ORIGINAL RESEARCH ARTICLE

Review of Over 15 Years Postmarketing Safety Surveillance Spontaneous Data for the Human Rotavirus Vaccine (Rotarix) on Intussusception

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Abstract

Introduction Rotavirus (RV) is the most common cause of acute gastroenteritis in children <5 years of age worldwide, and vaccination reduces the disease burden. Evidence from postmarketing surveillance studies suggested an increased risk of intussusception (IS) in infants post-RV vaccination. An overall positive benefit–risk balance for the human RV vaccine (HRV) *Rotarix* (GlaxoSmithKline [GSK], Belgium) has been established and recent findings indicate an indirect effect of reduced IS over the long term.

Objective The aim of this study was to discuss spontaneous data from the GSK worldwide safety database on IS post-*Rotarix* administration.

Methods The database was reviewed for all spontaneous IS cases from 2004 to 2020. Additionally, an observed versus expected (O/E) analysis was done for adverse events attributed to IS. Data were reviewed as overall worldwide and stratified by region (Europe/USA/Japan) and dose.

Results A male predominance of IS patients was observed, consistent with earlier reports. The most frequently reported events in confirmed IS cases (Brighton Collaboration Working Group [BCWG] level 1) with time to onset ≤ 30 days post-vaccination were vomiting (55.8%), haematochezia (47.2%), and crying (21.1%). The observations from the IS spontaneous cases review and results of the O/E analysis are consistent with the known IS safety profile of RV vaccines: a transient increased incidence of IS post-vaccination (primarily in Europe/Japan/worldwide), mostly within 7 days postdose 1.
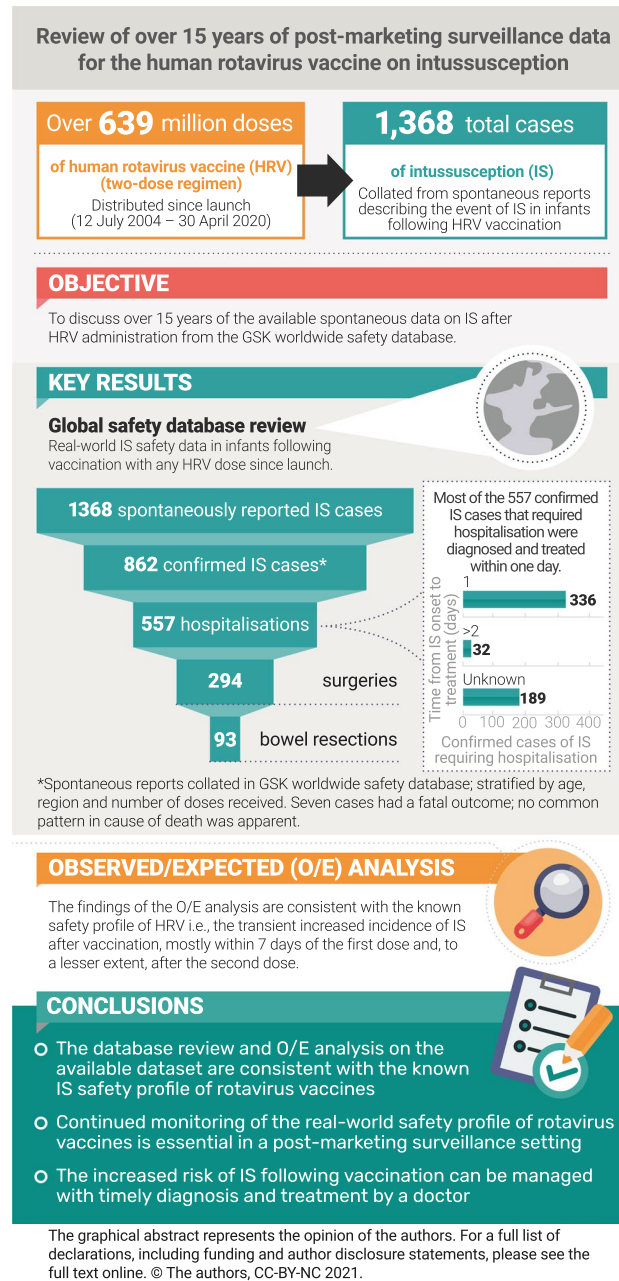
Conclusion Since the outcomes of early IS management are favourable over delayed management, healthcare professionals should inform parents about the importance of seeking immediate medical advice in case of unusual behaviour of the vaccinated infant. GSK continues to monitor the IS risk post-*Rotarix* administration through routine pharmacovigilance activities.

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Graphic abstract

Review of over 15 years of post-marketing surveillance data for the human rotavirus vaccine on intussusception

Over **639** million doses
of human rotavirus vaccine (HRV) (two-dose regimen)
Distributed since launch (12 July 2004 – 30 April 2020)

1,368 total cases
of intussusception (IS)
Collated from spontaneous reports describing the event of IS in infants following HRV vaccination

OBJECTIVE

To discuss over 15 years of the available spontaneous data on IS after HRV administration from the GSK worldwide safety database.

KEY RESULTS

Global safety database review
Real-world IS safety data in infants following vaccination with any HRV dose since launch.

1368 spontaneously reported IS cases

862 confirmed IS cases*

557 hospitalisations

294 surgeries

93 bowel resections

Most of the 557 confirmed IS cases that required hospitalisation were diagnosed and treated within one day.

Time from IS onset to treatment (days)

1 — 336
>2 — 32
Unknown — 189

0 100 200 300 400
Confirmed cases of IS requiring hospitalisation

*Spontaneous reports collated in GSK worldwide safety database; stratified by age, region and number of doses received. Seven cases had a fatal outcome; no common pattern in cause of death was apparent.

OBSERVED/EXPECTED (O/E) ANALYSIS

The findings of the O/E analysis are consistent with the known safety profile of HRV i.e., the transient increased incidence of IS after vaccination, mostly within 7 days of the first dose and, to a lesser extent, after the second dose.

CONCLUSIONS

- The database review and O/E analysis on the available dataset are consistent with the known IS safety profile of rotavirus vaccines
- Continued monitoring of the real-world safety profile of rotavirus vaccines is essential in a post-marketing surveillance setting
- The increased risk of IS following vaccination can be managed with timely diagnosis and treatment by a doctor

Plain language summary

Rotavirus (RV) is the most common cause of acute gastroenteritis and a major cause of death in young children worldwide. Vaccination has been instrumental in reducing the impact of RV disease. Real-world evidence suggests an increased risk of intussusception (an infrequent type of bowel obstruction) in infants following RV vaccination. We reviewed IS cases reported spontaneously worldwide in children following a two-dose vaccination with the human RV vaccine (*Rotarix*, GlaxoSmith-Kline [GSK]) since its launch in 2004. We observed that (1) IS occurred more frequently 7 days after the first dose and, to a lesser extent, after the second dose; (2) boys were more frequently affected than girls (56.3%); (3) of 862 confirmed reported cases, 557 required hospitalisation; and (4) surgical intervention was required for 294 of 557 hospitalised cases. We used statistical analysis to assess whether the number of cases observed would be higher or lower than the natural occurrence of IS (irrespective of vaccination). These results were in line with the known RV vaccine safety profile. It is important to

constantly monitor the real-world safety profile of RV vaccines in the postmarketing setting. Since the outcomes of early management of IS are favourable compared with delayed management, healthcare professionals should inform parents to seek immediate medical advice if they observe unusual behaviour in their vaccinated child. In conclusion, our analyses on data of a large patient pool for this rare event reinforce the favourable safety profile of human RV vaccine and the benefits of vaccination in young children.

Key Points

The human rotavirus vaccine (HRV) was first approved in 2004 for the prevention of rotavirus infection in young children.

As part of routine pharmacovigilance activities, we are monitoring the incidence of intussusception (IS) following vaccination with HRV, based on spontaneous reports.

Spontaneous reports collected since 2004 indicate a transient increased incidence of IS after vaccination with HRV, mostly within 7 days after the first dose and, to a lesser extent, after the second dose, which is in line with published literature.

Our analysis highlights the importance of early management of IS since this resulted in more favourable outcomes compared with delayed treatment.

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1 Introduction

Rotavirus (RV) infection represents the most common cause of severe, dehydrating gastroenteritis in infants and children below the age of 5 years worldwide [1–3]. However, implementation of RV vaccines has substantially decreased hospitalisations from RV as well as from all-cause acute gastroenteritis [4].

In Europe, most cases of RV infection occur in children under 2 years of age, with a peak incidence between 6 and 24 months of age. Primary infection after 3 months of age usually causes the most severe disease, while subsequent infections typically manifest with much milder symptoms [5, 6]. In developing countries, gastroenteritis due to RV infection remains a major cause of childhood death despite the introduction of RV vaccines. Globally, the number of deaths in children under 5 years of age caused by RV in 2013 was estimated at 215,000 [7, 8].

Intussusception (IS), a type of bowel obstruction, occurs in 0.5–4.3 per 1000 live births in Europe, North America, and Australia [9], and estimates from Latin America show similar rates to those identified in industrialised countries [10, 11]. While the aetiology of paediatric IS is typically idiopathic, several predisposing factors (mostly anatomic or infectious) have been identified [12, 13]. For instance, children with a medical history of IS, with uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract, or antecedent viral illness are prone to IS [9, 12]. Generally, IS is most common among children under 1 year of age [9, 14] and a male predominance has been noted worldwide [9].

An association between IS as a post-immunisation adverse event (AE) and RV vaccines was first identified for a tetravalent RV vaccine, *RotaShield* (Wyeth Lederle Laboratories), which was subsequently withdrawn from the market in 1999. As a potential causal link, the replication of the RV in the intestinal epithelium may trigger an inflammatory reaction and predispose to IS [15, 16].

Currently, four oral, live attenuated vaccines against RV are available internationally and are World Health Organization (WHO) prequalified: *Rotarix* (hereafter referred to as human RV vaccine [HRV], GSK, Belgium; liquid formulation prequalified in 2009); *RotaTeq* (referred to as human-bovine reassortant rotavirus vaccine [HBRV], Merck&Co., Inc., USA; prequalified in 2008); *Rotavac* (Bharat Biotech, Hyderabad, India; prequalified in 2018); and *Rotasiil* (Serum Institute of India PVT. Ltd, Pune, India; prequalified in 2018) [17]. All four vaccines are considered to be well tolerated and effective in reducing the burden of gastrointestinal disease caused by RV [18]. The WHO recommends including vaccination of infants against RV in all routine immunisation programmes (with the first dose of RV vaccine administered as soon as possible after 6 weeks of age, along with the diphtheria-tetanus-pertussis vaccination), especially in countries with high mortality caused by RV infection [7].

HRV contains the human RV strain RIX4414 (genotype G1P [8]) [19] and was first licensed in Mexico on 12 July 2004. Currently, HRV is approved in the US, all member states of the European Economic area/UK, Japan, and several other countries (vaccine introduction current/planned in more than 90 countries globally [20]), with an indication for active immunisation of infants aged 6–24 weeks to reduce the burden of gastroenteritis due to RV infection.

The risk of IS following vaccination with HRV has been evaluated in a large-scale post-approval safety study sponsored by GSK and conducted in Mexico, in collaboration with the Mexican Institute of Social Security [21]. Episodes of

IS were identified according to the case definition developed by the Brighton Collaboration Working Group (BCWG) for Intussusception [22]. Clustering of IS within 7 days of vaccination was observed postdose 1. An attributable risk of three to four additional cases of IS per 100,000 vaccinated infants was estimated [21]. In addition, various postmarketing surveillance studies were conducted providing risk estimates of IS after vaccination with HRV and HBRV [23–29]. The analytical period of these studies ranged from about 1.5–7 years. While some studies claim no increased risk of IS or IS-related hospital admission following vaccination [24, 30–32], there is a growing body of evidence for a slightly increased risk of IS post-vaccination (notably postdose 1) [25, 33–35] that translates into an increased risk of hospitalisation [36]. A meta-analysis of the available data up to 2013 was published to provide an overall estimate of the IS risk after vaccination with HRV and HBRV when considering the heterogeneity among the studies [25]. This meta-analysis of postmarketing surveillance data showed an increased risk of IS during the first 7 days after administration of dose 1 and, to a lesser extent, of dose 2. The overall (fixed-effect) estimate of IS risk during the 7 days after vaccination with HRV was 5.4 (95% confidence interval [CI] 3.9–7.4) after dose 1 and 1.8 (95% CI 1.3–2.5) after dose 2 [25]. Of note, as recently proposed by Vetter et al., the increased risk of IS following vaccination should be weighed against the risk of IS caused by naturally occurring RV infection [37]. A favourable benefit–risk balance for HRV has been suggested in various studies [35, 38–40]. However, the concern of IS occurring in temporal association with immunisation subsequent to the findings in 1999, among other reasons, has led to some hesitancy in the implementation of the RV vaccines in national immunisation programmes [41]. Continuous postmarketing surveillance is important for monitoring this safety concern, especially for the newly introduced RV vaccines, to provide real-time safety data for such less frequent events that are difficult to observe in prelicensure clinical trials or postmarketing data with a small proportion of the exposed population analysed.

As part of routine pharmacovigilance activities, GSK is monitoring the incidence of IS following RV vaccination since HRV launch and reports are being collected in a worldwide safety database. The objective of this article is to discuss the spontaneous cases of IS after HRV administration from the worldwide safety database received over the last 15 years.

2 Methodology

2.1 Spontaneous Report Data

Spontaneous report data were collated from unsolicited communications describing the event of IS with or without other AEs that occurred in infants who had received RV vaccination. These communications (referred to as 'spontaneous reports') were either submitted to GSK directly—voluntarily from individual reporters (who might be reporting for themselves or others) via local reception/call centres—or were collected by GSK from interactive digital media (i.e., social media or other such platforms). Follow-up questionnaires on IS were referred to for most of the scientific case evaluations. Individual reporters included healthcare professionals (HCPs), regulatory authorities, consumers, and others. All reported AEs were coded using the International Conference on Harmonisation (ICH) Medical Dictionary for Regulatory Activities (MedDRA®) [42]. One spontaneous report could contain more than one AE reported by the same individual. AEs were classified as serious if meeting the ICH regulatory definition: any untoward medical occurrence that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in disability/incapacity, is a congenital anomaly/birth defect in the offspring, or is a medically important event [43]. Reported AEs, while temporally associated with the product's use, may not necessarily be causally associated with it [44].

2.2 Data Extraction and Selection Criteria

For this review and all analyses, spontaneous report data were extracted from the GSK worldwide safety database (Oracle Argus) for the period 12 July 2004 (international launch date for *Rotarix*) until 11 July 2020 using an automated search for *Rotarix* in combination with the MedDRA® preferred term 'intussusception'. All identified reports were medically reviewed at GSK and were assessed according to BCWG criteria to determine the level of diagnostic certainty (as described by Bines et al. [22]). Reports that could be categorised as fulfilling BCWG criteria level I were classified as confirmed. Time to onset (TTO) for the event of IS was calculated as the occurrence of the first sign/symptoms related to IS since the date of vaccination with any RV vaccine dose (day 0), for reports containing this information. Thus, the risk period calculation was based on the TTO (when the event occurred after vaccine administration) and not on when the initial report was received. Analyses were conducted worldwide, in Europe, the US, and Japan, and for two risk periods after each vaccine dose: 7 days (day 0 to day 6) and 30 days (day 0 to day 29), in line with previous analyses [45–47]. In a descriptive analysis, for all confirmed IS cases with a TTO ≤ 30 days postvaccination, we described events reported in at least 5% of the cases, hospitalisation requirements, and duration between IS onset and initiation of treatment (i.e., 'time to treatment initiation'). To assess the impact of a delayed treatment initiation, we described the surgical management of cases requiring hospitalisation, in which there was a delay of > 2 days between TTO and
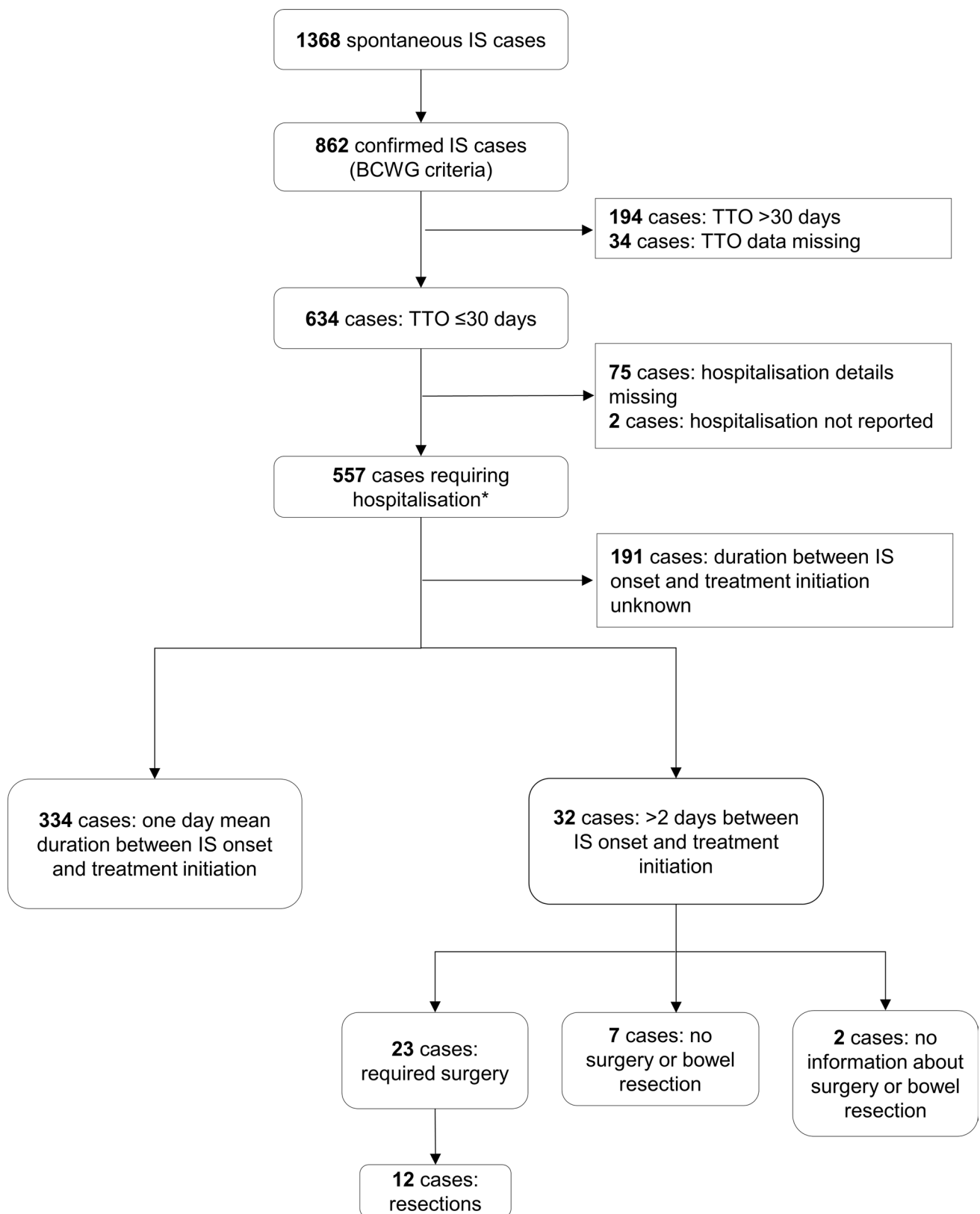
Fig. 1 Overview of the time to onset of intussusception, reported hospitalisation, duration between intussusception onset and treatment start, and required surgery with or without resection for all spontane- ous intussusception cases. *Duration of hospitalisation for these cases is detailed in electronic supplementary material 2. *BCWG* Brighton Collaboration Working Group, *IS* intussusception, *TTO* time to onset

treatment initiation. Medical assessment was performed for confirmed IS cases with TTO ≤ 30 days (please refer to the algorithm in Fig. 1).

Postmarketing collection and evaluation of safety data on an ongoing basis is part of GSK's systematic approach for the identification of potential safety signals. As information on the actual number of infants exposed to HRV worldwide is not available, patient exposure was approximated by the number of doses distributed from launch until 30 April 2020, which represents the most reliable data source for patient exposure to a vaccine in a postapproval setting. Of note, the sales database is subject to updates and corrections depending on information provided by GSK local country subsidiaries (e.g., vaccine doses may be returned by subsidiaries to the central warehouse). These constant updates may result in discrepancies between consecutive queries of the database. The time lag between an actual distribution to a country and recording in the database is 2 months on average. In order to minimise the risk of inaccuracy and to better reflect the exposure data, the sales information was retrieved with a data lock point (11 July 2020) minus 2 months (30 April 2020).

2.3 Observed versus Expected Analysis

The observed versus expected (O/E) analysis was performed to determine whether the observed number of AEs attributed to IS corresponded to the number of events expected to occur within a predefined risk period, under the null hypothesis of no association with HRV vaccination. The ratio of O/E number of IS cases was calculated for the period from 12 July 2004 until 11 July 2020. Background incidence rates were defined by the number of incident reports of a condition or event occurring naturally in the population, expressed in person-time [48]. These age and country-stratified background estimates were obtained from the literature [49–55], considering populations with similar characteristics as the RV target population. For the O/E analysis, only cases occurring in the predefined risk period were counted. All IS cases with BCWG level 1–3 that occurred within 7 and 30 days after each vaccine dose in infants under 1 year of age were considered. Conservatively, all infant IS case levels 1–4 BCWG occurring in the same post-vaccination periods were also considered for this O/E analysis. If TTO was missing, cases were considered as having occurred in the risk period for the respective analysis (7 or 30 days). When unknown, the dose number was imputed according to the dose distribution of the other cases in the same region. Cases with unknown age at vaccination were considered as under 1 year of age and included in the O/E analysis. The cases were analysed worldwide, in Europe, the US, and Japan. The exposures are all the sales of lyophilised and liquid HRV vaccine from the international birth date (12 July 2004) until 30 April 2020.

The observed number of cases was compared with the estimated number of cases computed from background incidence rates. Exact lower and upper 95% CIs were calculated around the number of observed cases. The small number of observed cases were considered as the largest source of statistical uncertainty, while exposure to the vaccine and background incidence rates were considered fixed numbers or with an uncertainty that was negligible compared with the uncertainty from the observed numbers. The number of observed cases and associated CIs were calculated from an exact Poisson distribution [56], which depends only on one parameter, i.e., the number of observed cases. Data were stratified worldwide and by region (Europe, the US, and Japan), and dose (first, second, or any dose [in a few instances, a third dose was administered]). A range of expected number of IS cases based on varying background incidence rates was calculated.

The reported numbers of cases and their 95% CIs were rescaled according to varying levels of reported fraction (RF) to obtain the observed number of cases. The RF is the proportion of cases reported among all those that occurred in the vaccinated population within the risk period, regardless of causality. Graphs of the observed numbers of cases and their 95% CI (y-axis) according to a range of RFs (x-axis) were developed for each analysis. The age-adjusted expected number of cases corresponding to selected background incidence rates were presented as horizontal reference lines. These reference lines allowed to perform an exploratory comparison of the observed number of cases to the expected number of cases: (1) higher than expected if the lower limit of the 95% CI computed from the observed is above the reference line of the expected; and (2) lower than expected if the upper limit of the 95% CI computed from the observed is below the reference line of the expected.

The number of cases expected to occur within a particular risk period following vaccination (Ne) was adjusted from the following simplified formula for the distribution of age (in months) at administration (Eq. 1):

$$Ne = \sum_{i=1}^{12} Inc \times Pd_i \times 12 \times Nd_i \times RP \tag{1}$$

where i is the identifier of the age classes by month during the first year of age; Inc is the incidence of intussusception in the first year of life (expressed as incidence per day); and Pd_i is the proportion of intussusception occurring in the ith month of age.

Regional age-specific distributions of IS were used. For Europe, these data were taken from surveillance in Switzerland (2003–2006) [57], and worldwide, US and Japan data were used [51, 58, 59].

Note: $Inc \times Pd_i \times 12$ is the age-specific incidence rate of IS, assuming that the monthly age classes are balanced in

the first year of age in the population; Nd_i is the number of doses of HRV used in the *i*th month of age, which is based on country-level sales data and an estimate of the age at vaccine administration based on the distribution of age at vaccination reported in spontaneous *Rotarix* cases available in the safety database (stratified by region and dose); and RP is the risk period after dose administration (7 or 30 days)

2.4 Background Incidence Data

The range of IS background incidence rates was based on studies listed in electronic supplementary material (ESM) 1. The maximum (i.e., 'high ref' on figures in the ESM) and minimum (i.e., 'low ref' on figures in the ESM) values of the IS background ranges used for Europe refer to an Irish [49] and German (unpublished work) study (24.2 to 96.7/100,000 person years), respectively. The minimum and maximum incidence range values used for the US were based on two US studies (33–54/100,000 person years) [54, 55], the values for Japan stemmed from two Japanese studies [50, 52, 53] (143.5–191/100,000 person years), and the lowest and highest values of the worldwide expected range (3.8–105.3/100,000 person years) was based on Latin American studies [51] since 32% of HRV doses are sold to Latin American countries.

3 Results

From launch until 30 April 2020, an estimated 639,391,442 doses of *Rotarix* were distributed. As an infant could receive one and two doses, depending on compliance with the vaccination schedule, the estimated number of infants exposed from launch until 30 April 2020 ranged between 319,695,721 and 639,391,442.

3.1 Overall Dataset of Spontaneous Adverse Event Reports

A total of 1368 spontaneous IS reports were retrieved from the GSK worldwide safety database for the analytical period, of which 862 were confirmed IS cases according to BCWG criteria, with IS occurring more frequently in males (56.4%) than in females (40.6%); for the remaining three percent, the sex was unknown. Mean age at IS onset was 4.2 months (Table 1). The occurrence of confirmed IS following HRV vaccination was more frequently observed after the first dose of HRV (in almost half of the confirmed cases) and relatively less frequently after the second dose (in about one-third of the confirmed cases) [Table 1; Fig. 2]. For approximately 20% of cases, the dose after which confirmed IS occurred was not detailed in the report (Table 1).

Table 1 Patient characteristics of the confirmed intussusception cases

	Confirmed IS cases [*N* = 862]
Age at onset, months	
Mean ± SD	4.17 ± 2.47
Median (minimum; maximum)	3.84 (0; 32.04)
Sex	
Male	486 (56.4)
Female	350 (40.6)
Unknown	26 (3.0)
Dose	
First	404 (46.9)
Second	290 (33.6)
Any[a]	696 (80.7)
Unknown	166 (19.3)

Data are expressed as number (%) of cases in each category unless otherwise specified

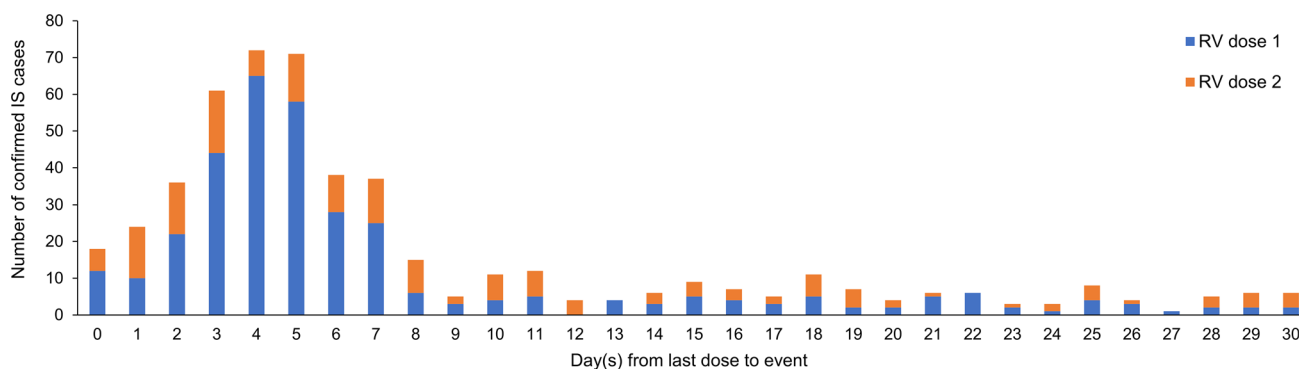*IS* intussusception, *N* number of confirmed cases, *SD* standard deviation

[a]Note that an extra third dose was administered in a few instances

Of the 862 confirmed IS cases, 634 had a TTO ≤ 30 days, 194 had an extended TTO (> 30 days), which makes a link with vaccination less likely, and 34 cases had an unknown TTO. Worldwide, the most frequently reported events in the 634 confirmed cases with a TTO of ≤ 30 days were vomiting (55.8%) and haematochezia (47.2%), followed by crying (21.1%) and abdominal pain (15.9%) [Table 2; region-wise data are available in this table]. The events listed in Table 2 were reported in at least 5% of the 634 confirmed cases that had a TTO of ≤30 days.

Most IS cases occurred in the first 7 days after infants received the RV vaccine dose (Fig. 2).

Among the 634 confirmed IS cases with a TTO of ≤ 30 days, hospitalisation occurred in 557 cases (Fig. 1) and there was no hospitalisations reported for two cases. For the remaining 75 cases, no details about hospitalisation were available. Of the abovementioned 557 IS cases with hospitalisation, 366 included details that allowed the calculation of the time between onset of IS and the treatment initiation. In these cases, the mean duration between the onset of IS and treatment initiation was 1 day. A delay of more than 2 days between onset of IS and treatment was observed for 32 cases. Surgery was required in 23 of these 32 cases, and in 12 of those cases with surgery, the patients underwent resection. Of the remaining 9 cases, 7 did not require any surgery or bowel resection, and for 2 cases, it was unknown if surgery or resection was performed (Fig. 1).

For approximately one-third of the 557 confirmed cases with hospitalisation, the duration of hospitalisation was 4 days or fewer (67 cases, ≤1 day; 52 cases, 2 days; 41 cases, 3 days; 37 cases, 4 days; duration of hospitalisation was

Fig. 2 Distribution of the time to onset of intussusception after administration of the rotavirus vaccine for the confirmed cases with a time to onset of ≤ 30 days (N = 634). Cases with a reported time to onset of 'less than one a day' or 'same day' are represented as 0 days from the last dose; cases with a reported time to onset of '2–3 days' are represented as 2 days from the last dose; cases with a reported time to onset of '< 7 days' are represented as 6 days from the last dose; and cases with a reported TTO of '1 week' are represented as 7 days from the last dose. *IS* intussusception, *N* total number of confirmed cases, *RV* rotavirus vaccine

Table 2 Frequently reported events in confirmed intussusception cases with a time to onset of ≤30 days [N = 634]

Co-reported events	n (%)				
	Europe[a]	Japan	US	Rest of the world[b]	Worldwide
Vomiting[c]	96 (15.14)	125 (19.72)	6 (0.95)	127 (20.03)	354 (55.84)
Haematochezia	76 (11.99)	127 (20.03)	2 (0.32)	94 (14.83)	299 (47.16)
Crying[d]	56 (8.83)	41 (6.47)	2 (0.32)	35 (5.52)	134 (21.14)
Abdominal pain[e]	39 (6.15)	13 (2.05)	1 (0.16)	48 (7.57)	101 (15.93)
Altered mood	0 (0)	73 (11.51)	0 (0)	0 (0)	73 (11.51)
Diarrhoea[f]	26 (4.10)	27 (4.26)	1 (0.16)	30 (4.73)	84 (13.25)
Abdominal mass	0 (0)	55 (8.68)	0 (0)	10 (1.58)	65 (10.25)
Pallor	33 (5.21)	14 (2.21)	0 (0)	14 (2.21)	61 (9.62)
Pyrexia[g]	18 (2.84)	14 (2.21)	1 (0.16)	21 (3.31)	54 (8.52)
Abdominal distension	11 (1.74)	6 (0.95)	0 (0)	36 (5.68)	53 (8.36)
Irritability	6 (0.95)	1 (0.16)	2 (0.32)	28 (4.42)	37 (5.84)
Decreased appetite	20 (3.15)	4 (0.63)	1 (0.16)	12 (1.89)	37 (5.84)

Data are expressed as number (%) of cases for respective events represented region-wise. Events reported in < 5% of the worldwide confirmed cases with a time to onset ≤ 30 days are not reported in this table

N total number of cases used for calculating the percentages

[a]Europe includes Austria, Belgium, Cyprus, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Lithuania, Luxemburg, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Turkey, and the UK

[b]Rest of the world excluding Europe, Japan, and the US

[c]Count includes projectile vomiting

[d]Count includes high-pitched crying

[e]Count includes both upper and lower abdominal pain

[f]Count includes haemorrhagic diarrhoea

[g]Count includes hyperpyrexia

unknown in 271 cases) [ESM 2]. In 18 of the 89 cases that required hospitalisation for more than 4 days, the delay in IS diagnosis or treatment could not be calculated due to missing information in the reports. In 62 of these 89 cases, the extended period of hospitalisation was unlikely to be due to a delay in IS diagnosis or treatment initiation because the period between IS onset and IS treatment start was 2 days or fewer. For 9 of these 89 cases, the delay in IS diagnosis or treatment initiation was at least 3 days, and in 4 of these 9 cases, patients underwent surgery with resection, 2 patients had surgery without resection, and it was unknown if resection was performed for the remaining 3 patients (ESM 3).

Of all the confirmed cases that required hospitalisation ($n = 557$), 294 required surgery, of whom 93 required bowel resections. In 31 of these 93 cases, hospitalisation occurred for more than 4 days (ESM 4a). The need for bowel resection in these 93 cases could not be easily attributed to a delay in IS diagnosis or treatment because the period between IS onset and IS treatment was 2 days or fewer in 52 cases, 3 days in 7 cases, 4 days in 4 cases, 17 days in one case, and unknown in 29 cases of bowel resection (ESM 4b).

Seven of the 862 confirmed IS cases had a fatal outcome. The deaths in these seven cases were reported to have historically occurred between 2006 and 2014. One death per year occurred from 2006 to 2011 and one occurred in 2014. The TTO of the first sign/symptom that was known for five cases varied from 3 to 7 days after patients received the first or second dose of HRV. In four fatal cases, sufficient information for adequate medical assessment was lacking, including two cases for which the TTO of the events was unknown. In two of the seven fatal cases, patients had an underlying condition and/or a medical history as a confounding factor. In one of the fatal cases, the physician advised the infant's parents to hospitalise the infant on the basis of a preliminary IS diagnosis 3 days after receiving the RV vaccine. The parents refused to comply with the doctor's advice and the infant died the next day. No common pattern in the cause of death was apparent from the analysis of these fatal cases.

3.2 Observed versus Expected Analysis

With an RF of 50%, the observed cases within 30 days after the second dose were far below the lowest estimate of expected number of cases for all geographic locations (ESM 5). Likewise, with an RF of 50%, the observed cases within 7 days after the second dose were below the lowest estimate of the expected number of cases in the US and Japan (ESM 6).

Worldwide and in Europe, the observed cases (all BCWG levels) within 7 days after the second dose were significantly higher than the lowest expected number of cases for RF less than 68% and 59%, respectively (ESM 7). Worldwide, the numbers of observed cases following any dose and dose 1 were within or below the expected range regardless of the risk period, the BCWG diagnostic levels, or the RF (Table 3, ESM 8). In Europe, the numbers of observed cases within 30 days following any dose and dose 1 were within or below the expected range whatever diagnostic levels were considered (Table 3). For the worst-case safety scenario that included unconfirmed cases with a 7-day risk period following dose 1 in Europe, the number of observed cases was above the expected range. For RF lower than 73%, the observed cases were above the highest expected cases for BCWG level 1 cases (ESM 9). In the US, the numbers of observed cases following any dose and dose 1 were below the expected

range irrespective of the risk period or the diagnostic levels considered, and for a large range of RFs (Table 3, ESM 10). In Japan, the numbers of observed cases following any dose and dose 1 were below or within the expected range for the 30-day risk period whatever the diagnostic levels considered (Table 3, ESM 11a and b). Considering a 7-day risk period following any dose or dose 1, the observed numbers of cases were above the expected range irrespective of the diagnostic levels considered (ESM 11c and d).

4 Discussion

Since its 2004 launch, over 639 million doses of HRV have been distributed worldwide. HRV has currently active marketing authorisation in more than 100 countries worldwide [60] and is prequalified by the WHO. HRV has a long-established safety and efficacy/effectiveness profile that has not altered after many years on the market, and a large proportion of the population has been vaccinated [18, 61–64]. Since evidence from postsurveillance studies pointed towards an increased risk of IS in infants following RV vaccination, GSK monitored the incidence of IS following RV vaccination as part of its routine pharmacovigilance activities. This risk of IS is also included in the packaging insert for HRV. Review of all confirmed IS cases retrieved from GSK's safety database showed that IS is more frequently observed in males than in females. Our findings are in line with earlier reports demonstrating a male predominance of IS patients [22].

A meta-analysis on data from postmarketing surveillance studies to further evaluate the association between RV vaccination and IS was performed in 2013 by GSK [25]. The conclusion of this analysis was that postmarketing safety studies indicated a transient increased incidence of IS after vaccination with HRV, mostly within 7 days after the first dose and, to a lesser extent, after the second dose, which is in line with our findings. As recently postulated, the low-level IS risk observed for HRV and HBRV may relate to the class effect of replicating RV vaccines [65, 66].

The benefits of RV vaccines have been well documented in prelicensure clinical efficacy studies and numerous postlicensure vaccine effectiveness and impact studies conducted in different parts of the world [41]. These benefits include impact on diarrhoea-related deaths, hospitalisations, and other health outcomes associated with RV gastroenteritis and may also go beyond reducing RV gastroenteritis-related mortality and morbidity (e.g., reduced incidence of childhood seizures [67] and improved hospital quality of care [68]). Additionally, while a short-term increased IS risk may exist following vaccination, this may not hold true for the long term [30, 67]. When taking into account the role of natural RV infection as an independent risk factor for IS, the

Table 3 Comparison of the number of spontaneous intussusception reports received and number expected to have occurred by chance in 30 days and 7 days after vaccination (worldwide, Europe, US, and Japan)

Risk period (days)	Dose	Total number of doses	Expected number of cases (range)	Observed number of cases (95% CI)		
				BCWG L1[a]	BCWG L1–3[a]	BCWG L1–4[a]
Worldwide						
30	First	319,695,721.12	614.4–17,025.2	440 (399.8–483.1)	469 (427.5–513.4)	741 (688.6–796.3)
30	Second	319,695,721.12	1,164.8–32,277.9	217 (189.1–247.9)	230 (201.2–261.7)	364 (327.6–403.4)
30	Any[b]	639,391,442.23	1,598.5–44,295.2	659 (609.6–711.3)	701 (650.1–754.9)	1108 (1043.7–1175.2)
7	First	319,695,721.12	143.4–3,972.5	321 (286.8–358.1)	342 (306.7–380.2)	559 (513.6–607.3)
7	Second	319,695,721.12	271.8–7,531.5	114 (94.0–136.9)	121 (100.4–144.6)	213 (185.4–243.6)
7	Any[b]	639,391,442.23	373.0–10,335.6	436 (396.0–478.9)	464 (422.7–508.2)	774 (720.4–830.5)
Europe						
30	First	16,029,101	170.2–680.2	187 (161.2–215.8)	199 (172.3–228.7)	325 (290.6–362.3)
30	Second	16,029,101	277.3–1,108.1	44 (32.0–59.1)	46 (33.7–61.4)	98 (79.6–119.4)
30	Any[b]	32,058,202	427.6–1,708.6	231 (202.2–262.8)	245 (215.3–277.7)	423 (383.6–465.3)
7	First	16,029,101	39.7–158.7	138 (115.9–163.0)	148 (125.1–173.9)	249 (219.0–281.9)
7	Second	16,029,101	64.7–258.5	22 (13.8–33.3)	23 (14.6–34.5)	51 (38.0–67.1)
7	Any[b]	32,058,202	99.8–398.7	160 (136.2–186.8)	171 (146.3–198.6)	300 (267.0–335.9)
US						
30	First	10,945,330	250.5–410.0	6 (2.2–13.1)	8 (3.5–15.8)	19 (11.4–29.7)
30	Second	10,945,330	307.2–502.7	6 (2.2–13.1)	6 (2.2–13.1)	13 (6.9–22.2)
30	Any[b]	21,890,660	576.4–943.3	13 (6.9–22.2)	15 (8.4–24.7)	34 (23.5–47.5)
7	First	10,945,330	58.5–95.7	5 (1.6–11.7)	6 (2.2–13.1)	14 (7.7–23.5)
7	Second	10,945,330	71.7–117.3	5 (1.6–11.7)	5 (1.6–11.7)	9 (4.1–17.1)
7	Any[b]	21,890,660	134.5–220.1	10 (4.8–18.4)	11 (5.5–19.7)	24 (15.4–35.7)
Japan						
30	First	3,406,093	109.5–145.8	105 (85.9–127.1)	110 (90.4–132.6)	140 (117.8–165.2)
30	Second	3,406,093	398.1–529.9	67 (51.9–85.1)	70 (54.6–88.4)	78 (61.7–97.3)
30	Any[b]	6,812,186	437.6–582.4	172 (147.3–199.7)	180 (154.7–208.3)	218 (190.0–248.9)
7	First	3,406,093	25.6–34.0	78 (61.7–97.3)	80 (63.4–99.6)	103 (84.1–124.9)
7	Second	3,406,093	92.9–123.6	36 (25.2–49.8)	37 (26.1–51.0)	43 (31.1–57.9)
7	Any[b]	6,812,186	102.1–135.9	114 (94.0–136.9)	117 (96.8–140.2)	146 (123.3–171.7)

BCWG L1, Brighton Collaboration Working Group level 1, *BCWG L1–3* Brighton Collaboration Working Group levels 1–3, *BCWG L1–4* Brighton Collaboration Working Group levels 1–4, *CI* confidence interval

[a]As defined by Bines et al. [22]

[b]Note that an extra third dose was admin in a few instances

benefit–risk profile of RV vaccination may in fact be even more advantageous than previously anticipated [37].

The current review of GSK's safety database has shown a relatively low number of confirmed reports in which the infants underwent surgery, making it difficult to confirm a correlation between time-to-treatment and the risk of surgery or resection.

The O/E analysis suggested that regardless of the region or risk period considered, the number of observed cases of IS following dose 2 are below the range of expected IS cases, even when considering the worst-case safety scenario (i.e., inclusion of unconfirmed cases). The findings of the O/E analysis are also consistent with the known IS safety profile of the vaccine, i.e., the transient increased incidence of IS

after vaccination, mostly within 7 days of the first dose and, to a lesser extent, after the second dose.

As with all vaccines, immediate medical advice should be sought in case of any reaction or event following the vaccine administration. As indicated in the summary of product characteristics for HRV, it is advisable that vaccination should be preceded by a review of the medical history (especially with regard to the contraindications) and a clinical examination [19]. Since the outcomes of early management of IS are favourable compared with cases with delayed medical attention [69, 70], the HCP should inform the parents about the importance of seeking immediate medical advice in case they observe any unusual behaviour of the vaccinated infant. Given the evidence of a 7-day IS risk period

following RV vaccination, parents/guardians are advised to promptly report any symptom indicative of IS (severe abdominal pain, persistent vomiting, bloody stools, abdominal bloating, and/or high fever), allowing HCPs to promptly follow-up on these symptoms [19].

While prelicensure clinical studies assess the vaccine's safety profile, continued monitoring of the vaccine's real-world safety profile in the postlicensure setting is essential. One of the main sources of safety information is the worldwide routine postmarketing surveillance of AEs reported spontaneously. One of the strengths of the passive safety surveillance is the rapid collection of data following real-world use of the product in the general population, including individuals with concurrent illnesses, concomitant medications, and rare or less frequent events difficult to observe in prelicensure clinical trials. Limitations of postmarketing passive surveillance that relies on spontaneous reports include reporting bias (which can be due to country-specific reporting environment, influences of media, or length of time the product has been on the market), underreporting, missing information such as lack of denominator data, misclassification or incorrect information, and the absence of an adequate comparator group [71]. Such limitations may have hindered full assessment and medical review of the reported IS cases. Additionally, a reporting bias may have artificially skewed the reported data towards specific regions or patient groups.

While interpreting the O/E analysis, it should be reminded that this is a signal strengthening tool aiming to support signal evaluation, and that it is only one method among other data sources and quantitative methods available for pharmacovigilance. O/E analyses are not suited to perform specific hypothesis testing or to measure the strength of associations between AEs and vaccines. Furthermore, it needs to be considered that there are specific factors impacting this presented analysis, pertaining to (1) the estimation of the background rate; (2) the uncertainty on the distribution of the age at which children are vaccinated (dose 1, dose 2, and any dose); (3) estimation of the exposure based on sales data; (4) underreporting of cases for spontaneous reports; (5) lack of gender stratification in background incidence rates; (6) some background incidence rates based on a population that includes vaccinated children; (7) uncertainty on the proportion of the disease by month of the first year of life; and (8) CIs did not take all uncertainty into account (i.e., coverage, precision of background incidence rates and RF). In addition, multiplicity of tests was ignored. The limitation of the current approach based on sales figures has been recognised, and to what extent the use of alternative data sources may provide additional information on the actual number of infants exposed will be investigated. However, we can already anticipate some difficulties linked to the complexity of the approach. Actually, several elements should be taken into consideration, such as availability and heterogeneity of data sources (between and within countries), multiple national immunisation schedules, specific mass vaccination campaign, incidence of the disease, and catch-up and outbreak containment. As detailed in the Methodology section, a time lag of 2 months was chosen to minimise the risk of inaccuracy due to constant updates/corrections of the database and to consider the time lag between dose shipment and dose administration. However, despite these limitations, the spontaneous and the O/E data analyses provide reassurance of a favourable safety risk profile for HRV with respect to IS.

5 Conclusions

Despite the known inherent limitations of postmarketing passive surveillance that relies on spontaneous AE reports, the presented review based on postmarketing spontaneous data on IS retrieved from a database and reported over 15 years since the launch of HRV is consistent with the known IS safety profile of the HRV vaccine. The presented data have thus not altered GSK's position regarding the overall positive benefit–risk balance of HRV vaccination for infants. The findings of the O/E analysis are also consistent with the known IS safety profile of the vaccine, i.e., postmarketing safety studies indicate a transient increased incidence of IS after vaccination, mostly within 7 days of the first dose and, to a lesser extent, after the second dose. GSK continues to monitor the safety concern of IS following administration of HRV through its ongoing pharmacovigilance activities.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Trademark statements Rotarix is a trademark owned by the GSK group of companies; RotaTeq is a registered trademark of Merck & Co., Inc.; Rotavac is a registered trademark of Bharat Biotech; and Rotasiil is a registered trademark of the Serum Institute of India Ltd.

Availability of data and material The data that support the findings of this work are available from the corresponding author on reasonable request.

Code availability Not applicable.

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