FOURTEENTH INTERNATIONAL

ROTAVIRUS SYMPOSIUM

MARCH 14–16 **2023** BALI INDONESIA

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Interchangeable vaccine dosage algorithm for available Rotavirus vaccine products in India: A pragmatic alternative strategy to single vaccine product regimen

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14th International Rotavirus Symposium

Rotavirus

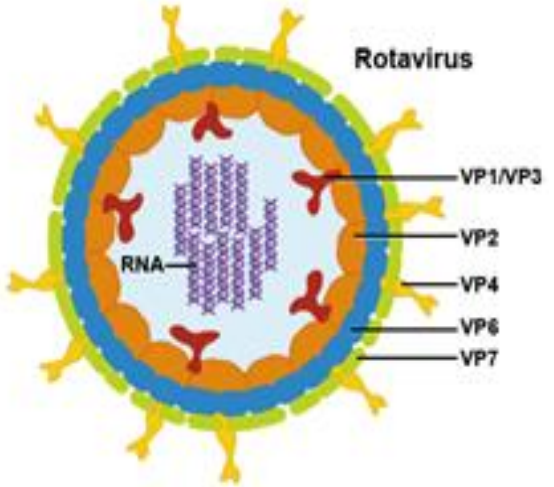
- Most common cause of severe diarrhoea among infants and young children.
- Genus of double-stranded RNA virus.
  - Nearly every child in the world has been infected with rotavirus at least once by the age of five.
- Immunity develops with each infection, so subsequent infections are less severe
  - Adults are rarely affected.
- 5 species
  - A, B, C, D, and E.
- Rotavirus A, the most common species causing more than 90% of infections among humans.

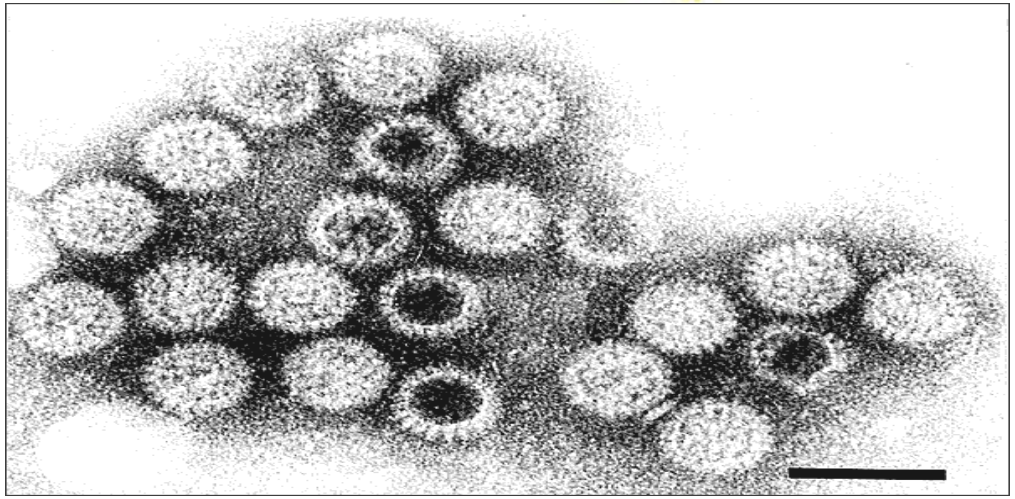
Responsible for up to 500,000 diarrheal deaths each year worldwide

Family: Reoviridae,

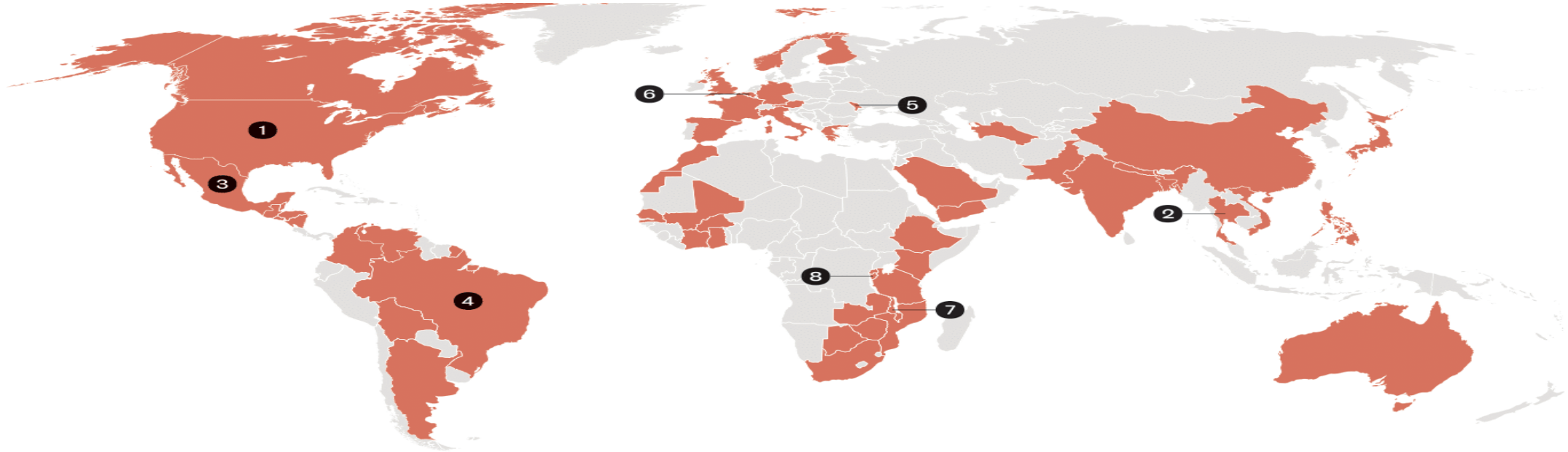
Double stranded,

Eleven segments of RNA





Global Impact of Rotavirus vaccination: Evidence as of May, 2020



1) U.S.[2-5]

The lab diagnosis of rotavirus declined 58–90% since rotavirus vaccines were introduced in 2006.

2) Thailand[6]

In a pilot introduction of rotavirus vaccine in one province, hospitalizations from rotavirus declined 88% over 2 years.

3) Mexico[7]

Deaths due to diarrhea in <5s fell 53% on average in post-vaccination years, preventing nearly 1,000 deaths/year.

4) Brazil[8]

Diarrheal deaths in children <5 were cut by more than half (55%) following vaccine introduction.

5) Moldova[9]

Rotavirus hospitalizations in two national hospitals fell 73% in infants by the second year following vaccine introduction.

6) Belgium[10]

A study of 12 hospitals found an 80% decline in the percent of hospitalized diarrhea due to rotavirus in children 2–24 months of age by the second year following vaccine introduction.

7) Malawi[11]

In Malawi, impact against diarrhea-associated mortality in infants was 31%.

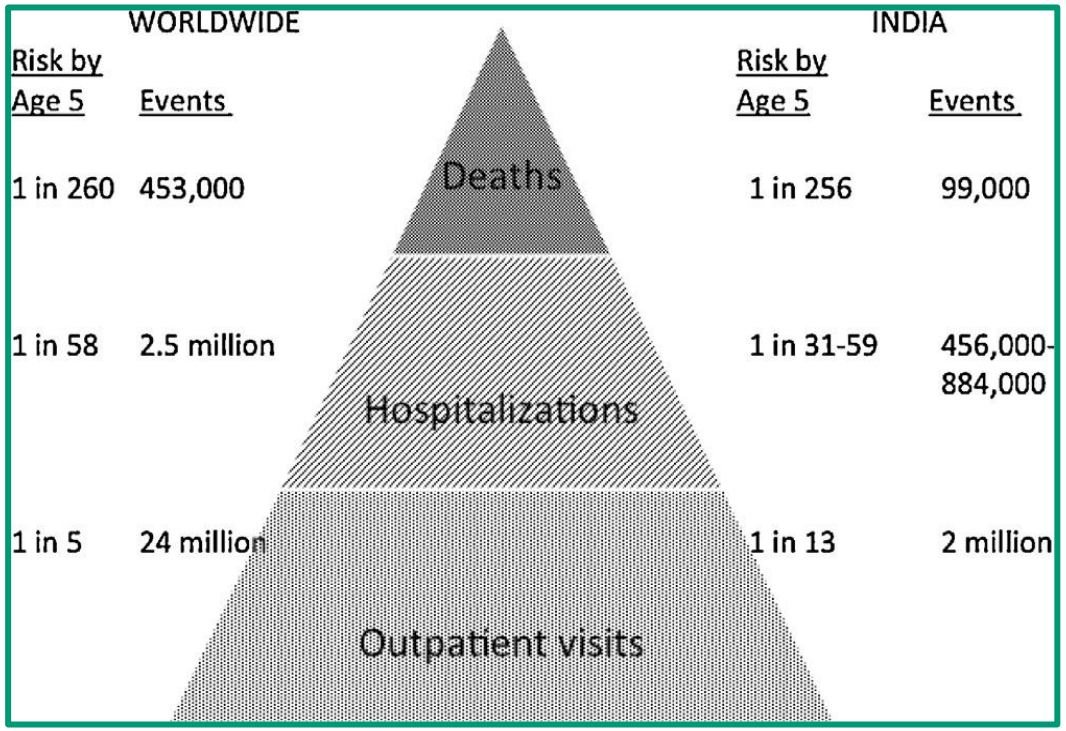
8) Rwanda[12]

With 99% vaccination coverage, hospital admissions due to rotavirus fell by 61–70% in <5s in two years post vaccine introduction.

Countries with ≥ 1 rotavirus vaccine impact study

Rotaviral disease burden – Worldwide vs. India (Pre -vaccine rollout)

- 2016 → Diarrhea was fifth major cause of global deaths among < 5 aged children. Among these, Rotavirus accounted for the highest number of diarrhoea-induced deaths.
- Burden in India in pre-vaccine rollout period
- Financial Burden → Average hospitalization cost/episode of Rotavirus diarrhoea → 3000 INR (36.3 $) → 7.6% of an average Indian family's total annual income.
- Rotavirus hospitalizations cost about US$ 73 million each year, while outpatient treatments cost about US$ 80 million in India.



Currently available WHO prequalified Rotavirus Vaccines

ROTARIX®

49–77% efficacy* In LMICs (Madhi et al. 2010)

- Monovalent, human, live attenuated vaccine. (G1P strain)
- Administered as a 2-dose series.

(GlaxoSmithKline Biologics)

RotaTeq®

43–64% protective* in LMICs (Zaman et al. 2010)

- Live, oral, & Made up of five human-bovine reassortant strains of rotavirus
- Three-dose schedule

(Merck & Co., Inc.)

ROTAVAC®

54% in 1st & 49% in 2nd year (Bhandari et al. 2014)

- Live, oral, attenuated Monovalent: Human-bovine natural re-assortant vaccine(116E)
- same dosing schedule as DTP1, 2, and 3.

(Bharat Biotech)

ROTASIIL®

36% in 1st , 49% in 2nd Year in India (Kulkarni et al. 2017) & 67% in Niger study

- Heat stable, live, oral, attenuated
- Pentavalent: G1, G2, G3, G4 & G9
- same dosing schedule as DTP1, 2, and 3.

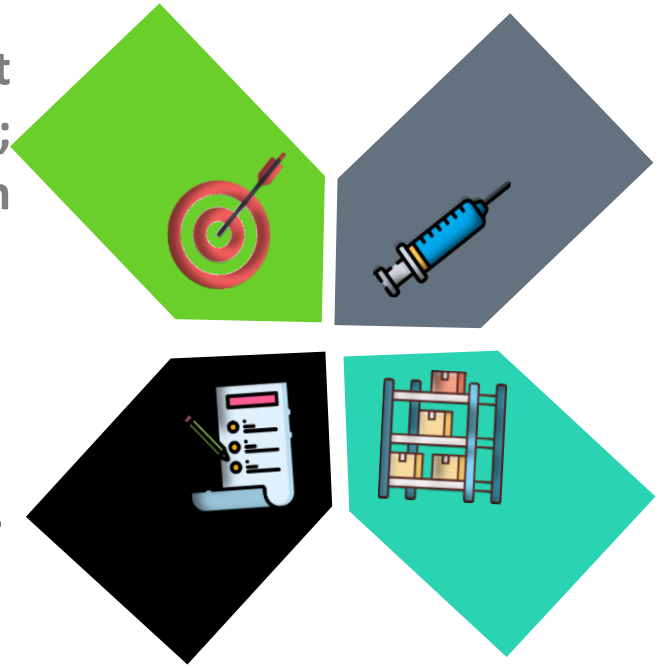
(Serum Institute of India)

***efficacy & protection is against severe rotavirus gastroenteritis**

Universal Immunization Programme (UIP): India

One of the largest Public Health Programmes

Annual target
~26.7 Million infants;
~29.1 Million pregnant women



Vaccine against VPDs
11 nation wide;
1 sub-nationally (JE)

~12 million sessions
planned per year

~29,000 cold chain points for
storage and distribution

Make in India: Largest vaccine manufacturing capacity in the world

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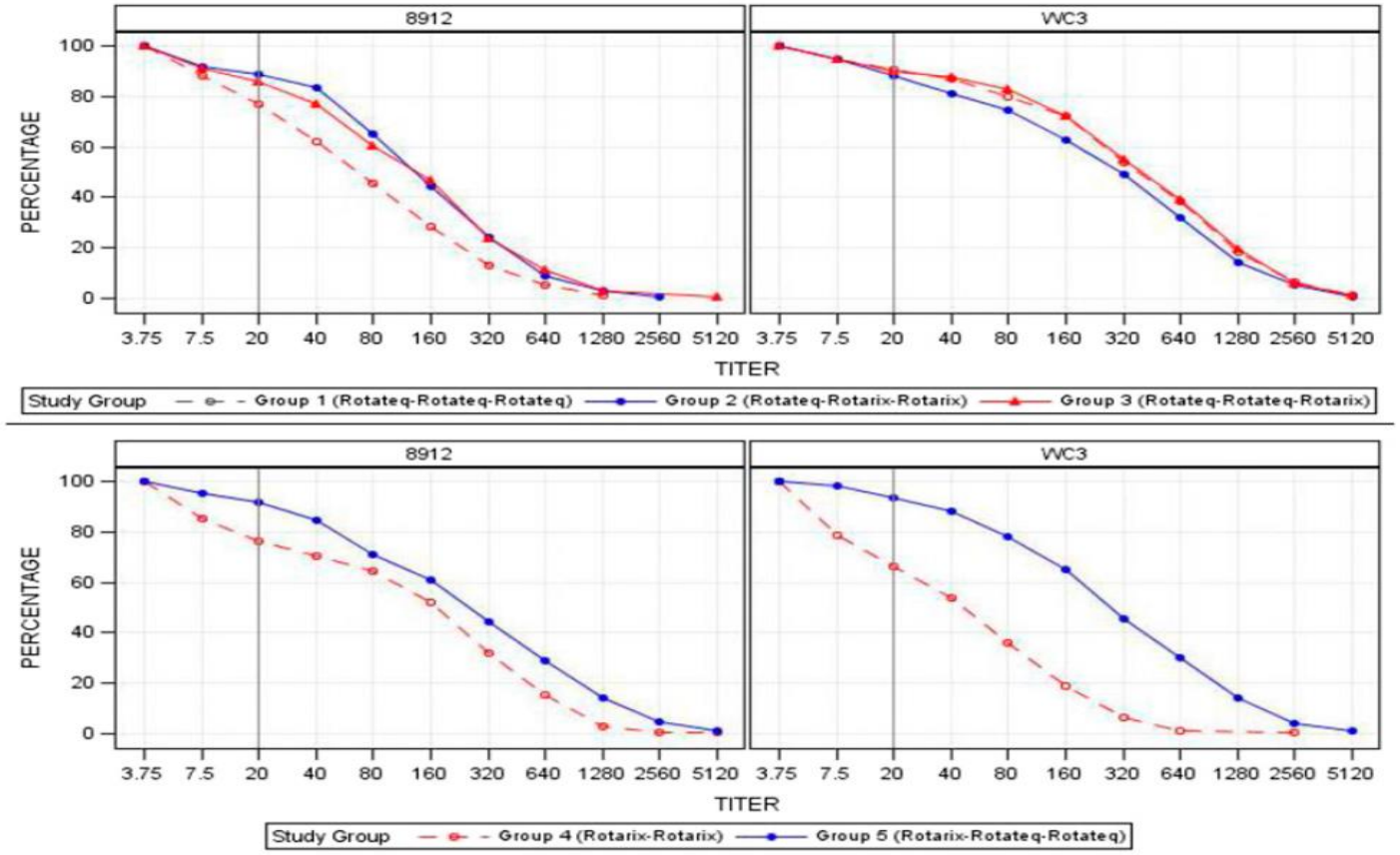
Studies supporting interchangeability – Evidence on RotaTeq (RV5) and Rotarix (RV1)

- Graph depicts proportion of infants with rotavirus IgA ≥20 U/mL post 3-6 wks of receiving last vaccine dose against both WC3 (RotaTeq) and 89–12 (Rotarix).
- Noticeably, for mixed vaccine product regimen Group 2, 3, & 5 achieved higher immunogenicity in comparison to single product regimen.
- ***Safety:*** Vaccines were well tolerated among all study groups with no serious adverse events reported.



89–12 - precursor to RV1
WC3 – backbone for RV5

Inter state Migration: Interchangeable vaccine product regimen a plausible approach

- As of March 2019, Under UIP Rotavac® was available in ten states (Assam, Tripura, Odisha, Madhya Pradesh, Uttar Pradesh, Haryana, Rajasthan, Himachal Pradesh, Andhra Pradesh and Tamil Nadu)
- Whereas, Rotasiil® was rolled out under UIP in one state (Jharkhand) with possible scale up to other states and union territories.
- To address issues of interstate migration; If a child after receiving one or two doses of a particular vaccine product migrates to other state where existing different vaccine product is available under the UIP → evidence of safety & immunogenicity is required for the interchangeability of Rotavac® and Rotasiil® used in the UIP in India.

Ref: OPERATIONAL GUIDELINES: Introduction of Rotavirus Vaccine in the Universal Immunization Programme, March 2019, MoHFW

Need for Assessing Interchangeability

- Initiated at the behest of the MoHFW
- Situation of potential vaccine shortage ← Due to issues - cost, purchase, and supply of the vaccine stocks in LMICs hinder administration of vaccines from a single manufacturer for each dose in a specific dosing regimen for logistic reasons
- Availability of two licensed vaccines in public health programs – Rotavac ® and Rotasiil ®
- Service accessibility have increased the chances of receiving antigenically different vaccines
- Immunogenicity and safety of a mixed regimen have not been studied much among Indian infants
- Limited evidence of dose switching of other rotavirus vaccines
- Evaluating the effect of mixed regimens needed as a national priority

Study Hypothesis

Primary Hypothesis

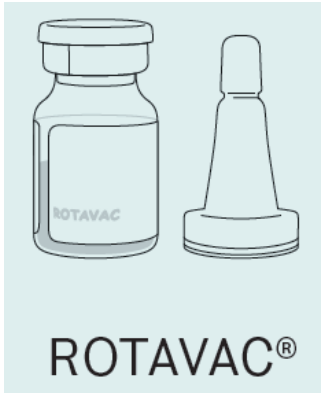
A three dose, mixed regimen of rotavirus vaccines (Rotavac ® and Rotasiil ®) administered orally, to healthy Indian infants, with the first dose given at 6-8 weeks, and subsequent doses given at 4-week intervals, is at least as immunogenic as Rotavac-only and Rotasiil-only regimens.

- The study was designed as a non-inferiority trial, with an expected seroconversion rate of 40% in the Rotavac-only or Rotasiil-only arms, and a non-inferiority margin of 10%.

Secondary Hypothesis

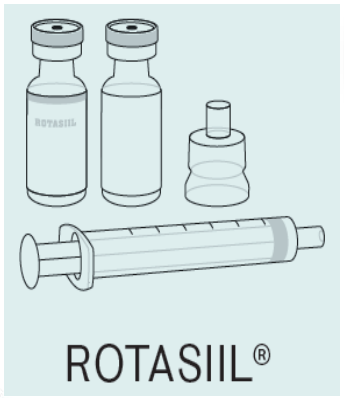
- Safety of mixed regime of Rotavac and Rotasiil is comparable to single vaccine (Rotavac only or Rotasiil only) arm.

Objectives



ROTAVAC®

01



ROTASIIL®

02

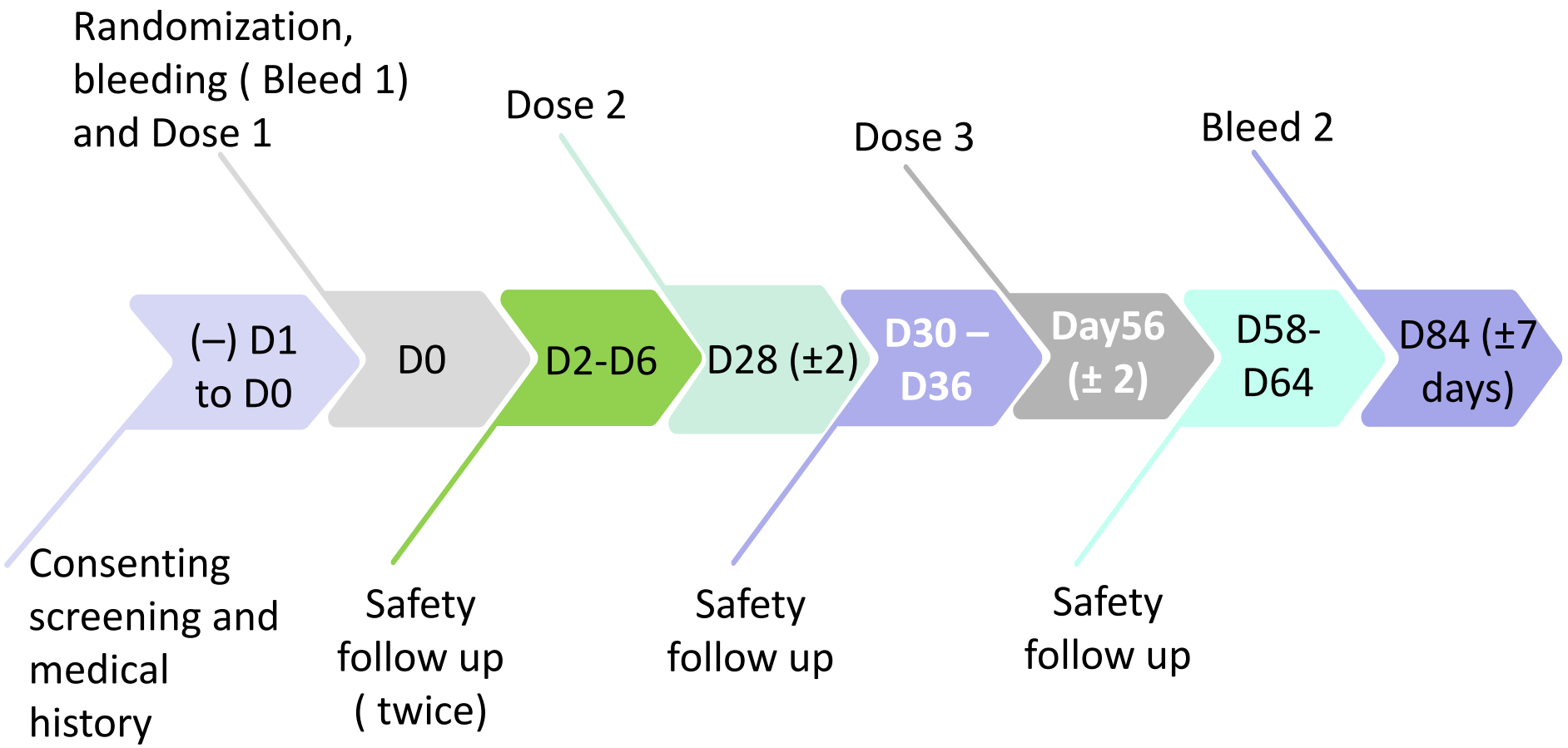
Primary:

To assess the safety and immunogenicity of mixed regimen of rotavirus vaccines (comprising of Rotavac ® and Rotasiil ®).

Secondary:

To assess vaccine safety (reactogenicity, adverse events [AEs], and serious adverse events [SAEs]) in recipients of a mixed regimen of rotavirus vaccines (comprising of Rotavac ® and Rotasiil ®).

Study Schedule (Flow diagram)



Study design

- Multi-centric, open label, non-inferiority, randomized, phase IV clinical trial with 1:1 allocation in 6 arms.
- Participants was enrolled from urban slums of Kolkata adjacent to NICED and from surveillance area under KEM HRC, Pune, to ensure close observation post-intervention
- Informed consent of parents were obtained
- Block randomization in blocks of at least 12 with equal allocation to six arms

Study Arms	Dose 1 (6-8 weeks)	Dose 2 (10-12 weeks)	Dose 3 (14-16 weeks)
Group 1: Comparator Arm	Rotavac	Rotavac	Rotavac
Group 2: Comparator Arm	Rotasiil	Rotasiil	Rotasiil
Group 3: Intervention Arm 1	Rotavac	Rotasiil	Rotavac
Group 4: Intervention Arm 2	Rotasiil	Rotavac	Rotasiil
Group 5: Intervention Arm 3	Rotavac	Rotasiil	Rotasiil
Group 6: Intervention Arm 4	Rotasiil	Rotavac	Rotavac

Justification for recruiting comparator arms

- Since efficacy trials for Rotasiil and Rotavac were carried out in similar areas, there was a concern that in order to limit the number of arms in the study, we could compare the immunogenicity from the four intervention arms with the data from historical comparator arms.
- **However, we proposed inclusion of two comparator arms because:**
  - Epidemiologically inexpedient to compare historical comparators with current intervention arms
  - Two comparators arms recruited and tested at different time points
  - Primary objective of previous trials was reduction of severe rotavirus gastroenteritis, slightly different from current hypotheses; immunogenicity studies were on smaller sub-samples with less power. Choosing those comparators would be inappropriate

Details of study participants at the two sites

Total participants completed the study : 1852

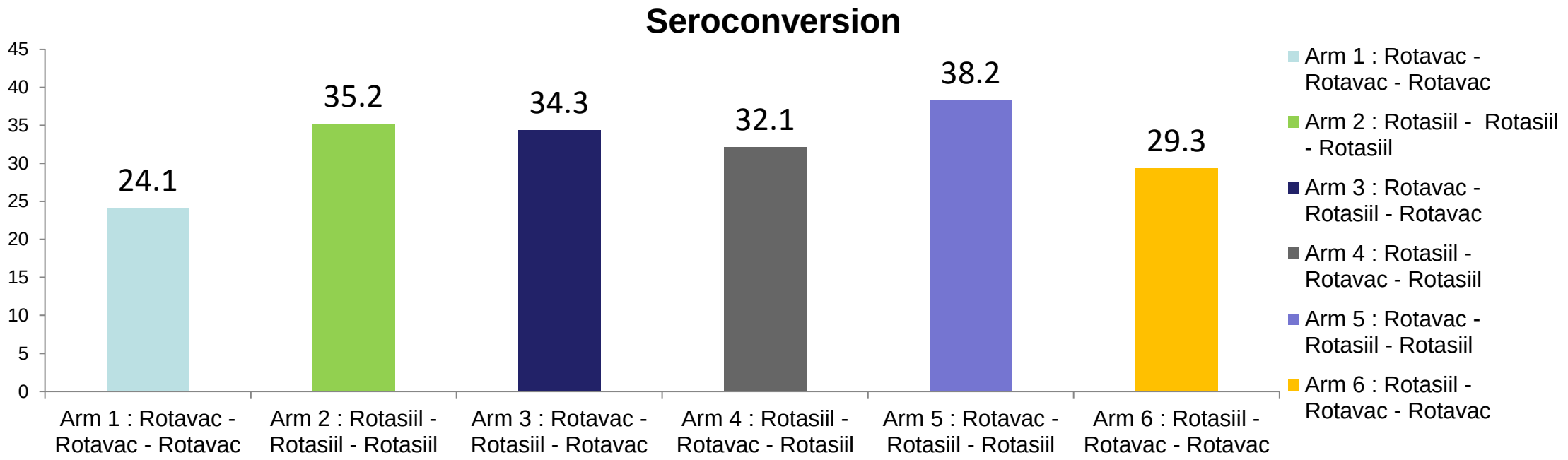
Baseline Characteristics:

- At baseline –
  - Male (%) : 50.3%, Female : 49.7%
  - Mean age (SD) - 47.28 days (3.97)
  - Mean weight (SD) - 4.20 kg (0.59)
  - Mean height (SD) - 54.20 cm (2.40)
- The six arms did not differ by age, gender, weight, and height at baseline.

Site	Consented	Drop out	Randomized	Visit 1	Visit 2	Visit 3	Visit 4	Early Termination
ICMR-NICED	1067	78	989	989	956	936	907	82
KEM	1042	52	990	990	969	958	945	45

Sero-response rate in each arm

- **Baseline serum IgA concentration <20 IU/ml –** sero-response defined as increase of serum rotavirus specific IgA ≥20 IU/ml
- **Baseline serum IgA concentration ≥ 20 IU/ml -** Sero-response is defined as Four-fold rise of rotavirus specific serum IgA concentration at four weeks after the administration of the third dose of rotavirus vaccine in any arm, compared to the baseline value for subjects



Maximum sero-response was observed in Arm 5 (38.2%) followed by Arm 3 (34.3%)

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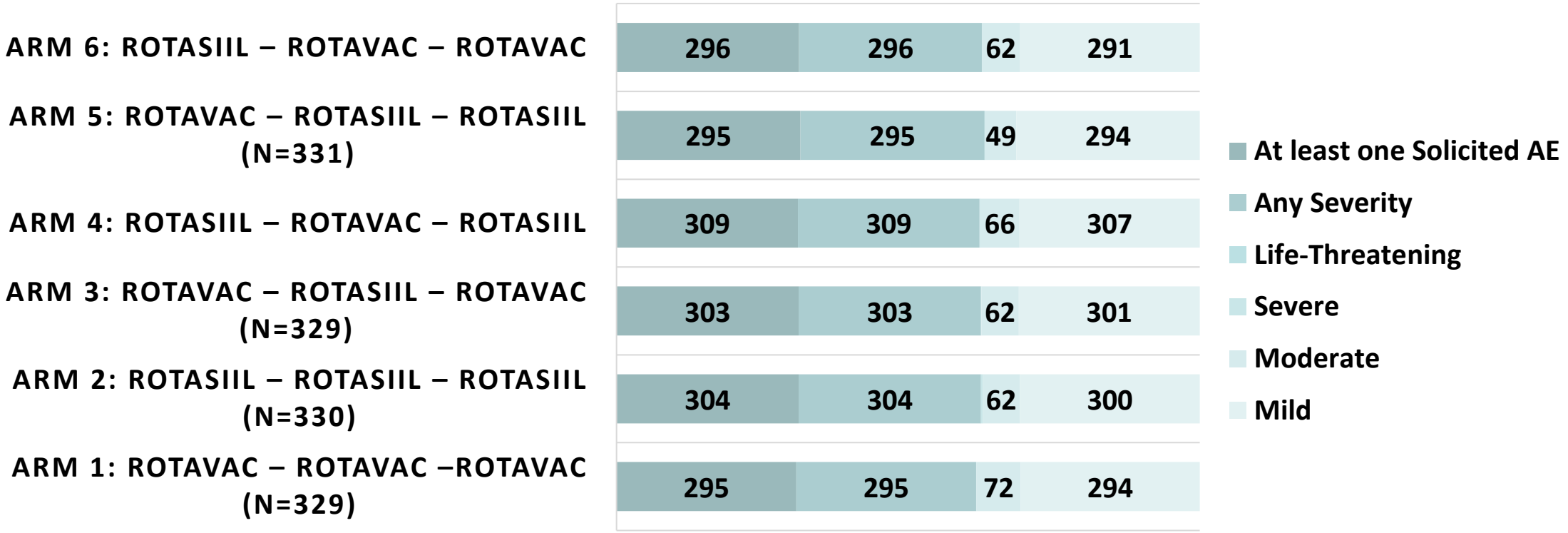
Sero-response in mixed and pure vaccine groups

- The SRR difference provide supporting evidence of non-inferiority since the lower limit of 95% Newcombe-Wilson confidence interval for SRR difference although crossed the actual null line but did not cross the non-inferiority margin -10%.

		Vaccine Group		SRR difference (95% CI)
		Mixed	**Pure**	
Sero-response	Total N	1238	601	
	Positive (n)	415	178	
	%	33.50%	29.60%	3.9% (-0.7 to 8.3)
Sero-response	95% LCL	30.90%	26.10%	
	95% UCL	36.20%	33.40%	

Profile of solicited Adverse events (AEs)



- ❖ No Life-threatening adverse events were noted.
- ❖ Among all arms, incidence of participants with any type (or at least one) of solicited AEs ranged from 89.1% (Arm 5) to 93.9% (Arm 4). Most of the events were of mild nature.

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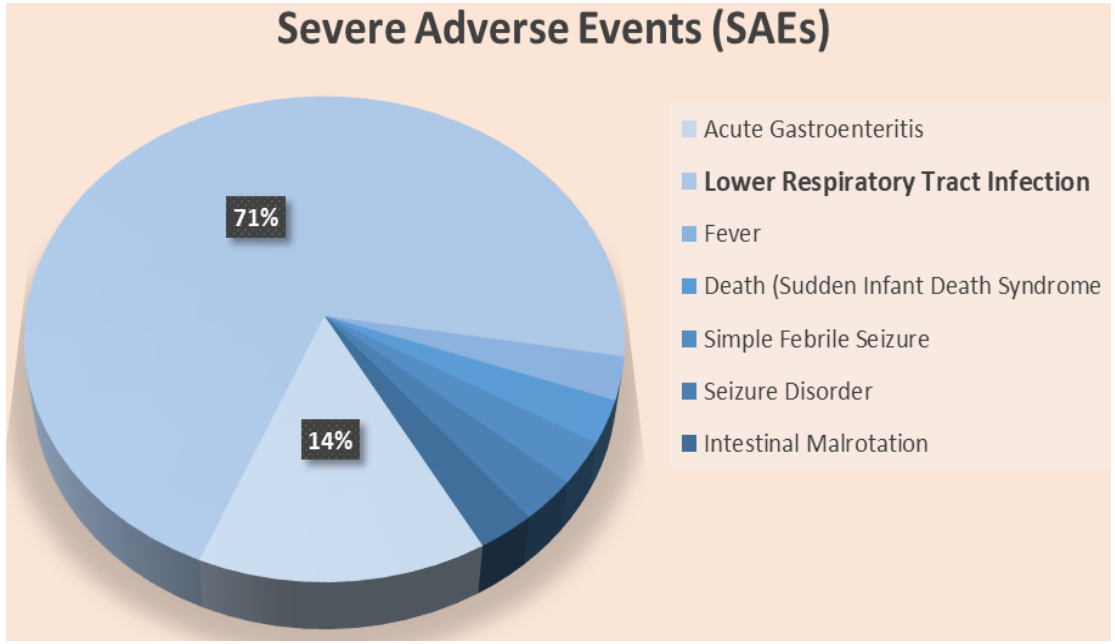
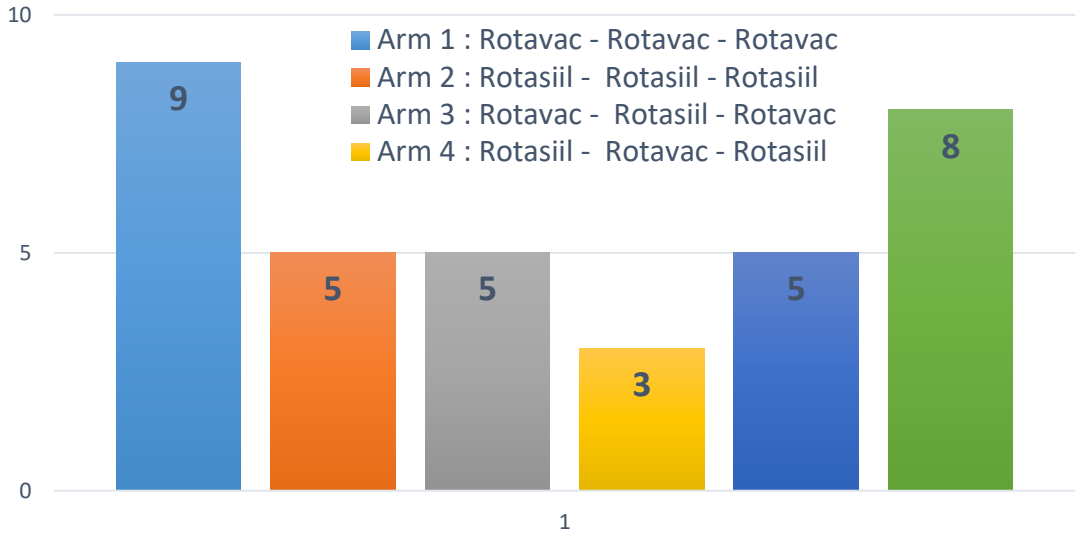
Severe adverse events reported

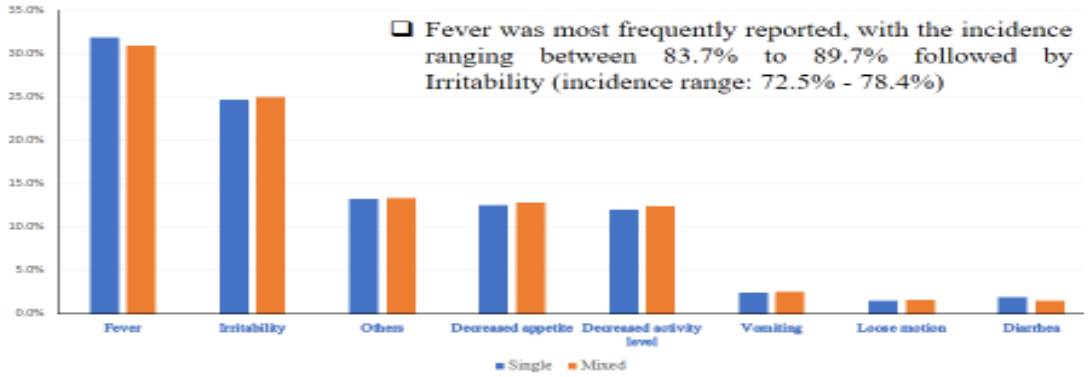




SAEs reported for each arm

- Out of 35 reported SAEs, 34 were classified as unrelated.
- There was one sudden infant death syndrome reported which was assumed to be unrelated.

Adverse events (%) in single and mixed vaccine regimen



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Points up for Discussion

- The present study reports that mixed vaccine regimen showed a 2.3% four-fold increase in IgA antibodies vs baseline titre of ≥20 IU/mL as compared to single vaccine regime showing 3% increase; thereby proving it a non-inferior alternate in areas of need.
- Rotavac and Rotasiil vaccines can be used interchangeably for routine immunization both in terms of sero response and safety.
  - Although sero-response is not considered as a direct proxy for efficacy it does demonstrate that the vaccines given in interchangeable manner is able to induce a robust immune response.
- Interchangeability of rotavirus vaccines has been approved by MoH, GoI in 2018* and this study (2017-2018) provides scientific support to the policy

*Ministry of health and Family Welfare. Government of India. Operational Guidelines: Introduction of Rotavirus Vaccination in the Universal Immunization Program. 2018, Available at : http://www.nhm.gov.in/New_Updates_2018/NHM_Components/Immunization/Guildelines_for_immunization/Operational_Guidelines_for_Introduction_of_Rotavac_in_UIP.pdf

Limitations of the study

- 6.48% participants' discontinuation from the study due to various reasons
- Long term immunogenicity of schedules was not assessed.
- The study was conducted in an unblinded manner
- Lastly, it is possible that some naturally occurring rotavirus infections could have influenced immunogenicity results but since the study was randomized, this would have happened across all study groups, including the pure vaccine groups.

Inference

- The present study demonstrates that administering mixed vaccine product combinations of Rotavac and Rotasiil provides a non-inferior sero-response rate as compared to single vaccine product regime.
- This study have also inferred that a mixed vaccine regime is safe and efficient against Rota virus infections among less than five year old population.
- This would combat the issue of vaccine shortages, along with the constraints of inter-state availability of particular vaccine products.
- The interchangeable dosing schedule will also help in addressing the issue of vaccination drop-out cases, which has previously been reported due to inter-state migration of the recipients.

Rotavirus vaccination implementation history in India

2014

ROTAVAC licencing from DCGI, India NTAGI recommendation for phased roll out

2016

26th March RVV PHASE-I implementation

Coverage – 2.4 million

2017

PHASE II & DCGI Licensing of ***ROTASIIL*** at end September

Coverage – 5.6 million

2018

PHASE III & Inclusion of ROTASIIL in UIP

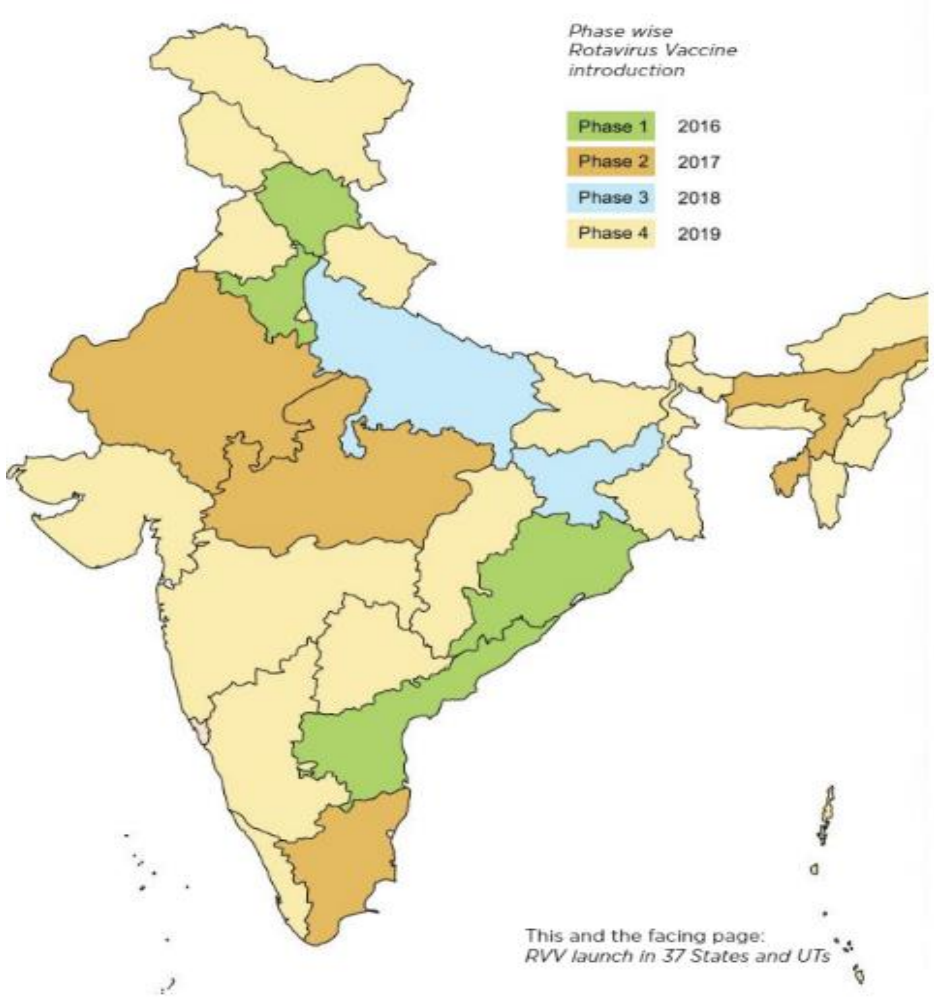
Coverage – 6.6 million

2019

PHASE IV

Coverage – 12.1 million

Annual coverage improvement Rate 6.7% achieved by the end of year 2019



Current status of Rotavirus vaccination in India

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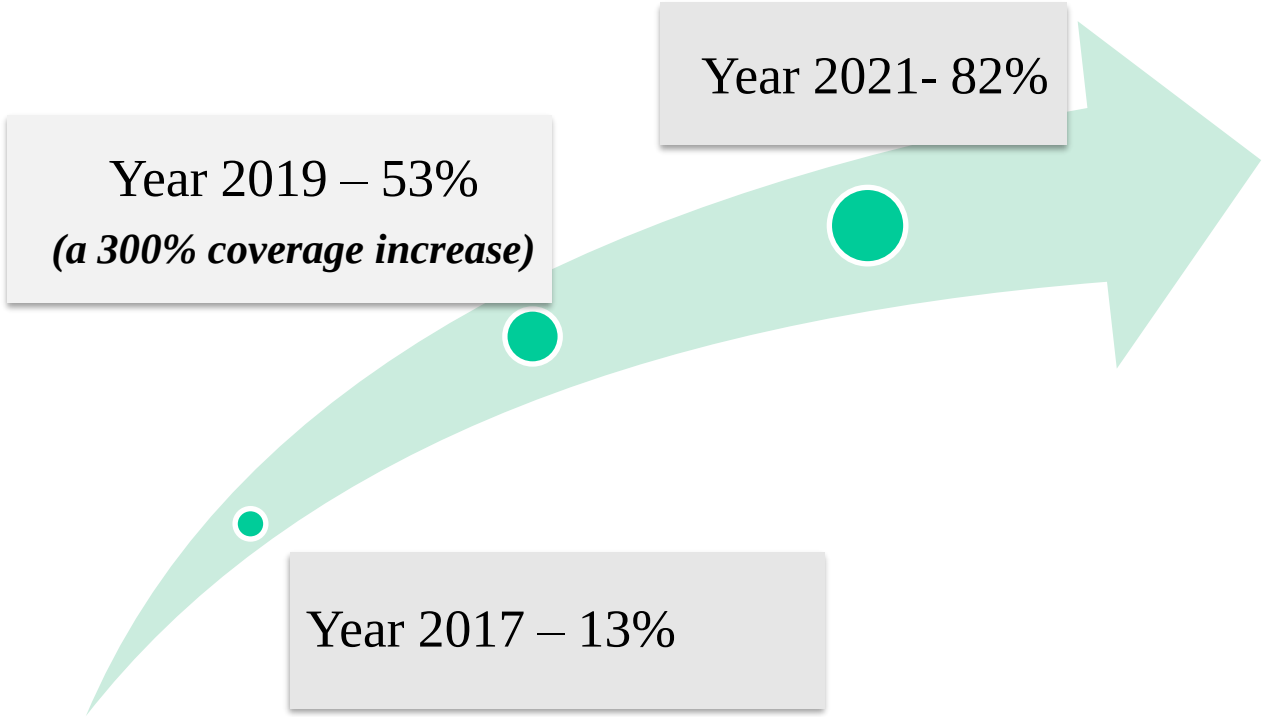
Landmark achievement of coverage through National roll-out of Rotavirus Vaccine in India under UIP



- 2016 → First country in WHO-SEAR to launch a Rotavirus vaccine developed indigenously
- 2019 → Scaled-up Rotavirus vaccine across 29 states and 8 union territories, with domestic funding.
- "100-days agenda" → Government expanded the Rotavirus vaccine to all states and union territories between July and September 2019.

- ***Currently, India produces two WHO-prequalified Rotavirus vaccines at less than a dollar-a-dose (64 INR/ Dose)***

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References

- Rheingans R, Anderson IV JD, Anderson B, Chakraborty P, Atherly D, Pindolia D. Estimated impact and cost-effectiveness of rotavirus vaccination in India: effects of geographic and economic disparities. Vaccine. 2014 Aug 11;32:A140-50.

- Rheingans R, Anderson IV JD, Anderson B, Chakraborty P, Atherly D, Pindolia D. Estimated impact and cost-effectiveness of rotavirus vaccination in India: effects of geographic and economic disparities. Vaccine. 2014 Aug 11;32:A140-50.

- Varghese T, Alokit Khakha S, Giri S, Nair NP, Badur M, Gathwala G, Chaudhury S, Kaushik S, Dash M, Mohakud NK, Ray RK. Rotavirus strain distribution before and after introducing rotavirus vaccine in India. Pathogens. 2021 Apr 1;10(4):416.
- Rao TS, Arora R, Khera A, Tate JE, Parashar U, Kang G, Indian Rotavirus Vaccine Working Group. Insights from global data for use of rotavirus vaccines in India. Vaccine. 2014 Aug 11;32:A171-8.
- Malik A, Haldar P, Ray A, Shet A, Kapuria B, Bhadana S, Santosham M, Ghosh RS, Steinglass R, Kumar R. Introducing rotavirus vaccine in the Universal Immunization Programme in India: From evidence to policy to implementation. Vaccine. 2019 Sep 16;37(39):5817-24.

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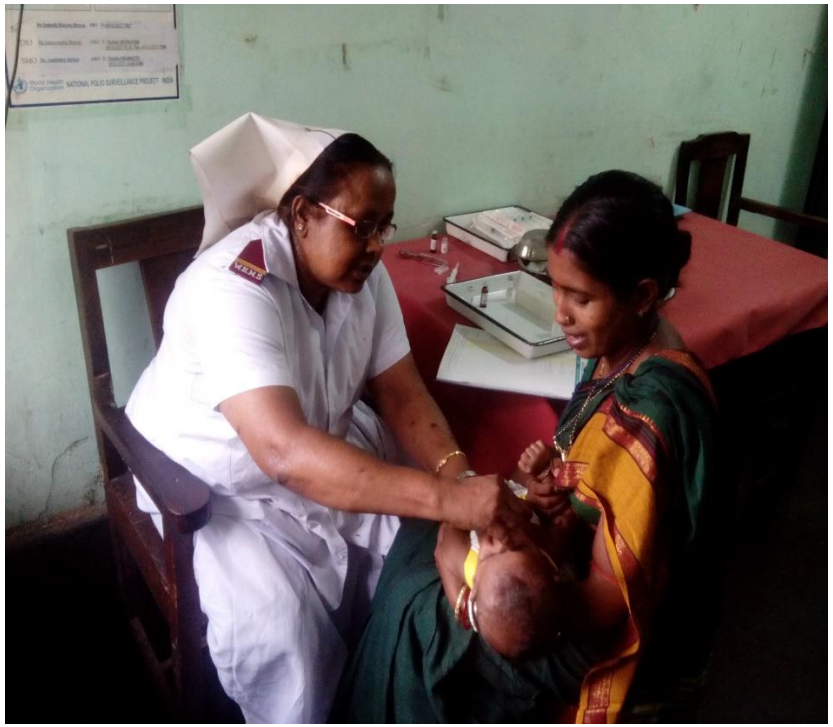

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