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Supplementary appendix 2

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Kanungo S, Chatterjee P, Bavdekar A, et al. Safety and immunogenicity of the Rotavac and Rotasiil rotavirus vaccines administered in an interchangeable dosing schedule among healthy Indian infants: a multicentre, open-label, randomised, controlled, phase 4, non-inferiority trial. *Lancet Infect Dis* 2022; published online May 16. https://doi.org/10.1016/S1473-3099(22)00161-X.

Supplementary table 1 Baseline characteristics of study participants by vaccine arms

		Single rotavirus vaccine regimen		Mixed rotavirus vaccine regimen			
		Arm 1: Rotavac - Rotavac - Rotavac (n=329)	Arm 2: Rotasiil - Rotasiil - Rotasiil (n=330)	Arm 3: Rotavac - Rotasiil - Rotavac (n=329)	Arm 4: Rotasiil - Rotavac - Rotasiil (n=329)	Arm 5: Rotavac - Rotasiil - Rotasiil (n=331)	Arm 6: Rotasiil - Rotavac - Rotavac (n=331)
Sex	Male n (%)	162 (49.2)	164 (49.7)	155 (47.1)	178 (54.1)	180 (54.4)	157 (47.4)
	Female n (%)	167 (50.8)	166 (50.3)	174 (52.9)	151 (45.9)	151 (45.6)	174 (52.6)
Age (days)	Mean (SD)	47.6 (4.0)	47.3 (4.0)	46.8 (3.7)	47.4 (4.0)	47.2 (4.1)	47.4 (4.0)
Weight (kgs)	Mean (SD)	4.2 (0.6)	4.3 (0.6)	4.2 (0.6)	4.2 (0.6)	4.2 (0.6)	4.2 (0.6)
Height (cms)	Mean (SD)	54.3 (2.4)	54.2 (2.4)	54.1 (2.4)	54.1 (2.5)	54.2 (2.5)	54.1 (2.2)

Supplementary table 2 Sero-response rate by vaccine arms

		Single rotavirus vaccine regimen		Mixed rotavirus vaccine regimen			
Sero-response*		Arm 1: Rotavac - Rotavac - Rotavac	Arm 2: Rotasiil - Rotasiil - Rotasiil	Arm 3: Rotavac - Rotasiil - Rotavac	Arm 4: Rotasiil - Rotavac - Rotasiil	Arm 5: Rotavac - Rotasiil - Rotasiil	Arm 6: Rotasiil - Rotavac - Rotavac
Number of participants		303	298	315	302	314	307
Number with sero-response		73	105	108	97	120	90
Sero response rate (95% CI)		24.1% (19.5, 29.1)	35.2% (30.0, 40.8)	34.3% (29.2, 39.7)	32.1% (27.0, 37.5)	38.2% (33.0, 43.7)	29.3% (24.4, 34.6)
With four fold raise in IgA antibodies compared to baseline titre of ≥ 20	n	6	12	6	10	6	6
	% (95% CI)	2.0% (0.8, 4.0)	4.0% (2.2, 6.7)	1.9% (0.8, 3.9)	3.3% (1.7, 5.8)	1.9% (0.8, 3.9)	2.0% (0.8, 4.0)
With IgA antibody titre of ≥ 20 compared to titre < 20 at baseline	n	67	93	102	87	114	84
	% (95% CI)	22.1% (17.7, 27.0)	31.2% (26.1, 36.6)	32.4% (27.4, 37.7)	28.8% (23.9, 34.1)	36.3% (31.1, 41.7)	27.4% (22.6, 32.5)

** Sero response was defined as four-fold raise in IgA antibody titres after third dose when baseline titre was ≥ 20 IU/mL OR IgA antibody titre of ≥ 20 IU/mL after third dose when baseline titre was < 20 IU/mL*

Supplementary table 3 Geometric mean titres (GMT) of IgA antibodies by vaccine arms

Visit		Single rotavirus vaccine regimen			Mixed rotavirus vaccine regimen				
		Arm 1: Rotavac – Rotavac – Rotavac	Arm 2: Rotasiil – Rotasiil – Rotasiil	Arms 1 and 2	Arm 3: Rotavac – Rotasiil – Rotavac	Arm 4: Rotasiil – Rotavac – Rotasiil	Arm 5: Rotavac – Rotasiil – Rotasiil	Arm 6: Rotasiil – Rotavac – Rotavac	Arms 3-6
Baseline: Prior to Dose 1	Number of participants for whom Results are available (n)	303	298	601	315	302	314	307	1238
	GMT (IU/mL)	3.94	3.41	3.67	3.64	3.88	3.41	3.75	3.66
	95% CI	(3.31, 4.66)	(2.83, 4.07)	(3.23, 4.15)	(3.07, 4.29)	(3.28, 4.57)	(2.88, 4.00)	(3.17, 4.41)	(3.37, 3.98)
Day 28 (+/- 7 Days) Post Dose 3	Number of participants for whom Results are available (n)	303	298	601	315	302	314	307	1238
	GMT (IU/mL)	12.31	15.74	13.91	16.15	18.57	18.47	14.00	16.69
	95% CI	(10.24, 14.77)	(12.90, 19.16)	(12.15, 14.77)	(13.48, 19.32)	(15.42, 22.33)	(15.42, 22.09)	(11.75, 16.65)	(15.25, 18.26)
Day 28 (+/- 7 Days) Post Dose 3	Number of participants who sero responded (n)	73	105	178	108	97	120	90	415
	GMT (IU/mL)	72.73	78.75	76.22	71.15	94.71	81.37	69.86	78.77
	95% CI	(55.74, 94.81)	(63.49, 97.62)	(64.50, 90.05)	(58.43, 86.59)	(74.92, 119.64)	(68.12, 97.16)	(57.53, 84.79)	(71.25, 87.09)

Supplementary table 4 Distribution of solicited and unsolicited adverse events within seven days post vaccination (all three doses combined) by vaccine arms

		Single rotavirus vaccine regimen		Mixed rotavirus vaccine regimen			
AE events		Arm 1: Rotavac - Rotavac - Rotavac (n=329)	Arm 2: Rotasiil - Rotasiil - Rotasiil (n=330)	Arm 3: Rotavac - Rotasiil - Rotavac (n=329)	Arm 4: Rotasiil - Rotavac -Rotasiil (n=329)	Arm 5: Rotavac - Rotasiil - Rotasiil (n=331)	Arm 6: Rotasiil - Rotavac - Rotavac (n=331)
Any Solicited AE	n (%), E	295 (89.7%), 1634	304 (92.1%), 1658	303 (92.1%), 1702	309 (93.9%), 1749	295 (89.1%), 1642	296 (89.4%), 1625
	95% CI	(85.6, 92.7)	(88.7, 94.8)	(88.6, 94.8)	(90.8, 96.2)	(85.3, 92.3)	(85.6, 92.5)
Diarrhoea	n (%), E	32 (9.7%), 36	33 (10.0%), 37	28 (8.5%), 30	32 (9.7%), 38	27 (8.2%), 28	22 (6.6%), 22
	95% CI	(6.7, 13.5)	(7.0, 13.8)	(5.7, 12.1)	(6.7, 13.5)	(5.4, 11.6)	(4.2, 9.9)
Vomiting	n (%), E	33 (10.0%), 41	44 (13.3%), 50	40 (12.2%), 53	38 (11.6%), 46	43 (13.0%), 48	40 (12.1%), 51
	95% CI	(7.0, 13.8)	(9.9, 17.5)	(8.8, 16.2)	(8.3, 15.5)	(9.6, 17.1)	(8.8, 16.1)
Fever	n (%), E	282 (85.7%), 588	289 (87.6%), 619	291 (88.4%), 618	295 (89.7%), 628	282 (85.2%), 579	277 (83.7%), 574
	95% CI	(81.5, 89.3)	(83.5, 90.9)	(84.5, 91.7)	(85.9, 92.7)	(80.9, 88.8)	(79.3, 87.5)
Decreased appetite	n (%), E	146 (44.4%), 238	141 (42.7%), 237	132 (40.1%), 230	156 (47.4%), 263	151 (45.6%), 249	145 (43.8%), 251
	95% CI	(38.9, 49.9)	(37.3, 48.3)	(34.8, 45.6)	(41.9, 53.0)	(40.2, 51.2)	(38.4, 49.3)
Decreased activity level	n (%), E	141 (42.9%), 235	132 (40.0%), 218	139 (42.2%), 238	145 (44.1%), 242	143 (43.2%), 245	130 (39.3%), 233
	95% CI	(37.4, 48.4)	(34.7, 45.5)	(36.9, 47.8)	(38.6, 49.6)	(37.8, 48.7)	(34.0, 44.8)
Irritability	n (%), E	251 (76.3%), 471	249 (75.5%), 465	249 (75.7%), 497	258 (78.4%), 499	240 (72.5%), 465	243 (73.4%), 471
	95% CI	(71.3, 80.8)	(70.4, 80.0)	(70.7, 80.2)	(73.6, 82.7)	(67.4, 77.2)	(68.3, 78.1)
Any Unsolicited AE	n (%), E	117 (35.6%), 217	133 (40.3%), 285	125 (38.0%), 266	132 (40.1%), 255	130 (39.3%), 237	124 (37.5%), 274
	95% CI	(30.4, 41.0)	(35.0, 45.8)	(32.7, 43.5)	(34.8, 45.6)	(34.0, 44.8)	(32.2, 42.9)

n (%): No. of participants (percentage), E: number of events

Supplementary table 5 Severity of solicited and unsolicited adverse events within seven days post vaccination (all three doses combined) by vaccine arms

	Single rotavirus vaccine regimen		Mixed rotavirus vaccine regimen			
Severity	Arm 1: Rotavac - Rotavac – Rotavac (No. of adverse events = 1851) n (%)	Arm 2: Rotasiil - Rotasiil – Rotasiil (No. of adverse events = 1943) n (%)	Arm 3: Rotavac - Rotasiil – Rotavac (No. of adverse events = 1968) n (%)	Arm 4: Rotasiil - Rotavac - Rotasiil (No. of adverse events = 2004) n (%)	Arm 5: Rotavac - Rotasiil – Rotasiil (No. of adverse events = 1879) n (%)	Arm 6: Rotasiil - Rotavac – Rotavac (No. of adverse events = 1899) n (%)
Mild n (%)	1595 (86.2)	1673 (86.1)	1689 (85.8)	1743 (87.0)	1634 (87.0)	1600 (84.3)
Moderate n (%)	252 (13.6)	265 (13.6)	273 (13.9)	256 (12.8)	237 (12.6)	295 (15.5)
Severe n (%)	3 (0.2)	5 (0.3)	6 (0.3)	5 (0.2)	8 (0.4)	4 (0.2)
Life threatening n (%)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 0.0 ()

Supplementary table 6 Serious adverse events (SAE) among study participants by vaccine arms

		Single rotavirus vaccine regimen		Mixed rotavirus vaccine regimen			
SAE Details		Arm 1: Rotavac - Rotavac - Rotavac (n=329)	Arm 2: Rotasiil - Rotasiil - Rotasiil (n=330)	Arm 3: Rotavac -Rotasiil - Rotavac (n=329)	Arm 4: Rotasiil -Rotavac - Rotasiil (n=329)	Arm 5: Rotavac -Rotasiil - Rotasiil (n=331)	Arm 6: Rotasiil - Rotavac - Rotavac (n=331)
At least one SAE	n (%), E	9 (2.7%), 9	5 (1.5%), 5	5 (1.5%), 5	3 (0.9%), 3	5 (1.5%), 5	8 (2.4%), 8
	95% CI	(1.3, 5.1)	(0.5, 3.5)	(0.5, 3.5)	(0.2, 2.6)	(0.5, 3.5)	(1.0, 4.7)
Any Severity	n (%), E	9 (2.7%), 9	5 (1.5%), 5	5 (1.5%), 5	3 (0.9%), 3	5 (1.5%), 5	8 (2.4%), 8
	95% CI	(1.3, 5.1)	(0.5, 3.5)	(0.5, 3.5)	(0.2, 2.6)	(0.5, 3.5)	(1.0, 4.7)
Life-Threatening	n (%), E	1 (0.3%), 1	0 (0.0%), 0	0 (0.0%), 0	0 (0.0%), 0	0 (0.0%), 0	0 (0.0%), 0
	95% CI	(0.0, 1.7)	(0.0, 0.9)	(0.0, 0.9)	(0.0, 0.9)	(0.0, 0.9)	(0.0, 0.9)
Severe	n (%), E	7 (2.1%), 7	5 (1.5%), 5	5 (1.5%), 5	3 (0.9%), 3	5 (1.5%), 5	7 (2.1%), 7
	95% CI	(0.9, 4.3)	(0.5, 3.5)	(0.5, 3.5)	(0.2, 2.6)	(0.5, 3.5)	(0.9, 4.3)
Moderate	n (%), E	1 (0.3%), 1	0 (0.0%), 0	0 (0.0%), 0	0 (0.0%), 0	0 (0.0%), 0	1 (0.3%), 1
	95% CI	(0.0, 1.7)	(0.0, 0.9)	(0.0, 0.9)	(0.0, 0.9)	(0.0, 0.9)	(0.0, 1.7)
Mild	n (%), E	0 (0.0%), 0	0 (0.0%), 0	0 (0.0%), 0	0 (0.0%), 0	0 (0.0%), 0	0 (0.0%), 0
	95% CI	(0.0, 0.9)	(0.0, 0.9)	(0.0, 0.9)	(0.0, 0.9)	(0.0, 0.9)	(0.0, 0.9)
At least one related SAE	n (%), E	1 (0.3%), 1	0 (0.0%), 0	0 (0.0%), 0	0 (0.0%), 0	0 (0.0%), 0	0 (0.0%), 0
	95% CI	(0.0, 1.7)	(0.0, 0.9)	(0.0, 0.9)	(0.0, 0.9)	(0.0, 0.9)	(0.0, 0.9)
At least one SAE resulting in death	n (%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	95% CI	(0.0, 1.7)	(0.0, 0.9)	(0.0, 0.9)	(0.0, 0.9)	(0.0, 0.9)	(0.0, 0.9)
At least one SAE resulting in hospitalization	n (%), E	8 (2.4%), 8	5 (1.5%), 5	5 (1.5%), 5	3 (0.9%), 3	5 (1.5%), 5	8 (2.4%), 8
	95% CI	(1.1, 4.7)	(0.5, 3.5)	(0.5, 3.5)	(0.2, 2.6)	(0.5, 3.5)	(1.1, 4.7)
At Least one SAE leading to Subject Discontinuation	n (%), E	0 (0.0%), 0	0 (0.0%), 0	0 (0.0%), 0	0 (0.0%), 0	0 (0.0%), 0	0 (0.0%), 0
	95% CI	(0.0, 0.9)	(0.0, 0.9)	(0.0, 0.9)	(0.0, 0.9)	(0.0, 0.9)	(0.0, 0.9)

n (%), E: No. of participants (percentage), No. of events

Supplementary Table 7. Causes of early termination

Reasons	Frequency (%)
Migrated away from the study area	40 (31.5%)
Parent withdrew consent	35 (27.6%)
Child presented after window period allowed by protocol	25 (19.7%)
Child received rotavirus vaccine from a different facility	10 (7.9%)
Investigator discretion	5 (3.9%)
Death or illness in family	4 (3.1%)
Lost to follow-up	4 (3.1%)
Illness of child	3 (2.4%)
Death	1 (0.8%)
Total	127

Supplementary Table 8. National Immunization Schedule of India (for infants). Rotavirus was included in the schedule while the trial was ongoing.

Vaccine	**When to give**	**Dose**	**Route**	**Site**
BCG	At birth or as early as possible till one year of age	0.1ml (0.05ml until 1 month of age)	Intra-dermal	Left Upper Arm
Hepatitis B Birth dose	At birth or as early as possible within 24 hours	0.5 ml	Intramuscular	Anterolateral side of mid thigh-LEFT
OPV Birth dose	At birth or as early as possible within the first 15 days	2 drops	Oral	-
OPV 1, 2 & 3	At 6 weeks, 10 weeks & 14 weeks	2 drops	Oral	-
IPV (inactivated Polio Vaccine)	14 weeks	0.5 ml	Intramuscular	Anterolateral side of mid thigh-RIGHT
Pentavalent vaccine (DPT, HBV, HiB) 1,2 & 3	At 6 weeks, 10 weeks & 14 weeks	0.5 ml	Intramuscular	Anterolateral side of mid thigh-LEFT
Rota Virus Vaccine	At 6 weeks, 10 weeks & 14 weeks	5 drops	Oral	-
Measles 1st Dose	9 completed months-12 months. (give up to 5 years if not received at 9-12 months age)	0.5 ml	Subcutaneous	Right Upper Arm
Vitamin A, 1st Dose	At 9 months with measles	1 ml (100,000 IU)	Oral	-