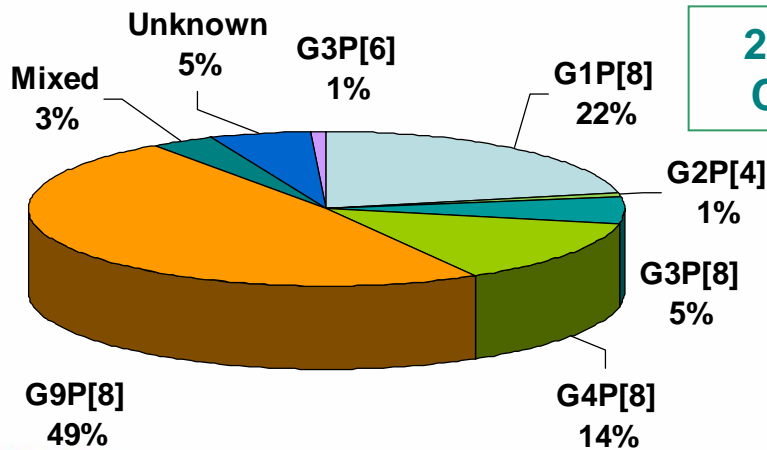
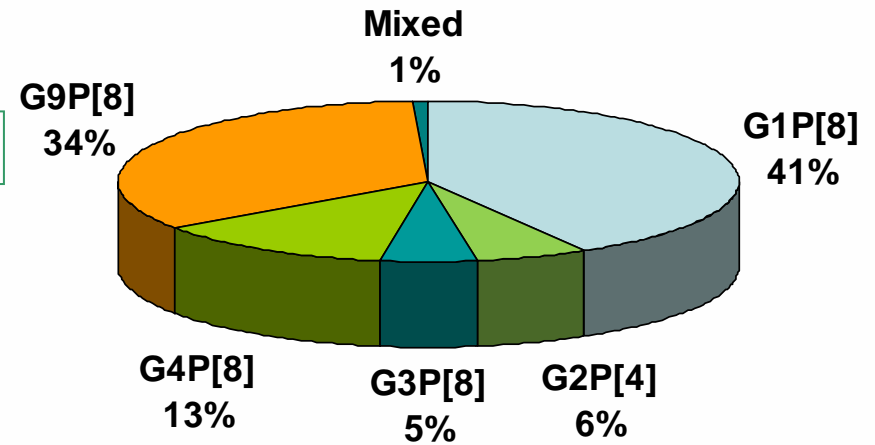
HRV Serotypes Distribution

1st and 2 years combined for Latin America and Europe

Rota-023 Latin America

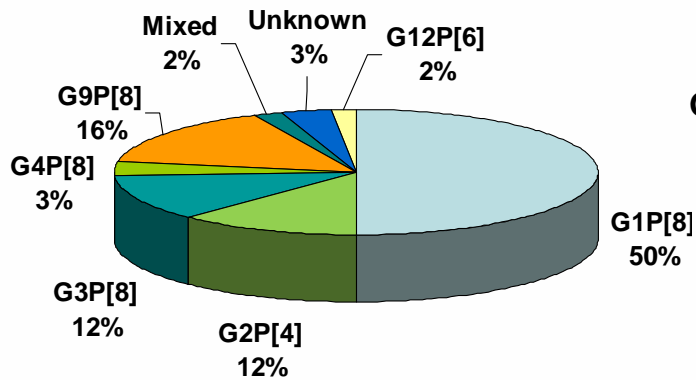


Rota-036 Europe

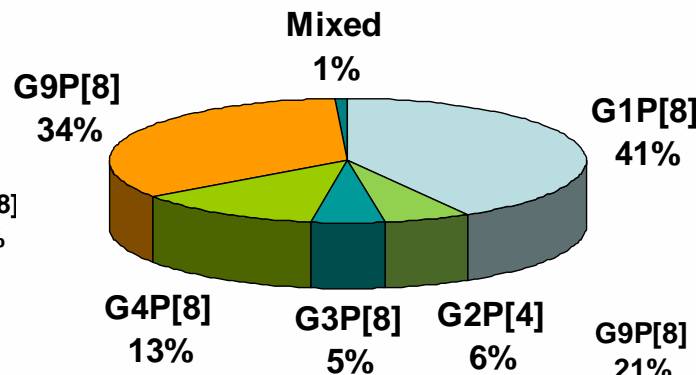


HRV Serotypes Distribution for Latin America, Europe (1st and 2 years combined) and Asia (2 years combined)

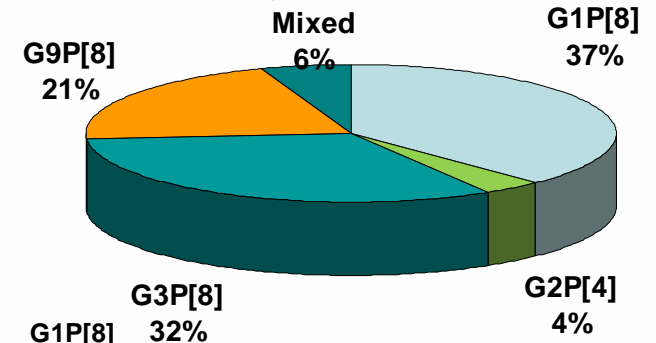
**Rota-023 Latin America
1st year**



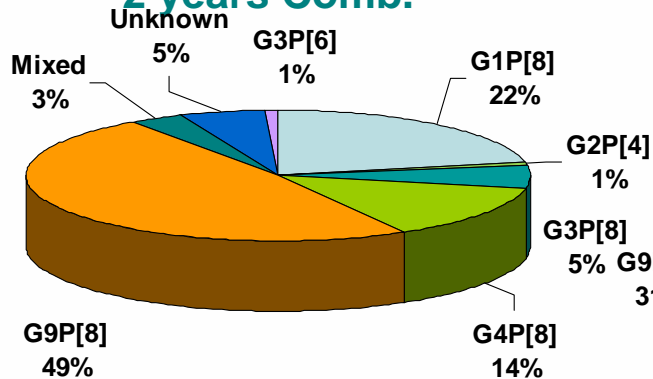
**Rota-036 Europe
1st year**



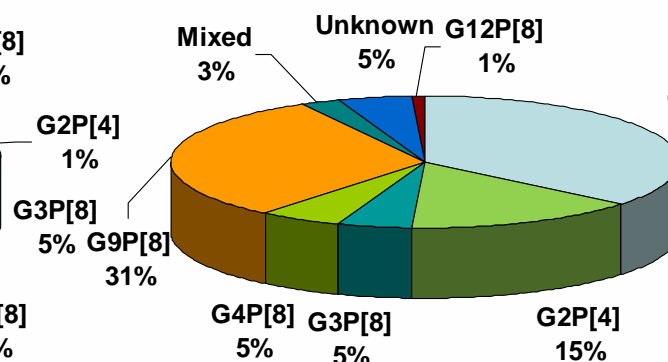
**Rota-028/029/030 Asia
2 years Comb.**



**Rota-023 Latin America
2 years Comb.**



**Rota-036 Europe
2 years Comb.**

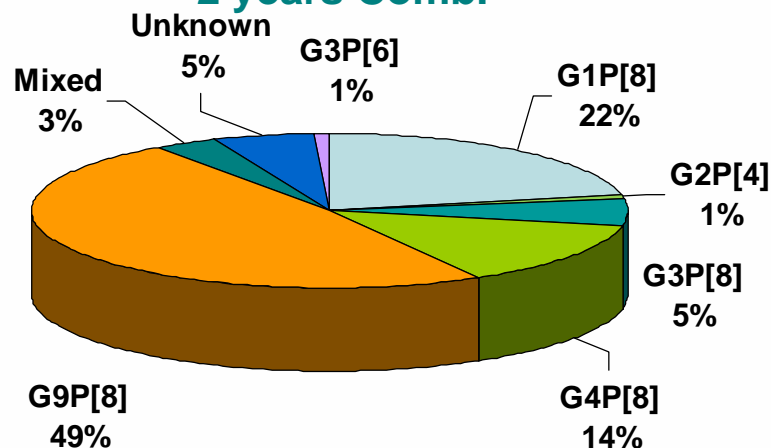


Vesikari T, et al. *Lancet* 2007 Nov 24;370(9601):1757-63.
 Linhares A.C. et al. *Lancet* 2007 Apr 05;371(9619):1181:1189
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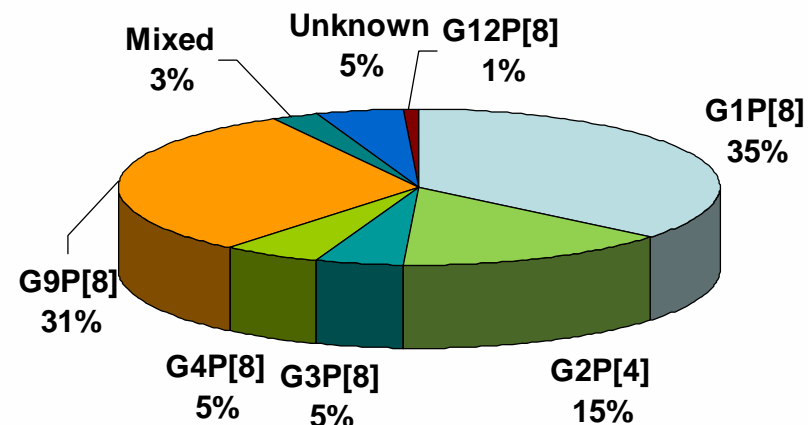


HRV Serotypes Distribution – 2 years combined for Latin America, Europe and Asia

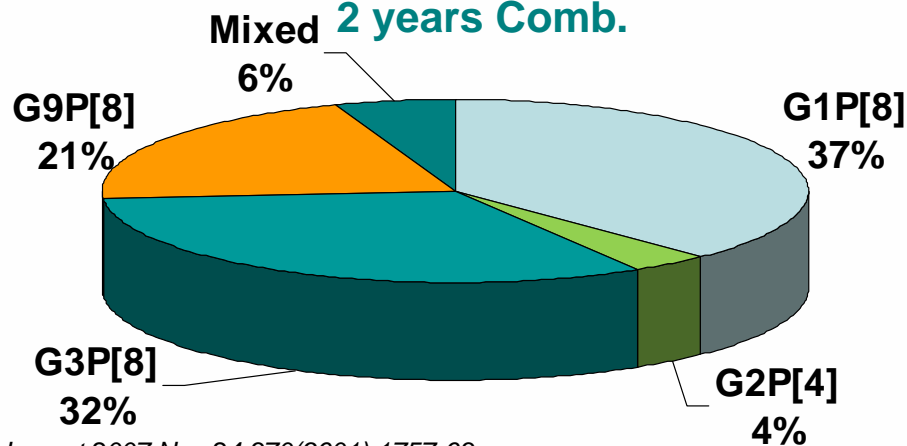
**Rota-023 Latin America
2 years Comb.**



**Rota-036 Europe
2 years Comb.**

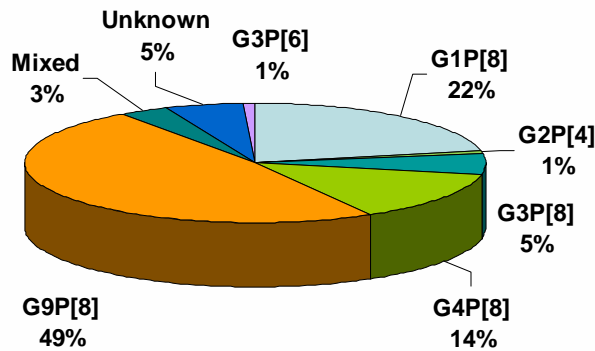


**Rota-028/029/030 Asia
2 years Comb.**

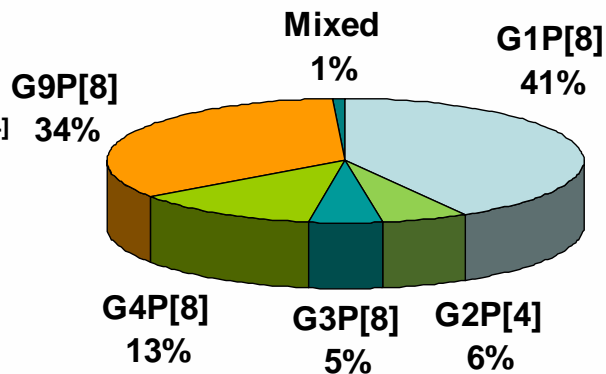


HRV Serotypes Distribution

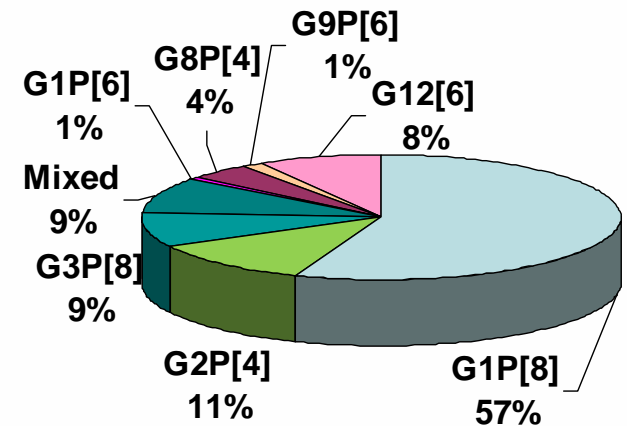
**Rota-023 Latin America
1st year**



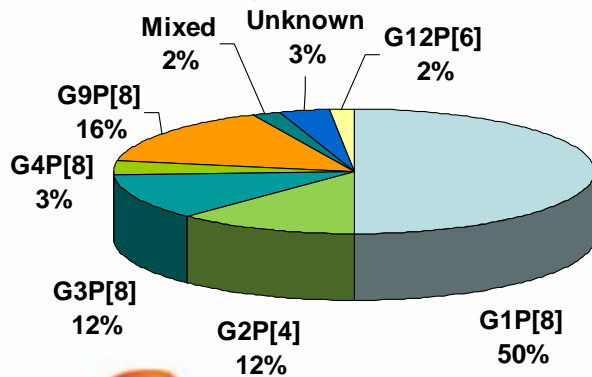
**Rota-036 Europe
1st year**



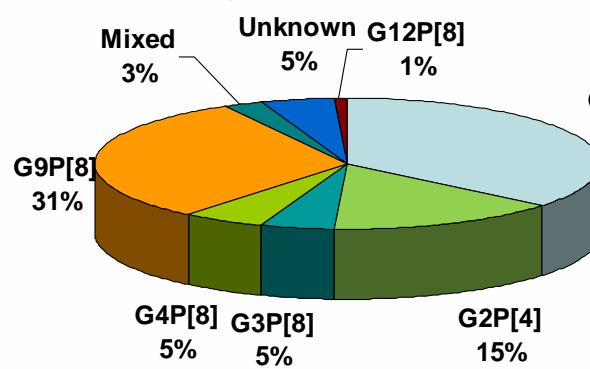
**Rota-037 South Africa
1st year**



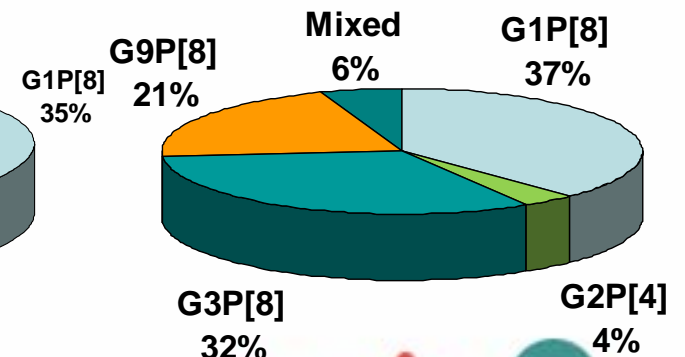
**Rota-023 Latin America
2 years Comb.**



**Rota-036 Europe
2 years Comb.**



**Rota-028/029/030 Asia
2 years Comb.**



GlaxoSmithKline

Vesikari T, et al. Lancet 2007 Nov 24;370(9601):1757-63. ; Data on File – Rota-028/029/030
Linhares A.C. et al. Lancet 2007 Apr 05;371(9619):1181:1189 ; Data on File – Rota-037

Rotarix