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Post-marketing safety surveillance of the rotavirus vaccine in India

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ABSTRACT

Background: ROTASIIL, an oral live attenuated bovine-human reassortant pentavalent rotavirus vaccine, was approved in 2017. This post-marketing surveillance (PMS) was conducted to collect real-world data on the safety of ROTASIIL in India.

Methods: Observational, active PMS was conducted in approximately 10,000 infants aged ≥ 6 weeks. ROTASIIL was administered as a 3-dose regimen, at least 4 weeks apart, beginning at ≥ 6 weeks of age concomitantly with other Expanded Programme on Immunization (EPI) vaccines. Participants were followed for one month after the last dose. The adverse events (AEs) and serious adverse events (SAEs), including intussusception (IS) reported during the follow up period were collected.

Findings: A total of 9940 infants were enrolled and were considered for safety analysis. Around 9913 (99.7 %) infants received 2 doses, while 9893 (99.5 %) infants completed all three doses. Total 3693 AEs were reported in 2516 (25.3 %) participants. Most of these AEs were pyrexia (78.01 % of events) and injection-site reactions (19.14 % of events). Nearly all AEs were causally unrelated to orally administered ROTASIIL and could be caused by the concomitant injectable vaccines. Only 4 AEs (2 events of vomiting and 1 event each of discomfort and pyrexia) in 4 (<0.1 %) participants could be related to ROTASIIL. AEs were of mild or moderate severity and all resolved without any sequelae. A total of 2 SAEs (acute otitis media and skull fracture) were reported in 2 (<0.1 %) participants and were not related to ROTASIIL and recovered without sequelae. No case of IS was reported.

Interpretation: ROTASIIL was safe and well tolerated in this study. No safety concerns were reported.

Funding: The study was funded by SIIPL which is the manufacturer of the study product.

Introduction

Rotavirus is the most common etiologic agent causing diarrheal illness in infants and children worldwide, predominantly affecting infants from 6 to 24 months of age [1]. Children of low- and lower-middle income countries (LMICs) are at the highest risk of diarrheal-associated mortality. The Democratic Republic of Congo, Nigeria, Angola, India, and Pakistan together accounted for more than half of all rotavirus deaths worldwide before the introduction of a rotavirus vaccine [2]. In India, an estimated 78,000 rotavirus-associated deaths occur annually of which 59,000 occur in the first two years of life [3].

Three rotavirus vaccines, a pentavalent bovine-human reassortant (BRV-PV) vaccine (RotaTeq, Merck Inc.) and two monovalent vaccines (Rotarix™, GSK Biologicals and Rotavac, Bharat Biotech,) are available for use worldwide [4–7]. In some settings, post-marketing surveillance of some rotavirus vaccines has detected a small increased risk of IS (about 1–2/100,000 infants vaccinated) shortly after the first dose [8–11] though, the impact of vaccination on morbidity and mortality outweighs the risk of IS [12]. The first approved rotavirus vaccine in the world, Rotashield was withdrawn in 1999 after IS cases were reported from the market at a frequency of 1 per 2500–9500 vaccinees [13]. The Global Advisory Committee on Vaccine Safety (GACVS) affirms that the safety profile of current rotavirus vaccines is acceptable, with the benefits of vaccination greatly exceeding the risks [14].

In addition to the above three vaccines, ROTASIIL, an oral live attenuated bovine-human reassortant pentavalent rotavirus vaccine

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(BRV-PV, manufactured by Serum Institute of India Pvt. Ltd., SIIPL) was authorized in 2017 and was prequalified by the World Health Organization (WHO) in 2018. ROTASIIL is indicated for immunization of infants as a 3-dose series at 6, 10 and 14 weeks of age. Two Phase III clinical trials found that ROTASIIL was safe and efficacious [15–16]. ROTASIIL was also found immunogenic and did not interfere with the immune response of the Expanded Programme on Immunization (EPI) vaccines [17–18]. The data did not show any increased risk of intussusception (IS) within 21 days after any dose.

ROTASIIL was introduced under the Universal Immunization Program (UIP) in India in April 2018 [19].

This post marketing surveillance was planned to generate additional safety data on ROTASIIL in real-world settings.

Methods

This active, non-interventional, post-marketing surveillance (PMS) was conducted from December 2019 to March 2021 in healthy infants across 417 sites and 19 states in India. The objective was to generate additional data on the safety and to assess the incidence of related serious adverse events (SAEs) of ROTASIIL.

Ethical aspects

The study was conducted in compliance with the principles of the Declaration of Helsinki (2013) and 'Ethical Guidelines for Biomedical Research on Human Subjects' issued by the Indian Council of Medical Research, 2017. Written informed consent was provided by the parent(s) of the study participants before enrollment. The study was approved by the Indian regulatory authority and the institutional ethics committee of the Translational Health Science and Technology Institute, Faridabad (THSTI).

Study population

The PMS was conducted on approximately 10,000 healthy male or female infants aged $\geq$ 6 weeks. The medical history and clinical examination were assessed to ensure eligibility to receive ROTASIIL as per prescribing information.

Study procedure

At the selected healthcare facilities, the parents attending clinics for the routine EPI vaccinations of their infants were approached for their child's participation in the PMS. If the parents agreed to give consent, the infants were screened at $\geq$ 6 weeks of age. The infants visited the facility at 6, 10 and 14 -weeks of age when they were administered three doses of ROTASIIL along with other EPI vaccines.

The study site investigators and their clinical staff monitored the safety of all study participants. Each participant was followed for one month after the last dose of ROTASIIL. During routine scheduled visits, parents were enquired about the any adverse event experienced by the study participants since last visit and, if any, the same was recorded by the physicians. The parents were requested to report all AEs occurring during this period to the Investigator. If any AEs requiring medical attention were reported during the PMS, parents were asked to contact the investigator and appropriate medical care was provided by the Investigators.

All AEs were graded for severity by the study investigator as Grade 1 (discomfort noted, but no disruption of normal daily activities; slightly bothersome; relieved with or without symptomatic treatment), Grade2 (discomfort sufficient to reduce or affect normal daily activity to some degree; bothersome; interferes with activities, only partially relieved with symptomatic treatment) and Grade 3 (discomfort sufficient to reduce or affect normal daily activity considerably (prevents regular activities for at least 24 h); not relieved with symptomatic treatment, would cause parent/legal guardian to seek medical advice).

The causality assessment of AEs was done by the study investigator based on their clinical judgement, medical history and/or physical examination at reporting considering all relevant factors, including the pattern of reaction, temporal relationship, or re-challenge, biological plausibility, confounding factors such as concomitant medication, concomitant diseases and relevant history.

For reporting of SAEs, a separate SAE form was provided to the sites. For any SAE, a narrative was written in the electronic case report form (eCRF).

All potential IS episodes were to be investigated as per the guidelines from the Intussusception Brighton Collaboration Working Group (Version dated January 30, 2002). Definite IS episodes were those confirmed radiographically, surgically or by post-mortem examination.

Table 1
Participant Disposition.

	ROTASIIL [n (%)]
Number of Participants in Enrolled Population	9940
Number of Participants in Safety Population	9940
ROTASIIL Vaccination Dose	
Dose 1	9940 (100.0)
Dose 2	9913 (99.7)
Dose 3	9893 (99.5)
Mean Interval between ROTASIIL Vaccination Doses (in Weeks)	
Dose 1 and Dose 2	4.69
Dose 2 and Dose 3	4.72

Study products

ROTASIIL (manufactured by SIIPL) is a lyophilized formulation of live attenuated human-bovine reassortant pentavalent rotavirus vaccine (BRV-PV) based on the UK bovine rotavirus and five human rotavirus strains (G1, G2, G3, G4, and G9). It is supplied as a vial of freeze-dried vaccine to be reconstituted with a liquid diluent in a vial containing citrate bicarbonate buffer. The buffer is prepared using 9.6 mg /ml citric acid monohydrate and 25.6 mg/ml sodium bicarbonate. Each dose of 2.5 ml of reconstituted vaccine contains $\geq$ $Log10^{5.6}$ fluorescent focus units (FFU) / Serotype. The vaccine is reconstituted with the help of an adapter and a syringe just prior to oral administration.

A total of 39 commercially available batches approved by the Central Drugs Laboratory (CDL), Kasauli were used in this PMS.

Statistical analysis

With a sample size of 10,000, the study provided a 95 % probability to detect a product-related AE occurring at a frequency of 0.03 %. Demographic and baseline characteristics were summarized for the enrolled population. Standard descriptive statistics were presented for the continuous variables of Age (weeks), Body weight (kg) and Length (cm). The data of concomitant vaccines were also tabulated for each dose using percentages.

The descriptive analyses were conducted for safety parameters such as AEs and SAEs. The safety analysis included all participants who have received at least the first dose of ROTASIIL. The overall percentage of infants experiencing at least one AE reported up to four weeks after the third vaccination was tabulated for each dose using frequency and percentages along with 95 % CI. The missing data was treated as missing and no imputation was done.

Results

A total of 9940 participants were enrolled in the study and were a part of the safety population (Table 1) (Supplementary Figure 1). There were total 17 sites who enrolled $\geq$ 100 participants, 43 sites enrolled $\geq$

Table 2
Demographic and Baseline characteristics – Enrolled population.

	ROTASIIL (N = 9940)
Age (in Weeks)	
n	9940
Mean	7.46
SD	2.162
Sex [n (%)]	
Male	5317 (53.5)
Female	4623 (46.5)
Body Weight (in kg)	
n	9940
Mean	4.211
SD	0.8432
Length (in cm)	
n	9940
Mean	52.446
SD	4.8845

50 and < 100 participants, whereas 58 sites have enrolled < 10 participants. The overall mean age (SD) of the participants at the time of enrollment was 7.46 (2.162) weeks. Overall, more than half of the participants 5317 (53.5 %) were male. The mean body weight (SD) was 4.211 kg (20.937) and the mean length (SD) was 52.446 (4.885) cm (Table 2).

All 9940 (100 %) participants completed Dose 1 of ROTASIIL, 9913 (99.7 %) participants completed Dose 2 whereas 9893 (99.5 %) participants completed all three doses of ROTASIIL (Table 1). A total of 47 participants were lost to follow-up during the study, 27 after receiving the first dose, and 20 after the second dose (Supplementary Figure 1). The mean age (SD) at dose 1 was 7.59 (1.998) weeks, at dose 2 was 12.27 (1.998) weeks whereas, for dose 3 it was 16.99 (2.449) weeks. A mean gap of 4.69 weeks was observed between Dose 1 and Dose 2, while 4.72 weeks gap was observed between Dose 2 and Dose 3 of ROTASIIL (Table 1).

Concomitant vaccinations

Various concomitant vaccines were administered along with 3 doses of ROTASIIL as per the UIP/EPI schedule. The majority were Pneumococcal vaccine, Hexavalent (DTP-HB-Hib-IPV) / Pentavalent (DTP-HB-Hib) / Quadrivalent (DTP-Hib) vaccine, OPV/IPV, BCG, Hepatitis B and DPT vaccines. Table 3 summarizes details of concomitant vaccinations received by the participants.

Safety results

Overall 3693 AEs were reported in 2516 (25.3 %) participants. Out of these, 1556 (15.7 %) participants reported 1640 AEs after receiving the first dose of ROTASIIL, 872 (8.8 %) participants reported total 882 events after second dose, whereas, 1171 events in 1055 (10.7 %) participants after third dose of the vaccine (Table 4).

Out of these 3693 AEs, 3634 events were of General Disorders and administration site conditions reported in 2467 (24.8 %) participants. The majority of them were pyrexia (2881 events reported in 1957 participants, 78.01 % of events) and injection site reactions (707 events reported in 663 participants, 19.14 % of events) attributing to concomitant injectable vaccinations (Table 5). Almost all participants had received the concomitant injectable vaccines like Pneumococcal vaccine, Hexavalent (DTP-HB-Hib-IPV) / Pentavalent (DTP-HB-Hib) / Quadrivalent (DTP-Hib) vaccine, Hepatitis B, DPT vaccines, etc. (Table 3). A total of 40 gastrointestinal disorders were reported in 40 (0.4 %) participants, including 35 (0.4 %) events of diarrhea, 3 (<0.1 %) vomiting and 2 (<0.1 %) abdominal pain (Table 5).

Most AEs were of grade 1 severity and recovered without sequelae. Only 4 AEs in 4 (<0.1 %) (95 % CI: 0.00, 0.08) participants were considered as related to ROTASIIL, which included 2 events of vomiting and one event each of discomfort and pyrexia. Three of these AEs were after the first dose whereas, one was after the second dose of ROTASIIL. All these related AEs occurred within 48 hours of vaccination, were also of grade 1 severity and recovered without sequalae.

Table 3
Concomitant Vaccinations.

Concomitant Vaccination	ROTASIIL Dose 1 (N = 9940)			ROTASIIL Dose 2 (N = 9913)			ROTASIIL Dose 3 (N = 9893)			Overall (N = 9940)		
	n	(%)	C	n	(%)	C	n	(%)	C	n	(%)	C
OPV	997	(10.0)	997	833	(8.4)	833	842	(8.5)	842	1010	(10.2)	2672
IPV	87	(0.9)	87	68	(0.7)	68	66	(0.7)	66	93	(0.9)	221
BCG	2	(<0.1)	2	0			0			2	(<0.1)	2
DPT	6	(<0.1)	6	4	(<0.1)	4	6	(<0.1)	6	8	(<0.1)	16
Pentavalent Vaccine	3477	(35.0)	3477	3236	(32.6)	3236	3181	(32.2)	3181	3518	(35.4)	9894
Hepatitis B	1	(<0.1)	1	0			1	(<0.1)	1	2	(<0.1)	2
Pneumococcal	6309	(63.5)	6309	6128	(61.8)	6129	6114	(61.8)	6114	6392	(64.3)	18,552
Hexavalent	4061	(40.9)	4061	4037	(40.7)	4037	4016	(40.6)	4016	4097	(41.2)	12,114
Qudravalent vaccine	0			11	(0.1)	11	43	(0.4)	43	46	(0.5)	54
Others	592	(6.0)	602	560	(5.6)	570	553	(5.6)	563	623	(6.3)	1735

n: Number of participants who received any concomitant vaccination; C: Number of concomitant vaccinations.

Table 4
Overall summary of Adverse Events.

	ROTASIIL Dose 1 (N = 9940)				ROTASIIL Dose 2 (N = 9913)				ROTASIIL Dose 3 (N = 9893)				Overall (N = 9940)			
	n	%	(95 % CI)	E	n	%	(95 % CI)	E	n	%	(95 % CI)	E	n	%	(95 % CI)	E
Any AE	1556	15.7	(14.94, 16.36)	1640	872	8.8	(8.23, 9.35)	882	1055	10.7	(10.05, 11.27)	1171	2516	25.3	(24.45, 26.16)	3693
Related AEs	3	<0.1	(−0.00, 0.06)	3	1	<0.1	(−0.01, 0.03)	1	0				4	<0.1	(0.00, 0.08)	4
SAEs	2	<0.1	(−0.00, 0.04)	2	0				0				2	<0.1	(−0.00, 0.04)	2

n: Number of participants with any event; E: Number of events.

Table 5
Adverse Events by System Organ Class (SOC) and Preferred Term (PT).

System Organ Class (SOC)Preferred Term (PT)	ROTASIIL Dose 1(N = 9940)				ROTASIIL Dose 2(N = 9913)				ROTASIIL Dose 3(N = 9893)				Overall*(N = 9940)			
	n	%	(95 % CI)	E	n	%	(95 % CI)	E	n	%	(95 % CI)	E	n	%	(95 % CI)	E
Participants with at least one AE	1556	15.7	(14.94, 16.36)	1640	872	8.8	(8.23, 9.35)	882	1055	10.7	(10.05, 11.27)	1171	2516	25.3	(24.45, 26.16)	3693
Gastrointestinal disorders	11	0.1	(0.04, 0.17)	11	25	0.3	(0.15, 0.35)	25	4	<0.1	(0.00, 0.08)	4	40	0.4	(0.27, 0.52)	40
Diarrhoea	8	<0.1	(0.02, 0.13)	8	24	0.2	(0.14, 0.33)	24	3	<0.1	(−0.00, 0.06)	3	35	0.4	(0.23, 0.46)	35
Vomiting	1	<0.1	(−0.01, 0.03)	1	1	<0.1	(−0.01, 0.03)	1	1	<0.1	(−0.01, 0.03)	1	3	<0.1	(−0.00, 0.06)	3
Abdominal pain	2	<0.1	(−0.00, 0.04)	2	0				0				2	<0.1	(−0.00, 0.04)	2
General disorders and administration site conditions	1539	15.5	(14.77, 16.19)	1616	843	8.5	(7.95, 9.05)	853	1050	10.6	(10.00, 11.22)	1165	2467	24.8	(23.97, 25.66)	3634
Pyrexia	1337	13.5	(12.78, 14.12)	1338	734	7.4	(6.88, 7.92)	734	808	8.2	(7.62, 8.70)	809	1957	19.7	(18.90, 20.47)	2881
Injection site pain	178	1.8	(1.53, 2.05)	178	77	0.8	(0.60, 0.95)	77	278	2.8	(2.48, 3.13)	278	498	5.0	(4.58, 5.43)	533
Injection site erythema	10	0.1	(0.03, 0.16)	10	13	0.1	(0.06, 0.20)	13	64	0.6	(0.48, 0.80)	64	87	0.9	(0.69, 1.05)	87
Injection site swelling	48	0.5	(0.34, 0.61)	48	14	0.1	(0.06, 0.21)	14	7	<0.1	(0.01, 0.12)	7	60	0.6	(0.45, 0.75)	69
Generalised oedema	22	0.2	(0.12, 0.31)	22	0				0				22	0.2	(0.12, 0.31)	22
Injection site nodule	7	<0.1	(0.01, 0.12)	7	6	<0.1	(0.01, 0.10)	6	2	<0.1	(−0.00, 0.04)	2	15	0.2	(0.07, 0.22)	15
Pain	5	<0.1	(0.00, 0.09)	5	8	<0.1	(0.02, 0.13)	8	1	<0.1	(−0.01, 0.03)	1	14	0.1	(0.06, 0.21)	14
Discomfort	3	<0.1	(−0.00, 0.06)	3	0				2	<0.1	(−0.00, 0.04)	2	5	<0.1	(0.00, 0.09)	5
Swelling	2	<0.1	(−0.00, 0.04)	2	1	<0.1	(−0.01, 0.03)	1	2	<0.1	(−0.00, 0.04)	2	4	<0.1	(0.00, 0.08)	5
Injection site inflammation	2	<0.1	(−0.00, 0.04)	2	0				0				2	<0.1	(−0.00, 0.04)	2
Injection site rash	1	<0.1	(−0.01, 0.03)	1	0				0				1	<0.1	(−0.01, 0.03)	1
Infections and infestations	4	<0.1	(0.00, 0.08)	4	0				0				4	<0.1	(0.00, 0.08)	4
Otitis externa	1	<0.1	(−0.01, 0.03)	1	0				0				1	<0.1	(−0.01, 0.03)	1
Otitis media acute	1	<0.1	(−0.01, 0.03)	1	0				0				1	<0.1	(−0.01, 0.03)	1

n: Number of participants with any event; E: Number of events.

Two SAEs (acute otitis media and skull fracture) were reported in 2 (<0.1 %) participants. Both SAEs were of grade 3 severity and were not related to ROTASIIL.

No case of potential IS was reported in the study.

Discussion

Active surveillance in around 10,000 healthy infants across India showed that ROTASIIL was well tolerated. No safety concerns were reported in the study.

Safety data were contributed by 9940 infants. A total of 29,746 doses of ROTASIIL were administered during this surveillance. To our knowledge, this is the largest PMS data for any rotavirus vaccine in India representing different demographic, sociocultural, and climatic conditions to collect real-world evidence regarding the safety of the vaccine.

Almost all the AEs were causally unrelated to ROTASIIL. The majority of the AEs were pyrexia (78.01 % of events) and injection-site reactions (19.14 % of events) related to concomitant injectable vaccinations. The results in this PMS are in line with the data from the pre-licensure studies [15–18]. In the Phase III study in India [15], the incidence of solicited AEs including diarrhea in ROTASIIL and placebo arms was similar. The Phase 3 study in Niger [16] also showed that the incidence of AEs was similar in vaccine and placebo arms, indicating that these events were actually caused by the concomitant vaccines. A recent Phase 4 study in India also showed a similar pattern [20]. Here 1320 infants received at least one dose of ROTASIIL. No vaccine-related SAEs were reported.

All the AEs recovered without any sequelae within 4 days. No case of IS was reported. Although with other rotavirus vaccines, a small increased risk of IS after the first dose was reported [8–11], our study did not report any such risk. However, this study was not powered to detect IS risk after vaccination.

The etiology of IS is most commonly idiopathic. However, several infectious pathogens are also reported to be associated with IS. Infections can cause lymphadenopathy which serve as the lead point for IS. In India, the background incidence of IS varies from 17.7 (Delhi, North India) [21] to 254 (Vellore, South India) [22] cases per 100,000 child-years. As per a literature review [23] IS is a very rare condition in most regions of the world, particularly among infants,3–4 months of age and its peak incidence is among those 4–7 months of age (97–126 per 100,000). The age of our study population was 6 weeks to 18 weeks and may explain the lack of cases. Generally, the parents follow with the same doctor for all the health-related issues of their children. Though it is possible that they may go to another doctor for other ailments but they will generally inform the same to their usual doctor. Hence it is unlikely that the AEs including IS cases were missed during the study.

The strengths of our study include a large sample size as well as the real-world setting. All administered vaccines were from marketed lots, and thus reflect the experience of the general population.

The sample size is not adequate to detect extremely rare events, particularly IS, which has been shown to be associated with rotavirus vaccination [8–11]. However, these results are in line with the overall clinical experience with this vaccine from the clinical trials as well as the post-marketing experience and therefore give confidence about the validity of the results.

As per the package insert, the doses of ROTASIIL are administered at 6, 10 and 14 weeks of age, but there was a small delay for many of the participants. The delay could be due to the Covid-19 pandemic situation. It is known that in any such pandemic situation routine immunizations are affected. In April 2020, the health management and information system data reported a decrease in the number of routine immunization sessions relative to the previous year. The number of fully immunized children also decreased over the same period [24]. Notably, our PMS was ongoing during the same period. Moreover, since the lockdown in the country was very strict, vaccinees could not visit the hospitals in time.

SIIPL also developed a liquid formulation of ROTASIIL referred to as the ROTASIIL-Liquid as a ready to use option of the same vaccine. The vaccine contains the same rotavirus strains at the same titer. These PMS data should also hold for ROTASIIL-Liquid, which has been evaluated in a Phase I study in adults [25] and in a Phase II/III study in 1500 infants in India [26], and subsequently approved in 2019 and also prequalified by WHO in 2021.

To conclude, the PMS demonstrated that ROTASIIL is safe and well tolerated. No safety concerns or IS cases were reported during this PMS.

Contributors.

Chetanraj Bhamare, Sajjad Desai, Bhagwat Gunale and Prasad S. Kulkarni Contributed to the study design and protocol development. Anand Lakhkar, Chetanraj Bhamare, Abhijeet Dharmadhikari, Jyoti Narwadkar and Arti Kanujia accessed and verified the data. Anand Lakhkar, Chetanraj Bhamare, Abhijeet Dharmadhikari, Jyoti Narwadkar, Sajjad Desai, Bhagwat Gunale, and Prasad S. Kulkarni contributed to the manuscript preparation. The manuscript was finalized with considerable input from all the authors.

Declaration of Competing Interest

Anand Lakhkar, Chetanraj Bhamare, Abhijeet Dharmadhikari, Jyoti Narwadkar, Sajjad Desai, Bhagwat Gunale and Prasad S. Kulkarni are employees of SIIPL. Cyrus S. Poonawalla is the chairman and managing director of SIIPL. The principal investigator, Gagandeep Kang served in an honorary capacity and received no payments for the study. All other authors declare no competing interests.

Data availability

The data that has been used is confidential.

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Role of funding source

The study was funded by SIIPL. The funder of the study was involved in study design, data interpretation, and writing of the report, but was not involved in data collection and data analysis.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvacx.2023.100362.

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