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The human rotavirus vaccine Rotarix™ in infants

An integrated analysis of safety and reactogenicity

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Abbreviations: AE, adverse event; CI, confidence interval; DBRCT, double-blind, randomized, placebo-controlled trial; RR, relative risk; RV, rotavirus; RVGE, rotavirus gastroenteritis; SAE, serious adverse event; SD, standard deviation

An integrated analysis of safety and reactogenicity data was undertaken for 28 randomized, placebo-controlled, double-blind Phase II and III trials (DBRCTs) of the oral live-attenuated human rotavirus vaccine, Rotarix™ (GlaxoSmithKline Vaccines). Healthy infants aged 6–20 wk received 2 or 3 doses of vaccine (n = 56562) or placebo (n = 45512) at 4- to 8-wk intervals. Solicited adverse events (AEs) were recorded for 8 d after each dose of vaccine or placebo. Unsolicited AEs, serious AEs (SAEs), and deaths were evaluated over 31-d post-vaccination follow-up periods. 95% confidence intervals (CIs) for the relative risk (RR) across studies excluding "1.0" signified potential imbalances between the 2 groups. The incidence of each solicited AE of any or Grade 3 severity was similar between groups. The incidence of all unsolicited AEs of any (RR = 0.99 [95% CI: 0.94–1.04]; $P = 0.72$) or Grade 3 severity (RR = 0.91 [95% CI: 0.77–1.08]; $P = 0.31$) was similar between groups. A significantly higher proportion of SAEs were reported in the placebo group compared with the vaccine group (RR = 0.9 [95% CI: 0.82–0.98]; $P = 0.01$). The incidence of death was low and similar between the 2 groups (0.13% in the vaccine group and 0.11% in the placebo group; RR = 1.14 [95% CI: 0.78–1.68]; $P = 0.54$). Very few cases of intussusception were reported (11 and 7 in the vaccine and placebo groups, respectively; RR = 1.39 [95% CI: 0.49–4.27]; $P = 0.66$). In conclusion, results of this analysis of DBRCTs show that the human rotavirus vaccine Rotarix™ has a reactogenicity and safety profile similar to placebo.

Rotavirus (RV) is a leading cause of severe acute diarrhea in infants and young children worldwide. RV gastroenteritis (RVGE) accounts for approximately 2.4 million hospitalizations and more than half a million deaths annually among children younger than 5 y.[1-3] The burden of RV disease varies widely, but is significant in both developing and developed countries. The availability of safe and effective vaccines against RV offers the potential to reduce the global burden of RVGE.[4] The World Health Organization (WHO) recommends that all infants be routinely immunized to prevent RV disease.[5] An oral live-attenuated human RV vaccine (Rotarix™, GlaxoSmithKline Vaccines) has been shown to be efficacious for the prevention of severe RVGE in large-scale clinical trials conducted in Latin America, Europe, Asia, Africa, and Japan,[6-10] and has been licensed in more than 120 countries worldwide.

This paper presents the results of an integrated clinical analysis of safety and reactogenicity data from 28 randomized, placebo-controlled, double-blind Phase II and III trials (DBRCTs) of the human RV vaccine, involving over 100 000 infants worldwide. Such a large safety database facilitates the detection of adverse events (AEs) that might occur at low frequencies, and which may therefore not be detected in individual studies. Because a previous RV vaccine (RotaShield™, Wyeth) was associated with an increased incidence of intussusception,[11,12] particular attention was focused on this event. Another adverse event of interest was Kawasaki disease. Regulatory authorities requested monitoring for this event following reports during prelicensure studies of the bovine-human reassortant pentavalent RV vaccine (Rotateq™, Merck Vaccines).[13]

The DBRCTs included in this analysis were conducted from May 2000 to July 2010 in countries spanning the global spectrum of development and national wealth (**Table S1**). Healthy infants aged 6–20 wk received 2 or 3 doses (3 studies only) of vaccine or placebo at 4- to 8-wk intervals. Solicited general AEs (irritability/fussiness, cough/runny nose [selected studies], fever, loss of appetite, vomiting, and diarrhea) were recorded for 8 d after each vaccine dose (days 0–7). Severity was assessed using a tiered grading system, where grade 0 was 'absent' and grade 3 was "severe" according to pre-specified criteria. Unsolicited AEs, serious AEs (SAEs) and deaths reported within 31 d post-vaccination (days 0–30) were also considered in this analysis, which was conducted on the total vaccinated cohort, including all infants who had received at least one dose of vaccine or placebo. The relative risk (RR) with 95% confidence intervals (CI) for vaccine vs. placebo was estimated for each safety endpoint. The 95% CI for the RR was based on the exact conditional likelihood approach

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Table 1. Summary of demographic characteristics for infants receiving at least one dose of the human RV vaccine or placebo in the 28 studies included in the integrated clinical safety summary (total vaccinated cohort)

Characteristic	Human RV vaccine (n = 56562)	Placebo (n = 45512)
Age at dose 1, weeks		
Mean (SD)	8.8 (2.62)	8.7 (2.64)
Median (range)	8.0 (1–19)	8.0 (2–20)
Gender, n (%)		
Female	27760 (49.1)	22250 (48.9)
Male	28802 (50.9)	23262 (51.1)
Ethnicity, n (%)		
Black	4443 (7.9)	2283 (5.0)
White/Caucasian	10055 (17.8)	6533 (14.4)
Oriental	1688 (3.0)	612 (1.3)
Arabic/North African	24 (0.0)	17 (0.0)
East/South East Asian	1825 (3.2)	677 (1.5)
South Asian	17 (0.0)	9 (0.0)
American Hispanic	28560 (50.5)	26775 (58.8)
Japanese	0 (0.0)	4 (0.0)
Other	9950 (17.6)	8602 (18.9)

adjusted for the study effect, but not adjusted for multiplicity. In this analysis, differences between the 2 groups were noted based on 95% CI for the RR across studies excluding "1". When a potential imbalance between groups was noted, the analysis by study was examined descriptively to assess the magnitude of the effect (data not shown).

A total of 102 074 infants across 28 DBRCTs were included in this analysis (56 562 in the vaccine group and 45 512 in the placebo group). Demographic characteristics were similar between the vaccine and placebo groups (**Table 1**). Median age at time of first vaccination was 8.0 wk in both groups. Data on solicited general AEs during the 8-d post-vaccination period after any vaccine dose were available for 9414 infants in the vaccine group and 3534 infants in the placebo group, with the exception of cough/runny nose for which data were available for 7754 and 2999 infants, respectively (**Table 2**). At least one solicited general AE was reported for 79.7% and 77.7% infants in the vaccine and placebo groups, respectively (RR = 1.00 [95% CI: 0.96–1.05]; P = 0.99). Irritability/fussiness was the most frequently reported solicited general AE, followed by cough/runny nose and fever. The incidence of all solicited general AEs (any or Grade 3 severity) was mostly similar between the vaccine and the placebo groups. A difference in the incidence of Grade 3 runny nose was observed (4.2% in the vaccine group and 3.0% in the placebo group; RR = 1.27 [95% CI: 1.00–1.63]; P = 0.05). However, this difference was not observed in any of the individual studies included in this pooled analysis.

Data on unsolicited AEs during the 31-d post-vaccination period after any vaccine dose were available for 11 856 infants in the vaccine group and 4778 infants in the placebo group (**Table 3**). At least one unsolicited AE was reported for 47.8% and 49.4% infants in the vaccine and placebo groups, respectively (RR = 0.99 [95% CI: 0.94–1.04]; P = 0.72). Unsolicited AEs for which the 95% CI excluded 1 were irritability, flatulence, and heat rash (which occurred more frequently in the vaccine group) and pharyngitis and rhinorrhea (which occurred more frequently in the placebo group). At least one unsolicited AE of grade 3 intensity was reported for 3.6% infants in the vaccine group and 4.6% in the placebo group (RR = 0.91 [95% CI: 0.77–1.08]; P = 0.31). No individual unsolicited AEs of grade 3 intensity were recorded for more than 1% of subjects in either group and no imbalance in the incidence of any unsolicited AEs of grade 3 intensity were seen between the 2 groups (data not shown). The most frequently reported individual unsolicited AEs of grade 3 intensity were fever, otitis media, and upper respiratory tract infection in both groups.

Data on the incidence of SAEs during the 31-d post-vaccination period after any vaccine dose were available for 56 562 infants in the vaccine group and 45 512 infants in the placebo group (**Table 4**). A significantly lower proportion of infants recorded SAEs during this follow-up period in the vaccine group than in the placebo group (2.09% and 2.25%, respectively; RR = 0.90 [95% CI: 0.82–0.98]; P = 0.01). SAEs due to gastroenteritis and diarrhea were less common in the vaccine group than in the placebo group. Gastroenteritis was recorded for 0.27% of infants in the vaccine group and 0.39% in the placebo group (RR = 0.65 [95% CI: 0.52–0.82]; P = 0.0002). Diarrhea was reported by 0.03% and 0.06% infants in the 2 groups, respectively (RR = 0.48 [95% CI: 0.24–0.94]; P = 0.03). Decreased appetite was reported more frequently in vaccinated infants than in those who received placebo (8 and 1 infants, respectively; RR = 7.98 [95% CI: 1.07–354.23]; P = 0.04). Excluding gastroenteritis and diarrhea, SAEs were reported for 1.88% of infants in the vaccine group and 1.99% of those in the placebo groups (RR = 0.92 [95% CI: 0.84–1.01]; P = 0.07). Intussusception was reported as an SAE during the 31-d post-vaccination period in 11 infants in the vaccine group and 7 infants in the placebo group (RR = 1.39 [95% CI: 0.49–4.27]; P = 0.66). An overview of these cases of intussusception, including age at onset and timing in relation to vaccination, is provided in **Table S2**. The incidence of Kawasaki disease was low and similar in both groups (only 1 case in each group; RR = 1.00 [95% CI: 0.01–78.35]; P = 1.00).

The incidence of death during the 31-d post-vaccination period was low and similar in both groups (0.13% in the vaccine group and 0.11% in the placebo group; RR = 1.14 [95% CI: 0.78–1.68]; P = 0.54). None of these deaths was considered by the investigators to be related to vaccination. Pneumonia was the most common cause of death during the 31-d post-vaccination period, occurring in 17 infants in the vaccine group and 13 infants in the placebo group (RR = 0.89 [95% CI: 0.40, 2.01]); P = 0.88). One infant in the vaccine group died due to intussusception (**Table S2**).

Table 2. Percentage of subjects reporting solicited general AEs (any and Grade 3 intensity) during the 8-d (days 0–7) period after any dose (total vaccinated cohort)

Symptom	Severity	Human RV vaccine			Placebo			Relative risk (vaccine over placebo)	
		N	n	% [95% CI]	N	n	% [95% CI]	RR [95% CI†]	*P* value
At least 1 symptom	All	9414	7504	79.7 [78.9–80.5]	3534	2747	77.7 [76.3–79.1]	1.00 [0.96–1.05]	0.99
Irritability/fussiness	All	9414	5726	60.8 [59.8–61.8]	3534	2025	57.3 [55.7–58.9]	1.02 [0.97–1.08]	0.41
	Grade 3	9414	709	7.5 [7.0–8.1]	3534	260	7.4 [6.5–8.3]	0.93 [0.8–1.07]	0.31
Cough/runny nose	All	7754	3526	45.5 [44.4–46.6]	2999	1332	44.4 [42.6–46.2]	0.99 [0.93–1.06]	0.83
	Grade 3	7754	323	4.2 [3.7–4.6]	2999	89	3.0 [2.4–3.6]	1.27 [1.00–1.63]	0.05
Fever	All	9414	3981	42.3 [41.3–43.3]	3534	1364	38.6 [37.0–40.2]	1.01 [0.94–1.07]	0.88
	Grade 3	9414	135	1.4 [1.2–1.7]	3534	41	1.2 [0.8–1.6]	1.05 [0.73–1.54]	0.85
Loss of appetite	All	9414	3228	34.3 [33.3–35.3]	3534	1118	31.6 [30.1–33.2]	1.04 [0.97–1.11]	0.27
	Grade 3	9414	122	1.3 [1.1–1.5]	3534	51	1.4 [1.1–1.9]	0.8 [0.57–1.14]	0.22
Vomiting	All	9414	1673	17.8 [17.0–18.6]	3534	602	17.0 [15.8–18.3]	1.00 [0.91–1.10]	0.99
	Grade 3	9414	250	2.7 [2.3–3.0]	3534	84	2.4 [1.9–2.9]	1.02 [0.79–1.33]	0.92
Diarrhea	All	9414	732	7.8 [7.2–8.3]	3534	264	7.5 [6.6–8.4]	0.99 [0.85–1.14]	0.87
	Grade 3	9414	457	4.9 [4.4–5.3]	3534	158	4.5 [3.8–5.2]	0.98 [0.81–1.18]	0.83

Solicited general AEs listed by decreasing order of frequency in the vaccine group. Data for solicited general AEs were collected in studies 003, 004, 005, 006, 007, 013, 014, 021, 022, 033, 036, 039, 041, 044, 045, 048, 051, 054, 056, 063, and 068; however, data for cough/runny nose were not collected in studies 003, 004, 013, 021, 033, 045, and 054. N, number of subjects with at least one documented dose; n/%, number/percentage of subjects reporting the symptom at least once; 95% CI, exact 95% confidence interval; 95% CI†, 95% confidence interval for relative risk (exact stratified conditional to total number of cases). *P* value, 2-sided exact stratified test conditional to number of cases.

Results of this analysis are consistent with previous findings.[14] The safety and tolerability profile of the human RV vaccine was found to be mostly comparable with that of placebo across 28 Phase II and Phase III DBRCTs. The observed decreased risk of serious GE and diarrhea in the vaccine group was expected and is in keeping with the proven efficacy of the vaccine against severe RVGE. Real-life data from effectiveness and impact studies in Latin America, Europe, and Australia demonstrate considerable reductions in hospital admissions and mortality due to RVGE and diarrhea of any cause in infants and young children following inclusion of the human RV vaccine into national immunization schedules.[15-22] Importantly, the rate of intussusception was found to be low and similar in the vaccine and placebo groups.

Results of a large post-marketing study undertaken in Mexico to further assess any potential temporal association between administration of the human RV vaccine and intussusception showed a small increase in risk for intussusception within 7 d of administration of the first vaccine dose.[23] However, no temporal association between vaccination and intussusception was seen post-dose 2. This was estimated to translate into an attributable risk of 3–4 additional cases of intussusception per 100 000 vaccinated infants, which is substantially lower than the risk of 10–20 additional cases of intussusception per 100 000 infants associated with RotaShield™.[24]

Another post-licensure evaluation of the potential risk of intussusception following vaccination with the human RV vaccine has been undertaken in Mexico and Brazil by local investigators in collaboration with the Pan American Health Organization and the Centers for Disease Control and Prevention.[25] A small temporal increase in the relative risk of intussusception within 7 d post-dose one was observed in Mexican infants, corresponding to a risk of approximately 2 additional hospitalizations for intussusception per 100 000 infants vaccinated. In Brazilian infants, no increase in the relative risk of intussusception was seen after the first vaccine dose; however, an increased risk was seen 1 to 7 d after the second dose, although this was smaller than that seen after the first dose in Mexico. Recent data from the Australian National Immunization Program also suggest a possible temporal clustering of intussusception episodes during the 7 d post-dose one; however, this finding was based on relatively few cases and no increase in overall risk of intussusception at 12 mo of age was reported.[26]

It has not yet been established whether RV vaccination has any impact on the overall incidence of intussusception. However, available data suggest that the known benefits of the human RV vaccine outweigh any potential small temporal increase in risk for intussusception within 7 d post-dose one. A quantitative benefit-risk analysis undertaken in Mexico estimated that there would be 282 RV-related hospital admissions and 332 RV-related

Table 3. Percentage of subjects with significant differences in incidence of unsolicited AEs within the 31-d (days 0–30) post-vaccination period (total vaccinated cohort)

	Human RV vaccine n = 11856		Placebo n = 4778		Relative risk (vaccine over placebo)	
Symptom	**n**	**% [95% CI]**	**n**	**% [95% CI]**	**RR [95% CI]‡**	***P* value§**
At least 1 symptom	5662	47.76 [46.85–48.66]	2362	49.43 [48.01–50.86]	0.99 [0.94–1.04]	0.72
Irritability*	730	6.16 [5.73, 6.60]	312	6.53 [5.85, 7.27]	1.15 [1.00, 1.31]	0.05
Rhinorrhea†	164	1.38 [1.18, 1.61]	112	2.34 [1.93, 2.81]	0.58 [0.45, 0.75]	<0.0001
Flatulence*	157	1.32 [1.13, 1.55]	50	1.05 [0.78, 1.38]	1.48 [1.07, 2.08]	0.02
Pharyngitis†	140	1.18 [0.99, 1.39]	63	1.32 [1.01, 1.68]	0.66 [0.48, 0.91]	0.01
Heat rash*	40	0.34 [0.24, 0.46]	3	0.06 [0.01, 0.18]	5.04 [1.60, 25.59]	0.002

*Significantly higher incidence in vaccine group. †Significantly higher incidence in placebo group. ‡RR calculations were performed based on the Poisson method on stratified studies (incidence rate was not directly dependent on the RR value generated). §*P* value: 2-sided Exact Stratified Test conditional to number of cases. AEs listed by decreasing order of frequency in the vaccine group. Note: studies 023, 024, 028, 029, 030, and 037 are not included in this part of the analysis since collection of unsolicited AEs in these studies was different from the others.

Table 4. Percentage of subjects reporting SAEs of frequency ≥0.1% in either group or for which differences between groups were statistically significant during the 31-d (days 0–30) period after any dose (total vaccinated cohort)

	Human RV vaccine n = 56562		Placebo n = 45512		Relative risk (vaccine over placebo)	
SAE	**n**	**% [95% CI]**	**n**	**% [95% CI]**	**RR [95% CI]‡**	***P* value§**
At least 1 SAE†	1181	2.09 [1.97–2.21]	1026	2.25 [2.12–2.39]	0.90 [0.82–0.98]	0.01
At least 1 SAE excluding gastroenteritis and diarrhea	1064	1.88 [1.77–2.00]	906	1.99 [1.86–2.12]	0.92 [0.84–1.01]	0.07
Bronchiolitis	244	0.43 [0.38–0.49]	192	0.42 [0.36–0.49]	0.97 [0.80–1.19]	0.83
Gastroenteritis†	155	0.27 [0.23–0.32]	176	0.39 [0.33–0.45]	0.65 [0.52–0.82]	0.0002
Pneumonia	185	0.33 [0.28–0.38]	161	0.35 [0.30–0.41]	0.92 [0.73–1.14]	0.45
Bronchopneumonia	63	0.11 [0.09–0.14]	49	0.11 [0.08–0.14]	1.00 [0.67–1.50]	1.00
Bronchitis	54	0.10 [0.07–0.12]	32	0.07 [0.05–0.10]	1.29 [0.81–2.08]	0.31
Urinary tract infection	44	0.08 [0.06–0.10]	44	0.10 [0.07–0.13]	0.75 [0.48–1.18]	0.23
Diarrhea†	17	0.03 [0.02–0.05]	27	0.06 [0.04–0.09]	0.48 [0.24–0.94]	0.03
Intussusception	11	0.02 [0.01–0.03]	7	0.02 [0.01–0.03]	1.39 [0.49–4.27]	0.66
Decreased appetite*	8	0.01 [0.01–0.03]	1	0.0 [0.00–0.01]	7.98 [1.07–354.23]	0.04

*Significantly higher incidence in vaccine group. †Significantly higher incidence in placebo group. ‡RR calculations were performed based on the Poisson method on stratified studies (incidence rate was not directly dependent on the RR value generated). §*P* value: 2-sided Exact Stratified Test conditional to number of cases. AEs listed by decreasing order of frequency in the vaccine group.

deaths averted by vaccination for each additional case of potentially vaccine-related intussusception.[25] Other recent conservative analyses found respective benefit-to-risk ratios for hospitalization and death of 841:1 and 395:1 in Latin America and 1093:1 and 71:1 in the US.[27,28]

The main strength of this analysis is the large sample size (102 074 subjects), permitting analysis of AEs which may be too rare to be observed in individual studies. We used differences between groups identified by assessment of RR to identify any potential imbalances in the occurrence of specific AEs between the 2 groups. These differences were not intended to be definitive or conclusive with respect to establishing causality. Limitations here are that any method used to identify safety signals has the potential to identify a large number of events that may or may not have a causal relationship to vaccination because of the multiplicity of endpoints, the difference in data processing between

studies, and power limitations (over-power to detect common clinically irrelevant events and under-power to detect rare clinically important events).

In summary, this analysis provides a detailed and comprehensive overview of the reactogenicity and safety profile of the human RV vaccine Rotarix™ from DBRCTs. which was found to be clinically acceptable and similar to that of placebo. While this analysis of over 100 000 infants in Phase II and III clinical trials was able to exclude a RR of the magnitude attributed to RotaShield™, it did not detect the lower level risks of IS reported in recent Mexican, Brazilian, and Australian post-marketing studies.[23,25,26] These studies involved up to 1.5 million infants with vaccine exposure in real-world settings and identified a low level risk of IS following both dose 1 or 2 in the 7- or 31-d period following vaccination. However, none of these studies has been able to evaluate whether the overall risk of IS is increased within the first 12 mo of life or beyond following vaccination. Further research is required to help address this important public health question.

Disclosure of Potential Conflicts of Interest

All authors are employed by the GlaxoSmithKline group of companies. Drs Han and Vinals declare having stock options.

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Supplemental Materials

Supplemental materials may be found here:
www.landesbioscience.com/journals/vaccines/article/26476

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