SUPPLEMENTARY MATERIALS

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Benefit Versus Risk Assessment of Rotavirus Vaccination in France: A Simulation and Modeling Analysis

Edouard Ledent[1*], Hugo Arlegui[2], Hubert Buyse[3], Peter Basile[3], Naveen Karkada[4], Nicolas Praet[5] and Gaëlle Nachbaur[6]

[1]Clinical Statistics, GSK, Rixensart, Belgium

[2]Clinical Research, NPI & Academic Alliances, Laboratoire GSK, Rueil-Malmaison, France

[3]Clinical Safety and Pharmacovigilance, GSK, Wavre, Belgium

[4]Clinical Statistics, GSK, Bangalore, India

[5]Clinical Research & Development, GSK, Wavre, Belgium

[6] Pharmaco-Epidemiology and Health Outcomes Research, Laboratoire GSK, Rueil-Malmaison, France

*Corresponding author: Edouard Ledent; Email: edouardDOTyDOTledentATgsk;com

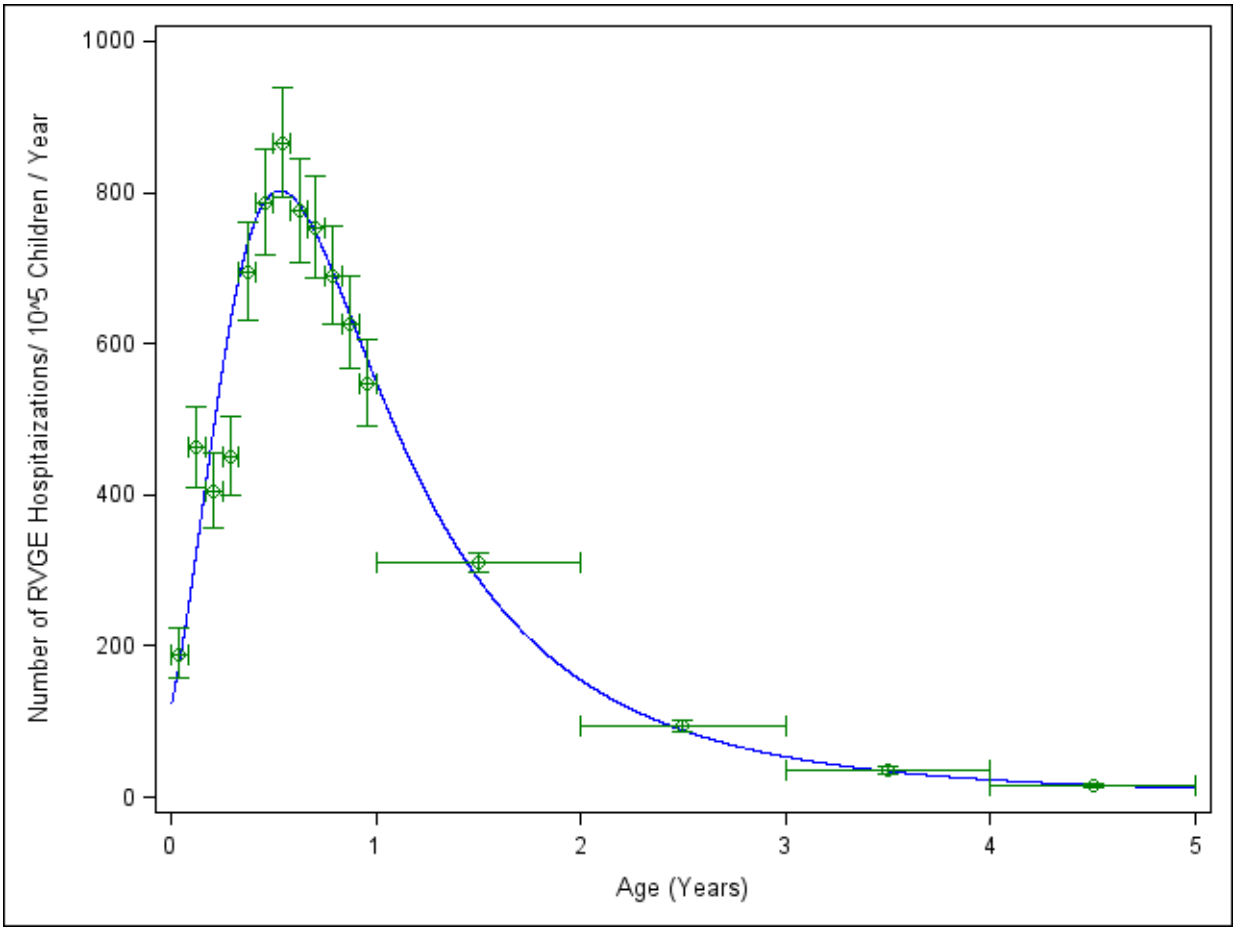
Supplementary Table S1. Sensitivity analysis of the estimated benefit and risk of vaccination with *Rotarix* in a cohort of 100 thousand (for hospitalization) and 1 million (for death) French children over 3 and 5 years post-vaccination, considering 21- and 30-day risk periods instead of 7 days for the increased risk of intussusception

Event	Risk period	Age group	B-R ratio (prev. RVGE/excess IS)		B-R difference (prev. RVGE minus excess IS)	
			Mean (SD)	Median (95% CI)	Mean (SD)	Median (95% CI)
Hosp.[a]	21 days	<3 y	439 (322)	399 (71–1142)	1325 (169)	1335 (970–1627)
		<5 y	464 (343)	419 (75–1216)	1403 (212)	1402 (983–1819)
	30 days	<3 y	260 (172)	240 (48–643)	1322 (169)	1332 (966–1625)
		<5 y	275 (184)	252 (51–684)	1400 (213)	1400 (980–1817)
Death[b]	21 days	<3 y	243 (245)	183 (27–827)	9.24 (3.29)	8.86 (3.96–16.71)
		<5 y	258 (264)	192 (28–888)	9.83 (3.73)	9.32 (4.04–18.52)
	30 days	<3 y	144 (136)	110 (18–474)	9.21 (3.29)	8.82 (3.92–16.68)
		<5 y	153 (146)	116 (19–510)	9.80 (3.74)	9.29 (4.00–18.49)

RVGE, rotavirus gastroenteritis; IS, intussusception; Hosp., hospitalization; B-R, benefit-risk; CI, credible intervals; y, years; SD, standard deviation.

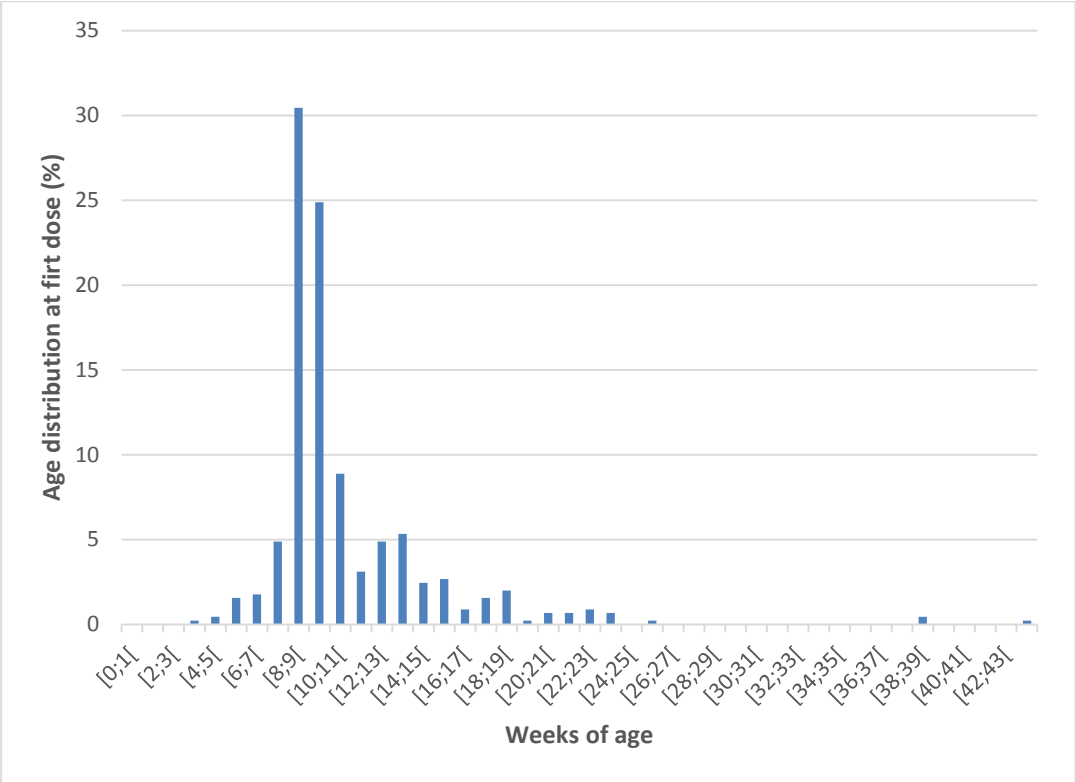
[a]Vaccine-prevented RVGE-related and vaccine-caused IS-related hospitalizations per 10^5 vaccinated children followed from birth to 3 and 5 years of age, respectively. [b]Vaccine-prevented RVGE-related and vaccine-caused IS-related deaths per 10^6 vaccinated children followed from birth to 3 and 5 years of age, respectively; IS-related - number of events caused during 2 risk windows of 21 or 30 days post-dose 1 and post-dose 2 of *Rotarix*. [c]The limit of the 95% credible intervals are determined using the 2.5% and 97.5% percentiles of the empirical distributions.

Supplementary Figure S1. Interpolation of age-specific rotavirus gastroenteritis hospitalization rates in children 0–5 years of age.

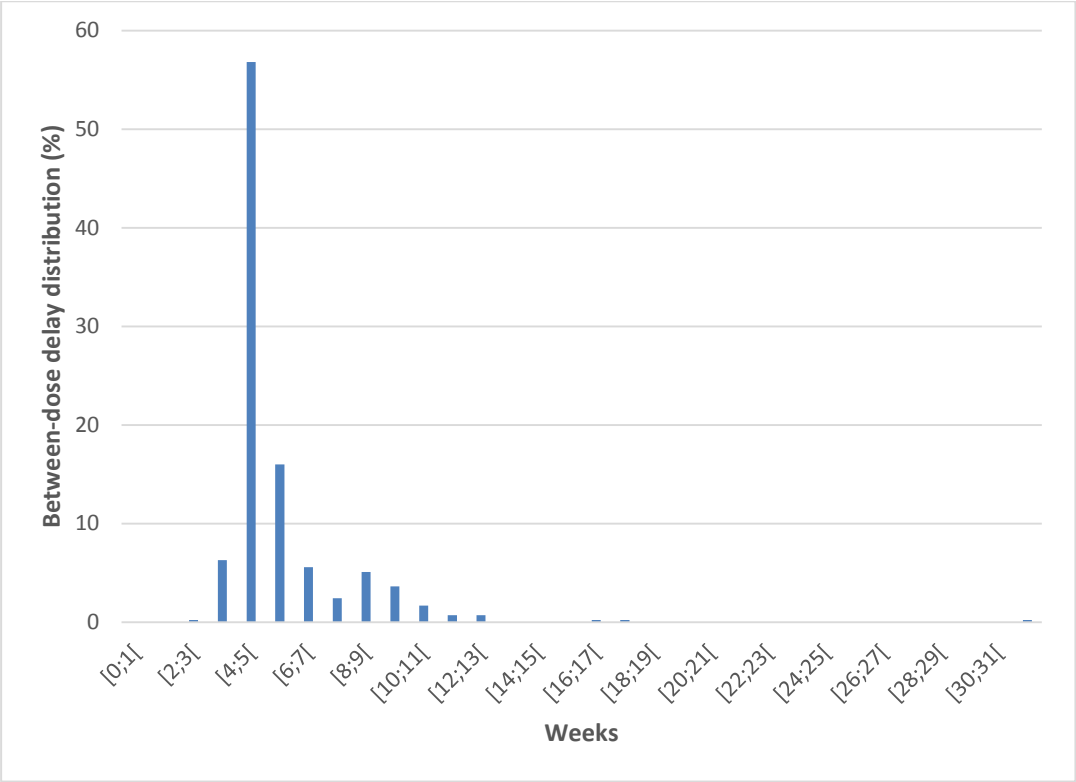


The observed values represent the baseline RVGE-incidence rate reported by Fourquet et al. [1] and the interpolation Exp[8.09*Exp(-0.236*t)-3.308*Exp(-3.762*t)] was implemented using least-squares method. *Vertical bars* define the 95 % credible interval around mean age-specific rotavirus gastroenteritis rates. *Horizontal bars* define the age range over which the hospitalization rate was estimated. The mean RVGE incidence rate over the first 5 years equal to 214.3 /10^5 children /year was calculated by integration of the curve and was verified to agree with the estimation provided by Fourquet. The *RVGE preventable fraction* of the RVGE incidence is calculated as the ratio between the post-vaccination area under the curve, accounting for vaccine efficacies after one and two doses, and the area under the curve using baseline rates. The RVGE preventable incidence following vaccination is calculated as the product of the RVGE preventable fraction and the baseline RVGE incidence calculated using HCSP estimation.

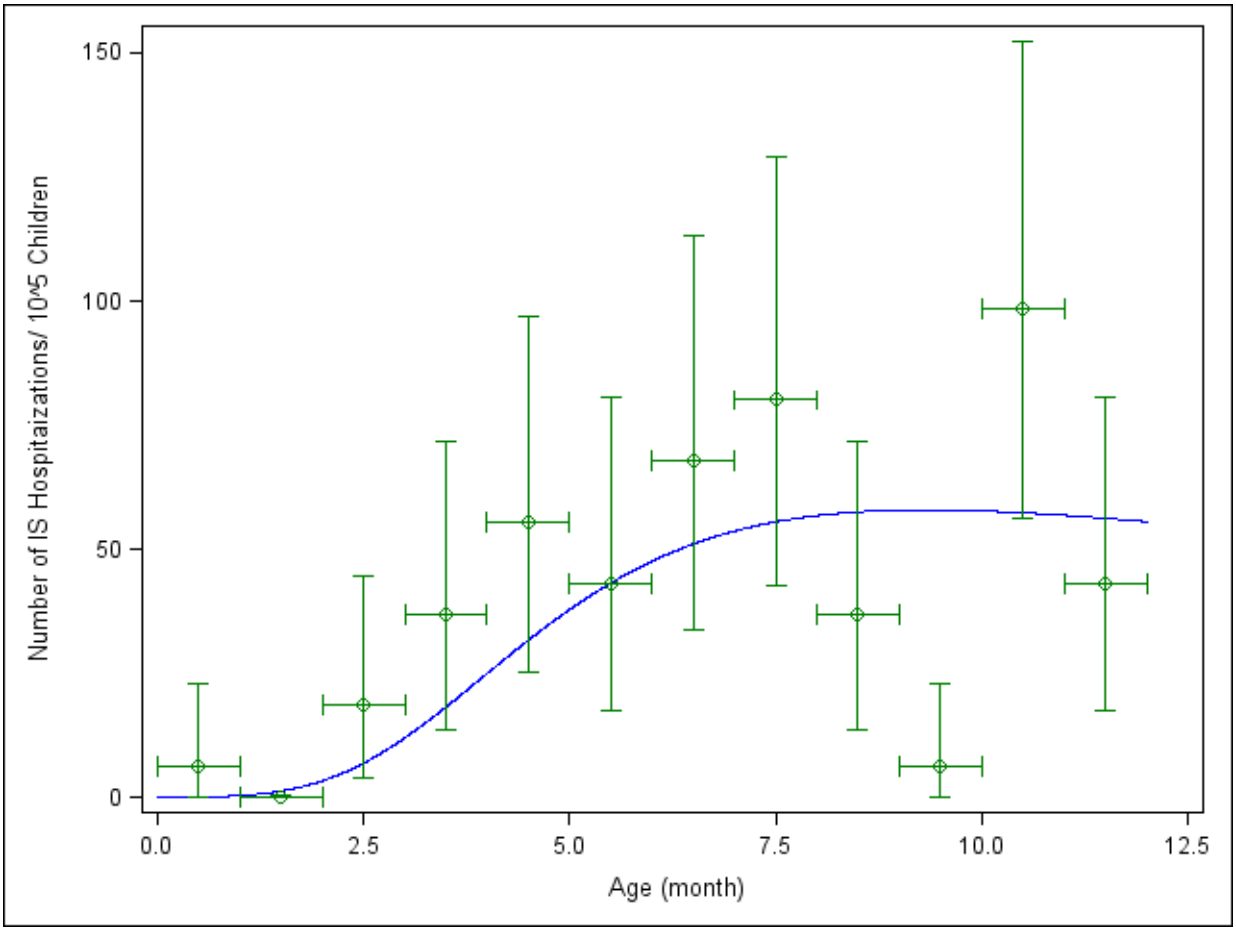
Supplementary Figure S2. Age distribution of children at first dose of *Rotarix*, as derived from unpublished *Vaccinoscopie*® study data.



Supplementary Figure S3. Distribution of the delays before administration of the second dose of *Rotarix*, as derived from unpublished *Vaccinoscopie*® study data.



Supplementary Figure S4. Interpolation of the age-specific intussusception hospitalization rates in infants of less than 1 year of age.



The observed values represent the intussusception hospitalization non-linear pattern as reported by Serayssol et al. [2] and scaled to the intussusception incidence rate calculated using the Grand-Est data reported by Fotso Kamdem et al. [3]. A non-linear model was fitted to the Serayssol et al. percentage data over the 0 – 36 months period. The coefficients of the fitted curve 435*10^(-3.31*Exp[-0.54*(t-0.362)]-0.68*Exp[0.0203*(t-1.278)]) were determined by least-squares method. The age-specific mean rates were used to calculate the mean intussusception rate over a 7-day risk window after each of the two vaccinations. The mean over the 0 – 12 period, calculated by mathematical integration of that function, was then made equal to the average IS rate reported by Fotso Kamdem et al. over the same period. Relative risks from Fotso Kamdem et al. and Serayssol et al. were combined with the age-specific rates over the 7-day window in order to calculate the attributable risk. Vertical bars define the 95 % credible interval around mean age-specific intussusception rates. Horizontal bars define the age range over which the hospitalization rate was estimated.

References

1. Fourquet F, Desenclos JC, Maurage C, Baron S. Acute gastro-enteritis in children in France: estimates of disease burden through national hospital discharge data. Arch Pediatr. 2003;10(10):861-8.
2. Serayssol C, Abbo O, Mouttalib S, Claudet I, Labarre D, Galinier P, et al. Seasonal pattern of intussusceptions in infants and children: is fall/winter predominance still worth consideration? A 10-year retrospective epidemiological study. Arch Pediatr. 2014;21(5):476-82.
3. Fotso Kamdem A, Vidal C, Pazart L, Leroux F, Savet C, Cornet C, et al. Épidémiologie de l'invagination intestinale aiguë chez l'enfant de moins de 1 an. Résultats préliminaires de l'étude Epistudy. Bull Epidémiol Hebd. 2012;10-11:138-43.