SMART SAFETY SURVEILLANCE

Ministry of Health & Family Welfare
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WHITE PAPER

Safety of Rotavirus Vaccine in India

Smart Safety Surveillance Approach

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Smart Safety Surveillance Approach

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Abbreviations

°C	Degree Celsius
AE	Adverse Events
AEFI	Adverse Event Following Immunization
AIIMS	All India Institute of Medical Sciences
AMN	Auxiliary Nurse Midwife
BBIL	Bharat Biotech India Ltd.
BIRAC	Biotechnology Industry Research Assistance Council
CDSCO	Central Drugs Standard Control Organization
CHRD SAS	Centre for Health Research and Development, Society for Applied Studies
CIOMS	Council for International Organizations of Medical Sciences
CLA	Licensing Authority
CMC	Christian Medical College
CRF	Case Reporting Form
DBT	Department of Biotechnology
DGCI	Drug Controller General of India
DIO	District Immunization Officer
DRCHO	District Reproductive and Child Health Officer
EMA	European Medicines Agency
EPI	Expanded Programme on Immunization
FCIF	Final Case Investigation Form
GA	General Anaesthesia
GACVS	Global Advisory Committee on Vaccine Safety
GoI	Government of India
GSK	GlaxoSmithKline
ICD	International Classification of Diseases
ICMR	Indian Council of Medical Research
INCLEN	International Clinical Epidemiological Network
IPV	Inactivated Polio Vaccine
IQR	Interquartile Range
IS	Intussusception
KEMHRC	KEM Hospital Research Centre
MA	Market Authorization
MAH	Market Authorization Holders
MHRA	Medicines Healthcare Products Regulatory Agency
MoHFW	Ministry of Health and Family Welfare of India
NDCT Rule	New Drugs and Clinical Trial Rule 2019
nHRV	Neonatal Human Rotavirus Vaccine
NTAGI	National Technical Advisory Group on Immunization
OPV	Oral Polio Vaccine
PAC	Post Approval Change
PCIF	Preliminary Case Investigation Form
PHC	Primary Health Centre
PMS	Post Market Surveillance
PPP	Public-Private Partnership

PSUR	Periodic Safety Update Report
RCT	Randomized controlled trials
RMP	Risk Management Plan
RNA	Ribonucleic Acid
RV	Rotavirus
RVV	Rotavirus Vaccines
SC	Steering Committee
SCCS	Self-Controlled Case Series
TAG	Technical Advisory Group
THSTI	Translational Health Sciences & Technology Institute
UIP	Universal Immunization Programme
US	United States
UT	Union Territories

Preamble

There is an evolving product landscape with new vaccines, drugs, and diagnostics that are made by multiple manufacturers in different geographies. New vaccines, drugs, and diagnostics are being developed to manage diseases that are endemic in these regions. Therefore, the use of these products and subsequent post-marketing safety surveillance cannot rely on existing safety data from developed economies, as has historically been the case.

At the time of market approval, new medical products often enter the market with limited safety data from clinical trials, which have small controlled populations. Therefore, for global health treatment and immunization programmes, post-marketing safety surveillance is essential to monitor the risk-benefit profile of a new medical product in the wider population.

The Smart Safety Surveillance (3S) initiative aims to strengthen pharmacovigilance (PV) systems in LMICs through product pilots, enhanced collaboration between relevant stakeholders, and the incorporation of best practices from previous PV strengthening initiatives. With a product-focused pilot, experience and competence is built within national regulatory agencies and PV centers through the end-to-end safety monitoring, data analysis, signal detection, and any necessary regulatory action for priority products of high public health value. The WHO has promoted the 3S approach with the support of Bill and Melinda Gates Foundation to strengthen PV systems in developing countries to ensure the safe and effective introduction of new health products.

The Smart Safety Surveillance (Triple S) Programme is a collaborative effort among regulators, the national immunization programme in India and other key vigilance stakeholders for vaccines, to strengthen pharmacovigilance capacity. World Health Organization (WHO) has promoted the Smart Safety Surveillance approach with the support of Bill and Melinda Gates Foundation, to strengthen PV systems in developing countries that are introducing new health products, for the safe and effective use of these products.

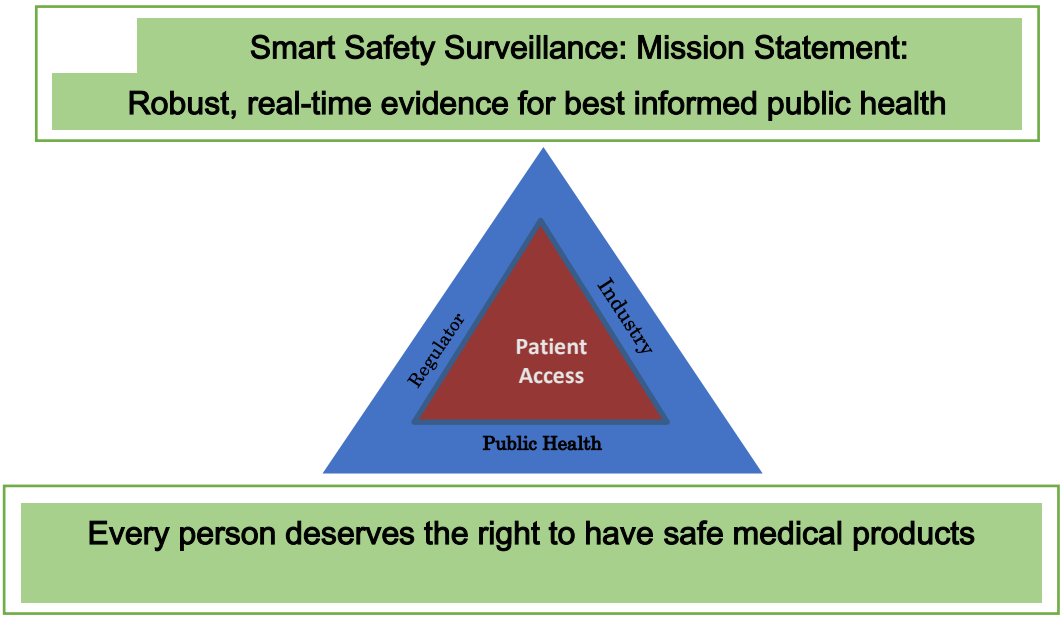
Rotavac, an oral rotavirus vaccine developed, tested and licensed in India, and introduced into the national immunization programme in 2016 for the prevention of rotavirus diarrhoea in young children, was selected as the vaccine pathfinder, to introduce and test the 3S approach. There have been rare adverse events such as intussusception linked to rotavirus vaccines and there is a continuing need to monitor the safety profile of the vaccine as it is scaled within the country. The 3S approach has led to a collaborative effort between regulators, the national immunization programme and other key vigilance stakeholders, to strengthen PV capacity and ensure the safety of the vaccine. In particular, the 3S approach for the *Rotavac* vaccine in India enabled:

I. Strengthening of the functionality of current PV systems
II. Building of capacity to analyse safety data
III. Improved capacity to use PV data for regulatory decision-making

IV. Support of collaboration between public health programmes, academic researchers conducting PV studies, and regulators

V. An improved understanding of the safety profile of the product

Figure 1: Smart Safety Surveillance



Project 3-S: Smart Safety Surveillance in India

The activities to drive the 3S programme in India were undertaken in 2019, focusing on strengthening the collaboration of key stakeholders on vigilance. Specific workshops for Periodic Safety Update Report (PSUR) and Risk Management Plan (RMP) assessment and writing, Signal Detection Management, and Risk-Benefit Assessment for vaccines were conducted.

There were two study visits organised to MHRA, UK and EMA, Amsterdam to understand their best practices of the risk-benefit assessment and vigilance processes. These culminated into collaborative workplans for partnering among the agencies in the coming years to strengthen vigilance capacity. The WHO, in collaboration with MHRA worked with the immunization programme, Ministry of Health and Family Welfare of India (MoHFW) and Central Drugs Standard Control Organization (CDSCO) to form a PV strengthening work plan for vaccines. The 3S priorities in India were to link PV activities between different stakeholders, for data sharing, signal detection, risk assessment, risk management, risk communication, and benefit harm evaluation for regulatory decision-making.

There were several learnings from the 3S activities implemented in India, which directly led to required next steps. One of these is the need for collating safety data from all sources for the safety assessment of the vaccines in the post-marketing period including routine data collection and special studies.

As part of the Smart Safety Surveillance for vaccines, India focused on the newly introduced Rotavirus vaccines and has available safety data from various sources. As part of special safety/impact studies, data are being collected at various sites including sentinel sites such as Adverse event following immunization (AEFI) Secretariat (Immunization Division) Ministry of Health and Family Welfare, Translational Health Sciences & Technology Institute (THSTI) (Department of Biotechnology, Ministry of Science & Technology), International Clinical Epidemiological Network (INCLEN), Centre for Health Research and Development, Society for Applied Studies (CHRD SAS) among others. In addition, the Central Drugs Standard Control Organization (CDSCO) is receiving safety reporting data periodically as PSURs. The Pharmacovigilance Programme of India (PvPI) also collects the vaccine AEFIs through E2B reporting by manufacturers, which is further shared with the Immunization Division.

Collation of these data and partnerships across all stakeholders were essential to characterize the safety profile of *Rotavac* vaccine. Thus, WHO, Immunization programme and the CDSCO coordinated the synthesis of all safety data from the following sources i) PSURs submitted to CDSCO by the manufacturer, ii) cases reported to and analysed by AEFI Secretariat (Immunization Division), iii) an early roll out study recommended by the National Technical Advisory Group on Immunization and conducted by the Centre for Health Research and Development, Society for Applied Studies and partners, and iv) sentinel sites established as recommended by WHO for post-marketing surveillance of rotavirus vaccines by the Translational Health Sciences & Technology Institute (Department of Biotechnology, Ministry of Science & Technology) and INCLEN. Data triangulation was conducted under this approach for *Rotavac* safety data by all stakeholders jointly and a White Paper was prepared, thus achieving the goal of using the *Rotavac* vaccine as a pathfinder to enhance national pharmacovigilance systems that support regulatory decisions for all vaccines throughout their lifecycle.

In all studies, over 1500 cases of intussusception were analysed. The majority of the intussusception cases were observed during 4-10 months of age, a part of the period overlaps with the age of primary doses of rotavirus vaccination. Nonetheless, self-controlled case series analysis demonstrated no increased risk of intussusception associated with *Rotavac* vaccination in two separate analyses. The synthesis of routine data and systematically designed studies adopting sound methodology in India has brought together all stakeholders in immunization safety to demonstrate that Smart Safety Surveillance can leverage multiple data sources to provide reassurance on the safety of a new vaccine. It is hoped that this approach leads to better characterized safety profile of Rotavirus vaccines and enhanced pharmacovigilance systems that support regulatory decisions for all vaccines throughout their lifecycle.

1. Rotavirus and disease

Until early 1970s, the causes of most cases of acute gastroenteritis in children were unidentified. However, in 1973 many round virus particles were seen in the intestinal biopsies of children with diarrhoea. This virus was named "rotavirus" adapted from *Latin* word *rota* because of its distinctive morphological appearance. Rotaviruses (RV) are double-stranded, nonenveloped Ribonucleic Acid (RNA) viruses having a complex three-layered structure that encircles 11 segments of RNA.[1] There are nine serological groups (A to I) into which the rotavirus genus is divided. Humans are infected by Groups A to C, and all groups infect animals.[2]

Rotavirus is the leading cause of severe childhood gastroenteritis. Almost every child will experience an episode of rotavirus gastroenteritis by the age of 5 years. In 2003, it was estimated that 1 in 5 children will visit a clinic, 1 in 65 will be hospitalized, and approximately 1 in 293 will die. Children in the poorest countries accounted for 82% of rotavirus deaths.[3] In 2015, diarrhoea was a dominant cause of death in children under 5 years of age, especially in low income countries, causing more than 500,000 deaths worldwide. According to the Global Burden of Disease estimates, three pathogens--rotavirus, *Cryptosporidium* spp, and *Shigella* spp. are responsible for the most deaths, among which rotavirus was the leading pathogen, with 199,000 diarrhoeal deaths.[4] Although mortality has declined significantly in the past few decades with increased access to care and oral rehydration, morbidity continues at high levels, because viral pathogens are transmitted through multiple modes of transmission and the morbidity burden is unaffected by hygiene and sanitation.

Rotavirus infections may be subclinical, or may cause mild watery diarrhoea for limited periods, or may result in severe dehydrating diarrhoea with vomiting and fever which can lead to shock, electrolyte imbalance, and death. Vomiting usually lasts for only one or two days and other gastrointestinal symptoms generally resolve in three to seven days. About one-third of affected children may develop fever with temperature more than 39°C.[5] Management of rotavirus infections focuses on prevention and treatment of dehydration. Children are usually treated with oral rehydration and in developing countries, oral zinc is recommended for two weeks. However, occurrence of severe vomiting hinders with the oral rehydration treatment, resulting in the need for intravenous rehydration which requires facility based care for parenteral therapy.[6]

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[1] Centers for Disease Control and Prevention. In: Hamborsky J, Kroger A, Wolfe S, editors. Epidemiology and Prevention of Vaccine-Preventable Diseases. Washington D.C: Public Health Foundation; 2015. Available from: https://www.cdc.gov/vaccines/pubs/pinkbook/rota.html.

[2] Robert F. Ramig. Pathogenesis of Intestinal and Systemic Rotavirus Infection. Journal of Virology, Oct. 2004, p. 10213–10220.

[3] Parashar et al. Global Illness and Deaths Caused by Rotavirus Disease in Children. Emerging Infectious Diseases • Vol. 9, No. 5, May 2003.

[4] GBD Diarrhoeal Disease Collaborators. Estimates of global, regional, and national morbidity, mortality, and aetiologies of diarrhoeal diseases: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Infect Dis. 2017; 17:909–948. [PubMed: 28579426]

[5] Crawford et al. Rotavirus infection. Nat Rev Dis Primers. ; 3: 17083. doi:10.1038/nrdp.2017.83.

[6] Raju B, Parikh RP, Vetter VV, Kolhapure S. Epidemiology of rotavirus gastroenteritis and need of high rotavirus vaccine coverage with early completion of vaccination schedule for protection against rotavirus diarrhea in India: A narrative review. Indian J Public Health 2019;63:243-50.

2. Rotavirus vaccines

In 2013, WHO recommended inclusion of rotavirus vaccines in Expanded Programme on Immunization (EPI) programmes of all nations, especially in countries where the mortality burden of diarrhoea was high. This decision was based on the high number of diarrhoeal deaths caused by rotavirus accounting to 453,000 deaths/year as estimated in 2008, with more than half of the deaths occurring in India, Pakistan, Nigeria, Ethiopia and Democratic Republic of the Congo. India alone accounted for 22% of deaths.[7] Further WHO also proposed to include rotavirus vaccines as part of a broad approach to control diarrhoeal diseases which includes promotion of early and exclusive breastfeeding, hand washing, improved water supply and sanitation.

This recommendation for universal use of rotavirus vaccines came fifteen years after the first rotavirus vaccine was licensed. In August 1998, a tetravalent rhesus-based rotavirus vaccine *Rotashield* (Wyeth-Ayerst) was licensed in the United States (US) for use among infants and was made part of the US national immunization programme. However, within a year, cases of intussusception, a condition in which one segment of bowel becomes enfolded within other segment resulting in bowel blockage, were reported, following which *Rotashield* was withdrawn from immunization programme in July 1999.[8,9] Subsequent analyses demonstrated that the risk of intussusception was approximately 1 in 11,000 children, and further pre-licensure vaccine trials were conducted in the early 2000s to be able to measure a risk of intussusception at least as great as that seen with *Rotashield*. The finding of intussusception also led to the development of the Brighton Collaboration's criteria for diagnosis of intussusception, which were later used for evaluation of intussusception cases in surveillance systems (Refer to Table 1).

Table 1: Brighton collaboration clinical case definition for the diagnosis of acute intussusception in infants and young children[10]

Level 1 of diagnostic certainty	Level 2 of diagnostic certainty	Level 3 of diagnostic certainty
Surgical criteria: the demonstration of invagination of the intestine at surgery; **and/or** ***Radiological criteria:*** the demonstration of invagination of the intestine by either air or liquid contrast enema; **or** the demonstration of an intra-abdominal mass by abdominal ultrasound with specific characteristic features[a] that is	***Clinical criteria:*** Two major criteria (see criteria for diagnosis below); **or** One major criterion[b] and three minor criteria (see criteria for diagnosis below).	***Clinical criteria:*** four or more minor criteria (see criteria for diagnosis below).

[7] Tate JE, Burton AH, Boschi-Pinto C, et al. 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. Lancet Infect Dis 2012; 12:136–41.

[8] Centers for Disease Control and Prevention. Withdrawal of rotavirus vaccine recommendation. MMWR Morb Mortal Wkly Rep 1999; 48:1007.

[9] Centers for Disease Control and Prevention. Intussusception among recipients of rotavirus vaccine—United States, 1998–1999. MMWR Morb Mortal Wkly Rep 1999; 48:577–81.

[10] Bines JE et al. Clinical case definition for the diagnosis of acute intussusception. Journal of Pediatric Gastroenterology and Nutrition, 39(5):511–518.

<table>
<tr><th>Level 1 of diagnostic certainty</th><th>Level 2 of diagnostic certainty</th><th>Level 3 of diagnostic certainty</th></tr>
<tr><td>proven to be reduced by hydrostatic enema on post-reduction ultrasound;
and/or
Autopsy criteria: the demonstration of invagination of the intestine.</td><td></td><td></td></tr>
<tr><td colspan="3">For any level
In the absence of surgical criteria with the definitive demonstration of an alternative cause of bowel obstruction or intestinal infarction at surgery (such as volvulus, congenital pyloric stenosis).
Major and minor criteria used in the case definition for the diagnosis of intussusception
Major criteria:
1) Evidence of intestinal obstruction
• History of bile-stained vomiting and either
• Examination findings of acute abdominal distension and abnormal or absent bowel sounds or
• Plain abdominal radiograph showing fluid levels <u>AND</u> dilated bowel loops.
2) Features of intestinal invagination
One or more of the following:
• abdominal mass;
• rectal mass;
• intestinal prolapse;
• plain abdominal radiograph showing a visible intussusceptum or soft tissue mass;
• abdominal ultrasound showing a visible intussusceptum or soft tissue mass;
• abdominal CT scan showing a visible intussusceptum or soft tissue mass.
3) Evidence of intestinal vascular compromise or venous congestion:
• Passage of blood per rectum; or
• Passage of a stool containing “redcurrant jelly” material; or
• Blood detected on rectal examination.
Minor criteria:
• predisposing factors: age <1 year and male sex;
• abdominal pain;
• vomiting[c];
• lethargy[d];
• pallor[d];
• hypovolemic shock;
• plain abdominal radiograph showing an abnormal but non-specific bowel gas pattern.</td></tr>
<tr><td colspan="3">[a] Target sign or doughnut sign on transverse section and a pseudo-kidney or sandwich sign on longitudinal section.
[b] If one major criterion is the passage of blood per rectum that is mixed in a diarrhoeal stool, then consideration should be given to infectious etiologies.
[c] If the vomiting is bile-stained, it cannot be counted twice as a major and minor criterion.
[d] Lethargy and pallor typically occur intermittently in association with acute spasms of abdominal pain. In patients with severe or prolonged intussusception, lethargy and pallor may become a constant feature associated with a deterioration in cardiovascular status and impending hypovolemic shock.</td></tr>
</table>

In 2004 and 2006, two new live oral rotavirus vaccines were licensed following phase 3 safety and efficacy studies in 60-70,000 children each. These vaccines, known as *Rotarix* (manufactured by GlaxoSmithKline, GSK) and *Rotateq* (manufactured by Merck Research Laboratories), showed no increased risk of intussusception in pre-licensure studies and are described in the next section.

As per the global introduction status of rotavirus vaccines, till June 2019, 98 countries have included rotavirus vaccine into their national immunization programmes, which includes 92 national and six sub-national introductions.[11] The Government of India (GoI) introduced rotavirus vaccine in its national immunisation programme in 2016 in a phased manner, achieving countrywide coverage in September 2019 with two India manufactured rotavirus vaccines.[12]

[11] Rota Council. Global Introduction Status; 2018. Available from: http://www.rotacouncil.org/vaccine-introduction/ global-introduction-status. [Last accessed on 2019 Oct 09]

[12] Malik et al. Introducing rotavirus vaccine in the Universal Immunization Programme in India: From evidence to policy to implementation. Vaccine Volume 37, Issue 39, 16 September 2019, Pages 5817-5824.

2.1. Types of vaccines

In India four WHO prequalified oral, live, attenuated rotavirus vaccines (RVV) are available, Rotarix (GSK) and Rotateq (Merck) which are licensed globally and Rotavac (Bharat Biotech) and Rotasiil (Serum Institute of India) which were first licensed in India. All four vaccines available in India are WHO pre-qualified.

Rotarix is derived from a single common strain of human rotavirus is a two-dose, live-attenuated rotavirus vaccine; Rotateq is a pentavalent bovine-human reassortant rotavirus vaccine given as three doses; Rotavac is a single-strain, naturally occurring bovine-human reassortant vaccine given as three doses; and Rotasiil is a pentavalent bovine-human reassotrant given as three doses. See Table 2.

Table 2: Rotavirus vaccines available in India.

Characteristic	Rotarix	Rotateq	Rotavac	Rotasiil
Manufacturer (location)	GlaxoSmithKline Biologicals (Belgium)	Merck & Co. Inc. (USA)	Bharat Biotech International Limited (India)	Serum Institute of India Pvt. Ltd. (India)
Composition	Monovalent, live attenuated human strain R1X4414 (G1P[8])	Pentavalent, live, bovine-human reassortant based on WC-3 strain with human G1, G2, G3, G4 and P[8]	Monovalent, live attenuated naturally occurring bovine-human reassortant strain 116E	Pentavalent, live bovine-human reassortant based on UK strain with human G1, G2, G3, G4 and G9
First licensure date	First approved in Mexico in 2004, licensed in India, 2007	Licensed in the USA and Europe in 2006, licensed in India, 2010	Licensed in India, 2014	Licensed in India, 2017
WHO prequalification date	12/03/2009	07/10/2008	05/01/2018	21/09/2018
Presentation	Liquid	Liquid	Liquid	Lyophilised active component to be reconstituted with excipient diluent before use
Doses in vial	1, 5	1	1, 5, 10	1, 2
Route	Oral	Oral	Oral	Oral
Dose	1 ml	2 ml	0.5 ml	2.5 ml
Schedule	2 doses at 2 and 4 months or per EPI	3 doses at 2, 4 and 6 months or per EPI	3 doses at 6, 10, 14 weeks	3 doses at 6, 10, 14 weeks

In December 2011, the Global Advisory Committee on Vaccine Safety (GACVS) first assessed the safety of Rotateq and Rotarix vaccines based on which, the committee noted that they were safe to use in infants but may cause increased risk of intussusception in 1 in 20,000 to 1 in 60,000 vaccinees. However, the committee also pointed out that the benefit of the vaccines outweighed the potential risk.[13]

A large post-introduction surveillance of intussusception in countries that had introduced Rotarix vaccine (Ethiopia, Ghana, Kenya, Malawi, United Republic of Tanzania, Zambia and

[13] World Health Organization. Weekly epidemiological record. 10 February 2012, 87th year No. 6, 2012, 87, 53–60. http://www.who.int/wer.

Zimbabwe at 28 sentinel paediatric hospitals, showed no increased risk of intussusception after either dose 1 or 2.13

Randomized controlled trials (RCT) reviewed in a Cochrane systematic review of the efficacy and safety of rotavirus vaccines showed no association in occurrence of serious adverse events in the use of Rotavac, Rotateq, Rotasiil and Rotavac in comparison to placebo.14

2.2. Efficacy and usage

The indigenously developed *Rotavac* (manufactured by Bhatrat Biotech International Ltd) vaccine is a neonatal human rotavirus vaccine (nHRV) derived from the naturally attenuated and reassorted RV strain, 116E. In 2014, safety and efficacy of *Rotavac* vaccine against severe rotavirus gastroenteritis was reported from a multi-centre trial in 6800 infants conducted in Delhi, Pune and Vellore in India. The vaccine was given as 3 doses at 6, 10 and 14 weeks of age in both rural and urban settings. The results of this double-blind placebo-controlled trial showed vaccine efficacy against severe rotavirus gastroenteritis of 56.4% in the first year of life. The findings from the trial also showed that *Rotavac* was well tolerated when administered in infants along with other childhood vaccines, and no safety signals were noted.

The efficacy of *Rotavac* is comparable to that of *Rotarix* and *Rotateq* evaluated in developing nations. *Rotarix* when assessed in Africa and Asia presented an efficacy of 58.9% and efficacy of *Rotateq* assessed in Africa was 61.2% against rotavirus gastroenteritis in the first year of life.[15] There was no difference in the occurrence of severe adverse events, deaths and intussusception between vaccines and ones who received placebo.[16]

A randomized, open-labelled, non-inferiority phase 4 clinical trial conducted from 2015 - 2016 in four sites in India, also confirmed similar safety profiles and immunogenicity when compared to *Rotarix*.[17]

The efficacy of *Rotavac* vaccine against severe gastroenteritis in the second year of life slightly reduced to 48.9% when compared to efficacy in first year of life (56.4%).

The safety and efficacy of another indigenously developed rotavirus vaccine, *Rotasiil* was also evaluated in a double-blind, randomized, placebo-controlled, endpoint-driven study in 7500 Indian infants initiated in 2014. The findings from the trial showed that *Rotasiil* has an overall efficacy of 39.5% against severe rotavirus gastroenteritis and 22.6% against rotavirus gastroenteritis of any severity which was maintained till second year of life.[18] No increase intussusception was seen in vaccine recipients. Efficacy of *Rotasiil* was also evaluated among

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[14] Soares-Weiser K, Bergman H, Henschke N, Pitan F, Cunliffe N. Vaccines for preventing rotavirus diarrhoea: vaccines in use. Cochrane Database of Systematic Reviews 2019, Issue 3. Art. No.: CD008521. DOI: 10.1002/14651858.CD008521.pub4.

[15] Bhandari et al. Efficacy of a Monovalent Human-Bovine (116E) Rotavirus Vaccine in Indian Infants: A Randomised Double Blind Placebo Controlled Trial. *Lancet*.2014 June 21;383(9935):2136–2143.

[16] N. Bhandari et al. Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian children in the second year of life. Vaccine. 32S (2014) A110-A1[16] P.S. Kulkarni et al. A randomized Phase III clinical trial to assess the efficacy of a bovine human reassortant pentavalent rotavirus vaccine in Indian infants. Vaccine. 35 (2017) 6228–6237

[17] R Ella et al. A randomized, open-labelled, non-inferiority phase 4 clinical trial to evaluate the immunogenicity and safety of the live, attenuated, oral rotavirus vaccine, ROTAVAC_ in comparison with a licensed rotavirus vaccine in healthy infants. Vaccine 37 (2019) 4407–4413. https://doi.org/10.1016/j.vaccine.2019.05.069.

[18] P.S. Kulkarni et al. A randomized Phase III clinical trial to assess the efficacy of a bovine human reassortant pentavalent rotavirus vaccine in Indian infants. Vaccine. 35 (2017) 6228–6237.

infants of Niger in a randomized placebo-controlled trial and the efficacy after three doses of *Rotasiil* was found out to be of 66.7% against severe rotavirus gastroenteritis.[19]

2.3. Rotavirus Vaccine in Universal Immunization Programme of India

ICMR in 2005 established the Indian (later National) Rotavirus Surveillance Network to streamline the monitoring of diarrhoea associated hospitalization of children under five years of age to estimate rotavirus disease burden. With a short gap in surveillance, the programme was continued until 2015. Based on the findings of this surveillance network and other data on the burden of disease, the National Technical Advisory Group on Immunization (NTAGI) recommended to the MoHFW, GoI to introduce rotavirus vaccine in 2014. Since rotavirus vaccine introduction was based on burden and vaccine efficacy on a small number of children, the NTAGI recommended that an early roll out be conducted in the national immunization programme at the sites where the phase 3 trial was conducted to gather more safety data, particularly on intussusception and that sentinel surveillance be conducted as recommended by WHO. The MOHFW made key decisions on phased introduction of rotavirus vaccine in the national immunization schedule, choosing four states (Haryana, Himachal Pradesh, Andhra Pradesh and Odisha) first for introduction in 2016 and then expanding to the rest of the country over time.

Among Asian nations, India became one of the first to include an indigenously manufactured rotavirus vaccine in their national immunization schedule in 2016 (See Table 3). Rotavirus vaccine was introduced in a phased manner with the first two phases with *Rotavac* vaccine covering nine states of the country accounting for nearly 35% of the annual birth cohort of the country.[20] Subsequently, *Rotavac* use was further expanded, and *Rotasiil* vaccine was introduced first in Jharkhand, and in 2019 in other states.

Table 3: National Immunization Schedule in India[21]

Vaccine	Age
For Infants	
Bacillus Calmette Guerin (BCG)	At birth till one year
Hepatitis B - Birth dose	At birth within 24 hours
Oral Polio Vaccine (OPV) - 0	At birth
OPV 1, 2 & 3	At 6 weeks, 10 weeks & 14 weeks
Pentavalent 1, 2 & 3	At 6 weeks, 10 weeks & 14 weeks
Fractional dose of Inactivated Polio Vaccine (fIPV) 1 & 2	At 6 weeks & 14 weeks
Rotavirus Vaccine (RVV) 1, 2 & 3	At 6 weeks, 10 weeks & 14 weeks
Pneumococcal Conjugate Vaccine (PCV) 1, 2 & PCV – Booster#	At 6 weeks, 10 weeks & 9 months
Measles & Rubella (MR) - 1	At 9 completed months - 12 months
Japanese Encephalitis (JE) – 1*	At 9 months - 12 months
Vitamin A (1st Dose)	At 9 months
For Children and Adolescent	
Diphtheria, Pertussis & Tetanus (DPT) Booster - 1	16 - 24 months

[19] S Isanaka, O Guindo et al. Efficacy of a Low-Cost, Heat-Stable Oral Rotavirus Vaccine in Niger. N Engl J Med 2017; 376:1121-1130.DOI: 10.1056/NEJMoa1609462.

[20] 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):5817-5824. doi: 10.1016/j.vaccine.2019.07.104.

[21] https://nhm.gov.in/New_Updates_2018/NHM_Components/Immunization/report/National_Immunization_Schedule.pdf

Vaccine	Age
MR – 2	16 - 24 months
OPV Booster	16 - 24 months
JE – 2*	16 - 24 months
Vitamin A (2nd to 9th Dose)	At 16 months. Then, one dose after every 6 months.
DPT Booster - 2	5 - 6 years
Tetanus Toxoid (TT)/ Tetanus & adult Diphtheria (Td)	10 years & 16 years
For Pregnant Woman	
TT/Td – 1	Early in pregnancy
TT/Td – 2	4 weeks after TT – 1
TT/Td Booster	If pregnancy occur within three years of last pregnancy and two TT doses were received

1. *JE in 231 endemic districts
2. PCV in selected states/districts as per details below:
   Bihar, Himachal Pradesh, Madhya Pradesh, Uttar Pradesh (12 districts) & Rajasthan (9 districts).

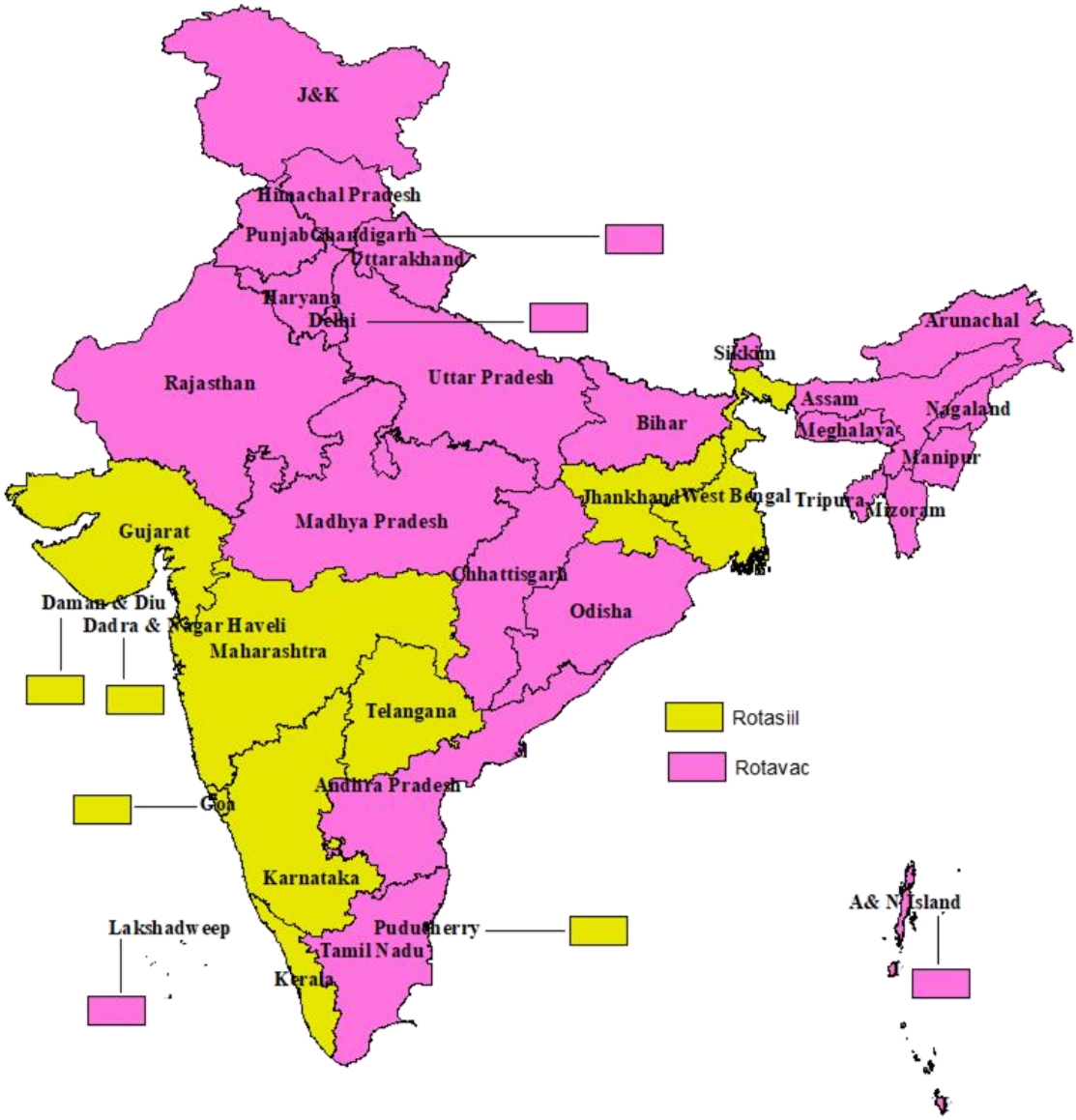
In the private Indian market, currently four rotavirus vaccines supplied by four different manufacturers are available (See Table 2). However, only two vaccines namely *Rotavac* and *Rotasiil* are used under the Universal Immunization Programme (UIP). At present, under UIP, *Rotavac* is available in 70% of Indian states and union territories (UTs) (Himachal Pradesh, Odisha, Haryana, Andhra Pradesh, Tripura, Rajasthan, Madhya Pradesh, Assam, Tamil Nadu, Uttar Pradesh, Manipur, Bihar, Sikkim, Arunachal Pradesh, Chhattisgarh, Chandigarh, Nagaland, Delhi, Punjab, Uttarakhand, Mizoram, Andaman & Nicobar Island, Meghalaya, Jammu & Kashmir and Lakshadweep) and *Rotasiil* is supplied to eleven states and UTs (30%) (Jharkhand, Daman & Diu, Gujarat, Goa, Maharashtra, Dadra & Nagar Haveli, West Bengal, Karnataka, Puducherry, Telangana, Kerala) (Refer to Figure 2). See Annexure 1 for state-wise launch dates.

Rotavac is a liquid vaccine for oral administration and is supplied with citrate buffer as a combipack. *Rotavac* is presented as 1, 5 and 10 doses in glass vial and citrate bicarbonate buffer is presented as 5 doses in glass vial. The Marketing Authorization was amended to being given without the buffer in 2018 as a Post Approval Change (PAC) from the CDSCO, the national regulatory authority.

Seven other countries namely Australia, Belgium, Germany, Italy, Latvia, Philippines and United States also have mixed rotavirus vaccination programmes, using both *Rotarix* and *Rotateq* vaccines. One study conducted to evaluate interchangeability of *RotaTeq* and *Rotarix* suggests that infants receiving mixed vaccine doses of *RotaTeq* and *Rotarix* appear to be successfully and safely immunized against Rotavirus gastroenteritis. However, evidence to evaluate performance of mixed vaccine course of *Rotavac* and *Rotasiil* are not published, although a study is being conducted in India.[22] As per the recommendations of US Advisory Committee for Immunization Practices for use of *Rotarix* and *Rotateq*, rotavirus vaccines series should be completed with the same product whenever possible, but vaccination should not be deferred because of unavailability of previously used vaccine product. In case, after a first dose of *Rotarix*, a second dose of the same vaccine is not available, two additional doses of *Rotateq* should be given. If *Rotateq* was given for the first dose and is no longer available, two additional doses of *Rotarix* should be given to make a complete three dose schedule.

[22] Payne Daniel C., Interchangeability of Rotavirus Vaccine Products, 13th International Rotavirus Symposium, Minsk, August 2018.

Figure 2: Rotavirus vaccines in use under universal immunization programme in India



India's National Technical Advisory Group on Immunization has not highlighted any safety issue regarding use of mixed vaccine course of *Rotavac* and *Rotasiil*. Hence, it has been summarized, that if a child starts the schedule with product "A" then the child should preferably complete the schedule using the same product "A". However, in case of inter-state migration, vaccination should not be deferred or denied because the product used for the previous dose (s) is unknown or is different from the product available in the state where the child's family has migrated. The 3-dose vaccination schedule will be completed using the product available in that state under the UIP.[23]

[23] Ministry of Health Family Welfare. Operational guidelines, introduction of rotavirus vaccine in universal immunization programme. March 2019.

3. Rotavirus Vaccine safety

3.1. Risk of Intussusception

Intussusception is a condition in which intestinal invagination leads to bowel obstruction. Vomiting, abdominal pain, lump in abdomen and blood in stools are the most common clinical manifestations of intussusception. In July 1999, the first licensed vaccine *Rotashield* was withdrawn from United States immunization programme because of its association with risk of intussusception approximating to 1 case of intussusception in 10,000 recipients. The risk of this critical condition was greatest after the first dose of *Rotashield*.

Thereafter, in view of intussusception seen with administration of *Rotashield*, pre-clinical trials of two next generation rotavirus vaccines *Rotateq* and *Rotarix* evaluated risk of intussusception in approximately 70,000 infants and no elevated risk was detected.[24]

In July 2007, *Rotateq* and *Rotarix* were introduced in the National Immunization Programme of Australia. Excess intussusception cases were reported in children up to 1-3 months of age receiving both vaccines.[25] The association of routine vaccination with *Rotarix* and intussusception was assessed in Brazil and Mexico using self-controlled case series and case-control methodology.[26] The study enrolled 285 infants in Mexico and 330 infant in Brazil with intussusception and a total of 2050 controls. In Mexico, an elevated risk of intussusception was found in infants during 1-7 days after vaccination with the first dose. On the other hand, in Brazil, no significant risk of was seen after the first dose but an increased risk was seen during the first seven days after the second dose of *Rotarix*.

3.2. WHO recommendations on vaccine safety

In 2005, the Global Advisory Committee on Vaccine Safety for the first time raised concern regarding association of *Rotashield* and intussusception and highlighted importance of post marketing surveillance in reviewing safety of vaccine and protocol pertaining to same was later launched by WHO in 2009.[27]

Considering the available evidences on *Rotarix* and *Rotateq* and its association with intussusception, GACVS in its annual meeting in December 2011 recommended the need of active surveillance of intussusception in African and Asian countries planning to introduce rotavirus vaccines. because the data accrued would eventually provide additional benefit–risk information related to these important vaccines.

Data from study conducted in Australia and spontaneous reporting system of United States was reviewed by the committee in 2013, following which GACVS confirmed the risk of intussusception after administering first and second dose of *Rotateq* and *Rotarix*. The risk was more specific during the first seven day following first dose. The committee reiterated the

[24] World Health Organization. Weekly epidemiological record. 1 February 2013, 88th year. No. 5, 2013, 88, 49–64

[25] Buttery JP et al. Intussusception following rotavirus vaccine administration: post-marketing surveillance in the National Immunization Program in Australia. Vaccine, 2011, 29:3061–3066.

[26] Patel MM et al. Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. New England Journal of Medicine, 2011, 364:2283–2292

[27] World Health Organization. Weekly epidemiological record. 13 January 2006, 81th year. No. 2, 2006, 81, 13–20.

need of active surveillance studies for intussusception along with rotavirus disease surveillance system.[28]

The impact of rotavirus vaccines, updated Cochrane review and data from Africa and Asia were reviewed during the committee session in 2017. Clinical trials of all the four RVV showed reduction in severe gastroenteritis by 52-94% after 1 year of follow-up. African Intussusception Surveillance Network analysed the association of *Rotarix* with intussusception using self-controlled case series model and found no risk of intussusception either after first or second dose. Similar self-controlled case series (SCCS) study in South Africa also confirms the above findings of no risk following dose 1 but slight risk was observed after dose 2 during the first seven days following vaccination. The committee also recommended assessment of risk of new vaccines by countries in which they are licensed and introduced.[29]

WHO in its guidelines on post marketing surveillance highlights the role of post marketing surveillance in identifying adverse events, association of specific vaccines with rare adverse events and their casual association with vaccination. The purpose of post-marketing surveillance is also estimate incidence of adverse events. WHO recommends active hospital/health facility-based surveillance and a stimulated passive surveillance based primarily on spontaneous reporting as the two components of routine surveillance.[30]

[28] World Health Organization. Weekly epidemiological record. 14 February 2014, 89th year. No. 7, 2014, 89, 53–60.

[29] World Health Organization. Weekly epidemiological record. 19 January 2018, 93th year. No. 3, 2018, 93, 17–32.

[30] World Health Organization. Post-marketing surveillance of rotavirus vaccine safety. March 2019. WHO/IVB/09.01.

4. Safety surveillance in India

4.1. Periodic Safety Update Reports

The erstwhile Schedule-Y of Drugs and Cosmetics Rules mandated that after approval of any "New Drug" by the Drug Controller General of India (DCGI), the Market Authorization Holders (MAH) should conduct the Post Market Surveillance (PMS) study and periodically submit the PSUR data to DCG(I) office. The PSUR shall be submitted every six months for the first two years after approval of the drug is granted to the applicant. For subsequent two years – the periodic safety update reports need to be submitted annually. The Licensing Authority (CLA) [as defined in Rule-21(b) of the said Rule) may extend the total duration of submission of PSUR if it is considered necessary in the interest of public health. Periodic safety update reports due for a period must be submitted within thirty calendar days of the last day of the reporting period. As per the 5th Schedule (meant for Post market Assessment) of "New Drugs and Clinical Trial (NDCT) rule-2019" (introduced by gazette notification on 19 March 2019, hereinafter called "Rule") has also mandated the same provisions. Now all "vaccines" are defined as "New Drugs" under Rule 122E of the said "Rule". Therefore, the provisions made under NDCT-2019 will be applicable on Vaccines for continuous monitoring, unless otherwise stated by the DCG(I).

Bharat Biotech India Ltd. (BBIL) Hyderabad, India developed *Rotavac*, Rotavirus Vaccine (Live Attenuated, Oral), that underwent extensive Phase-III, multi-centric clinical Trial on Indian Children and was subsequently licensed for manufacture and market under the trade name "*Rotavac*". The multi-centric, phase-III, efficacy and safety clinical trial on *Rotavac* was India's first and largest efficacy clinical trial on vaccines. It was successfully completed in September 2013 after a 2-year follow up of the infants. Results of this study were published in the Lancet. The Rotavirus strain (116E) was isolated from asymptomatic neonates at All India Institute of Medical Sciences (AIIMS), New Delhi (1986-88). *Rotavac* was developed as a Social Innovation Project under a public-private partnership involving highly regarded national and international organizations.

The company (MAH) M/s BBIL has submitted so far 6 PSUR for their Rotavirus (Live attenuated 116E strain, oral) vaccine, which is currently marketed under two trade names, *Rotavac* (by BBIL) and *Rotasure* (by Abbott India Limited) and both have the approved indication "for active immunization of infants from age of 6 weeks for the prevention of Rotavirus gastroenteritis".

Rotavac is currently registered in 5 countries (India, Cambodia, Mozambique, Palestine, Lebanon). Market Authorization (MA) was granted as India (30 Apr 2015), Cambodia (13 Jan 2017) and Mozambique (16.04.2018).

4.2. Adverse Event Following Immunization Surveillance

AEFI surveillance is an important component of the UIP aimed at improving vaccine safety and maintaining confidence of the community in vaccines and in the immunization programme. AEFI surveillance is part of the post marketing surveillance of vaccines. The objectives for an effective AEFI surveillance system are to identify cases and find the cause of

adverse events following vaccination. Causality assessments of AEFI can support identification of problems with vaccine lots or brands (vaccine quality defect related reactions), known and expected reactions caused due to inherent properties of a vaccine (vaccine product related reactions), events due to errors in vaccine preparation, handling, storage or administration (immunization error related reactions), known cause unrelated to the immunization (coincidental), unknown reactions and indeterminate reactions. The AEFI surveillance system also helps to maintain confidence by responding to parent/community concerns, while increasing awareness (public and professional) about vaccine risks; generating new hypotheses about vaccine reactions that are specific to the population of the country/region; estimating rates of occurrence of AEFIs in the local population compared with trial and international data, particularly for new vaccines that are being introduced into immunization programmes. Most AEFI reporting systems are passive surveillance systems with the objective of eliciting signals (adverse reaction data for patterns that suggest new safety information). The AEFI surveillance system in India is implemented as per the National AEFI Surveillance and Response Operational Guidelines- 2015 (MoHFW, GoI).

To reduce reporting bias, AEFIs are reported as minor, serious and severe AEFIs. Serious AEFIs -include any death, hospitalization, cases occurring in clusters, disability or community/parental concern cases following vaccination. Minor AEFIs are local reactions such as pain, swelling and redness at the injection site and systemic reactions are low grade or mild fever, malaise, irritability, crying, loss of appetite, etc. for two-three days following vaccination. Severe AEFIs are minor AEFIs with increased severity or serious AEFIs which would have been hospitalized normally but were not due to difficulties in access to medical care or hospitals or when domiciliary treatment is acceptable. Examples of severe AEFIs are high grade fever post vaccination which is treated at home, local pain and swelling persisting beyond 2-3 days, etc.

All AEFIs are recorded in an AEFI register at the Primary Health Centre (PHC)/health facility by Auxiliary Nurse Midwife (AMN) and medical officers. Serious and severe AEFIs are further reported in Case Reporting Forms (CRF) by the medical officer of the PHC or health facility and shared with the District Immunization Officer (DIO)/District Reproductive and Child Health Officer (DRCHO) who investigates it (findings of which are recorded in Preliminary and Final Case Investigation Formats). In cases of hospitalization, all hospital records (including case records, laboratory investigation reports, discharge summaries, etc.) should be collected and submitted with the Preliminary Case Investigation Form (PCIF) and Final Case Investigation Form (FCIF). In cases of deaths, post mortems should be encouraged and reports sent with PCIF and FCIF. In case of deaths in which there is no hospitalization and post mortem has not been done, Verbal Autopsy Format for AEFI should be filled and sent with the PCIF/FCIF. A reported adverse event can be either a true adverse event i.e. actually a result of the vaccine or the immunization process or a coincidental event which is not due to the vaccine or the immunization process but is temporally associated with immunization.

All reporting and investigation formats of serious and severe AEFIs along with supporting records and reports are shared with the experts who are members of the State AEFI

Committee. They conduct the causality assessment of the cases and decide whether it is due to the vaccine or due to other reasons. Cases are classified as per causality into coincidental cases, vaccine-product related reactions (known and expected vaccine reactions), vaccine quality defect related reactions (manufacturing issues), anxiety related reactions, programme error related reactions (due to issues with storage, transportation, handling and administration of vaccines), indeterminate cases and unknown reactions. Of these, vaccine-product related, immunization-error related and to a certain extent, anxiety related reactions are preventable.

The country's AEFI surveillance system works closely with the national drug regulator (the Drug Controller General of India, CDSCO and the Pharmacovigilance Programme of India and other partners) by sharing information related to AEFIs. The AEFI surveillance was assessed as part of the National Regulatory Authority for vaccines by the WHO in 2017 and was assessed with a Maturity Rating of 4 as per Global Benchmarking Tool of WHO. Some of the challenges of the AEFI surveillance system is awareness of process of reporting of AEFIs, under reporting of AEFI cases, poor completion of investigations at district level and quality of causality assessment at state level. The functionality of AEFI committees at district level is not being monitored by the state AEFI Committees. There is a fear of reporting of AEFIs amongst ANMs and medical officers. Recording of minor AEFIs on an electronic line-list for analysis is yet to be implemented. Some initiatives have been taken to improve reporting through a software (Surveillance and Action for Events following Vaccination), tools to monitor functioning of district AEFI committee meetings and an improved system of feedback to the states and districts based on performance indicators as well as setting up quality management systems for AEFI surveillance in states and districts.

Causality assessment is also done at the national level and the results are shared with the National AEFI Committee which sends the results of the analysed cases to the MoHFW for further action and sharing in the public domain as well as the states/districts. AEFIs are reported for all vaccines including those given in the private sector and for international travel. Adverse events which are elicited as part of studies or active surveillance are not included in the data set for AEFI surveillance as these cases were actively solicited.

As stated above, because intussusception is an event that can occur in the absence of rotavirus vaccination and is a common surgical emergency in infancy, identification of intussusception as an AEFI following rotavirus vaccination through a passive surveillance system can be challenging. Hence, when *Rotavac* was to be introduced into the country, the recommendation of the CDSCO for periodic safety updates, of the NTAGI for early implementation and monitoring under the CDSCO and MoHFW and Department of Biotechnology and ICMR and of the WHO for sentinel surveillance was considered by the vaccine development and immunization partners, and special surveillance programmes were developed.

4.3. Sentinel Surveillance by CHRD SAS

Early implementation of rollout of rotavirus vaccine in the public health system under monitoring

An Indian vaccine (*Rotavac*) based on a neonatal rotavirus strain 116E developed as a Public-Private Partnership (PPP), under the Indo-US Vaccine Action Programme completed a multicentre Phase III clinical trial in India; this vaccine was found to be efficacious (53.6%; 95% CI 35.0 to 66.9%) against severe rotavirus gastroenteritis. Licensure for production and use in India was granted to the manufacturer by the government in January 2014. The clinical trial on the efficacy of the *Rotavac* vaccine did not detect an increased risk of intussusception among vaccinated infants; however, the trial was not large enough to detect a small risk from rare side effects. The competent body of the Government of India, NTAGI, recommended a phased rollout of the indigenous rotavirus vaccine in the Indian public health system under monitoring. NTAGI and WHO recommended that it was necessary to generate adequate data to rule-out the risk of intussusception associated with the Rotavirus vaccines introduced in India using robust passive surveillance system with support from National academic institutes, government agencies and centres. The rollout was done under the oversight of an Inter-ministerial Inter-agency Steering Committee co-chaired by Secretary, Department of Biotechnology (DBT) and Secretary, Department of Health Research and Director General ICMR with the Secretariat at BIRAC of the Department of Biotechnology, Government of India. The Steering Committee (SC) included members selected by DBT, ICMR and BIRAC who reviewed the implementation plan, approved all technical decisions and convened periodic review meetings. A Project Management Committee (PMC) constituting of senior scientists and government representatives provided continued technical guidance and assistance in problem solving. The PMC was assisted by a Central unit based at the Centre for Health Research and Development, Society for Applied Studies (CHRD SAS), New Delhi. Three sites were identified for this pilot rollout of Rotavirus vaccine i.e. Vellore, Tamil Nadu; Pune, Maharashtra and Himachal Pradesh in North India. An observational study was therefore designed, the primary objective of this multi-site passive surveillance was to estimate the risk of developing intussusception (as per Brighton Diagnostic Level I Criteria) within 21 days of the first two doses of *Rotavac* vaccination using the SCCS method among Indian infants, post roll-out of Rotavirus vaccines in the public health system.

The sentinel surveillance in each state was supported by identified institutions: Christian Medical College (CMC), Vellore; KEM Hospital Research Centre (KEMHRC), Pune and CHRD SAS, Delhi.

The surveillance covered a population of over 1,83,00,000 and 6 sentinel hospitals in Tamil Nadu, over 9,00,000 and 11 sentinel hospitals in Maharashtra and 70,00,000 and 18 sentinel hospitals in Himachal Pradesh. The INCLEN provided technical assistance to the public health system for vaccine delivery process, development of training modules for future use during *Rotavac* introduction, redesigned the immunization card and trained the health professionals.

Health facility survey and health utilization surveys were conducted at all the sites to identify hospitals most often used by the population for severe illnesses in children. Systems were set

up at each hospital to ensure that information on hospital diagnosed cases of intussusception reach the team as soon as possible after diagnosis. The teams identified cases from the outpatient, wards and radiological departments. For all cases of intussusception identified, hospital records (history, clinical findings, test results, outcomes) were examined. Information on immunization history was collected independently. Documented records of age and *Rotavac* immunization were obtained through the health system for each case. All documents pertaining to the identified intussusception cases were sent to the Central Unit who then sent the same to the Rare Side Effects Case Adjudication Committee for review. The Rare Side Effects Case Adjudication Committee submitted their report after review of intussusception cases as per Brighton Diagnostic Level I Criteria. These criteria have been used globally to diagnose cases of intussusception post rotavirus vaccine introduction.

Ethical approvals were obtained from the relevant institutional review committees for providing support to the relevant State Governments and in implementing passive surveillance for identification of rare side effects after immunization, including intussusception events in sentinel hospitals.

The primary objective of this multi-site passive surveillance was to estimate the risk of developing intussusception (as per Brighton Diagnostic Level I Criteria) within 21 days of first two doses of *Rotavac* vaccination among Indian infants, post roll-out of Rotavirus vaccines in the public health system. An analysis was carried out in Stata (V 14) using the pseudo-likelihood method of the Self-Controlled Case Series with analytical models that covered the stated objectives of the study.

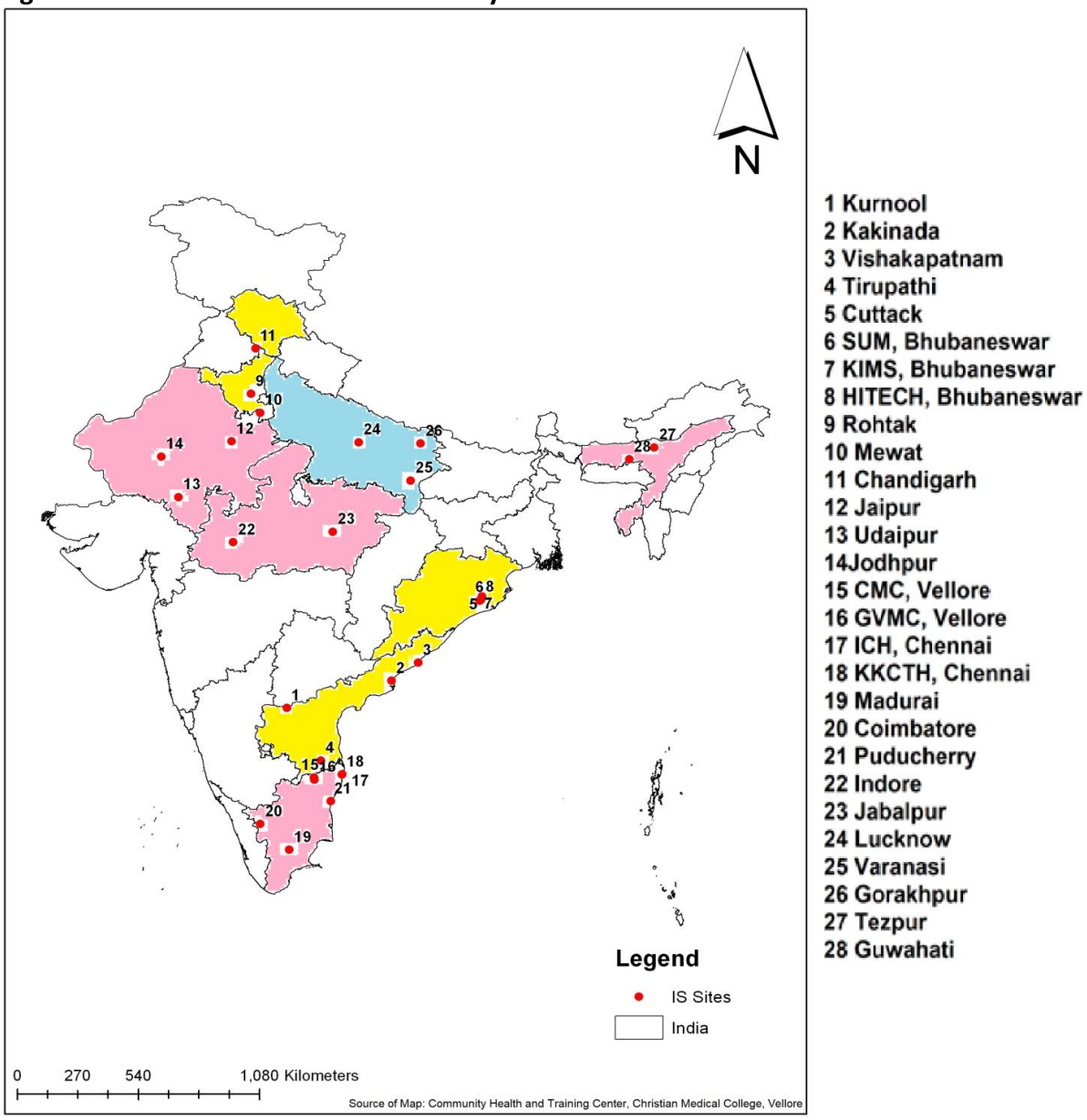
4.4. Sentinel Surveillance by THSTI

Evaluation of safety of rotavirus vaccine after introduction into universal immunization programme of India

Active intussusception surveillance was conducted at 27 sentinel hospitals located in ten states of India (See Figure 3 & Table 8). Initial establishment of surveillance started in April 2016 and was expanded to different states in a phased manner parallel to the vaccine introduction. Surveillance was conducted at tertiary care hospitals which had ability to diagnose and manage intussusception cases. All children less than two years of age with intussusception presenting to sentinel hospitals and meeting level 1 diagnostic certainty for intussusception as per Brighton collaboration criteria were eligible for recruitment. Diagnostic certainty as per level 1 Brighton collaboration criteria are the confirmation of intussusception during surgery and/or by specific radiologic findings (if reduced by pneumatic/hydrostatic/contrast enema) or at autopsy. Once an eligible case was identified, the surveillance staff completed a CRF with information on clinical features, dates of symptom onset, mode of treatment, socio-demographic characteristics and obtained a copy of ultrasound report along with image, hospital procedure/treatment notes. From the parents/guardian of enrolled children, we collected information on rotavirus vaccination status along with a copy of the vaccination record, if available. The dates of first, second and third doses of vaccination were recorded from the vaccination cards. For children with recorded vaccination history of unvaccinated or partial vaccination with *Rotavac* vaccine

(0/1/2 doses), an attempt was made to recontact the corresponding health sub-centre/primary health centre where the child was immunized to reconfirm the exact vaccination status of child for rotavirus vaccine. This study was approved by the institutional review board of Christian Medical College, Vellore and institutional ethical committees of all the participating sentinel hospitals. A written informed consent was obtained from the parents/guardians of all enrolled cases and controls.

Figure 3: Sentinel sites under THSTI Study.



Statistical analysis: To detect a relative incidence of 2, with a 21-day risk period after first dose, with 80% power and 5% level of significance, we required 263 intussusception cases vaccinated with *Rotavac*. The self-controlled case-series method was used to assess the intussusception risk after *Rotavac* administration. Incidence rate ratios of intussusception during the risk periods of 1-7 days, 8-21 days and 1-21 days post-*Rotavac* administration for doses 1, 2 and 3 were estimated. In the SCCS method, each case of intussusception acts as its

own control. The risk period was the 21 days duration after each dose of vaccination and the rest of duration was considered as control period. Pseudo-likelihood method was used to allow the contraindication of vaccination after an episode of intussusception and as per standard method, the event ascertainment was independent of vaccination status. The analysis was restricted to children aged 28-365 days at the time of symptom onset considering the minimum and maximum ages at which vaccination could be given. Children admitted with a recurrent episode of intussusception were excluded from analysis. Children whose vaccination history was confirmed were included in SCCS analysis. Children with only the parent/guardian report of vaccination history and without a photocopy of vaccination card were excluded from SCCS analysis. All children whose vaccination status could not be reconfirmed or who had received a rotavirus vaccine other than *Rotavac* were excluded from final analysis. To adjust for variations in background incidence of intussusception by age during the first one year of life, all vaccinated and un-vaccinated children were included in final analysis. The incidence rate ratios were calculated using conditional Poisson regression analysis by comparing the incidence in the risk period with the incidence in all other observational periods for each case. Age was controlled in the model using a 14-day window period. The confidence interval estimates were derived by bootstrapping with 1000 iterations. For all children included in SCCS analysis, an attempt was made to follow up at approximately 18 months of age. During follow up of children, data was collected about the vital status of child (alive/dead) after discharge from hospital, repeated episode of Intussusception and vaccination with rotavirus vaccine after an episode of Intussusception.

4.5. INCLEN Intussusception Network Surveillance Study

In view of limited information from India regarding the burden of intussusception and its regional variation, this network was established to document a reliable baseline information on intussusception epidemiology to monitor the trend over time and identify potential risk factors.

Study sites and participating hospitals: This prospective hospital-based sentinel surveillance was conducted during April 2016 to September 2017, at 19 major tertiary care hospitals considering regional representation. From the four regions (north, south, east, and west), 3-6 six hospitals including medical colleges and at least one private-sector hospital were selected through a systematic process. There were five sites from three states (Odisha, Andhra Pradesh and Haryana) where the *Rotavac* vaccine was introduced under universal immunization program in Phase 1.

Case definition, case selection and data collection: Children aged >1month and <24months admitted to the hospitals with a diagnosis of intussusception were recruited. All the patients admitted were actively screened to identify suspected cases, who were followed to document the final diagnosis and identify the confirmed intussusception cases. The confirmed intussusception cases were recruited after informed consent from parent or legally authorized representative. For the recruited cases, the data on clinical features, hospital course, treatment and outcome, socio-demography, and immunization from definite source document were collected. The cases were reviewed by an independent case adjudication

committee (paediatrician, paediatric surgeon, and radiologist) to assign the diagnostic certainty level, according to Brighton Collaboration criteria.[31]

Quality Assurance: Multilevel quality assurance and data quality-checking processes were put in place to ascertain protocol adherence, rigor and completion of surveillance at all sites. The data team reviewed all the CRFs from the sites and any data-related query was resolved with the site teams with reference to the source documents. Each site was visited by external experts to assess the case surveillance and tracking, consent, and data extraction quality and completeness. The TAG members checked data extracted in CRFs for few randomly identified cases with the clinical case sheets to assess their completeness and quality. Subsequently members from the core team visited the study sites and checked the admissions for the study period from the medical records section using diagnoses and International Classification of Diseases (ICD) codes (ICD-9/10, whichever used), to identify any missed cases. The detailed methodology has been published earlier.[32]

[31] Bines JE, Kohl KS, Forster J, Zanardi LR, Davis RL, Hansen J, et al. Acute intussusception in infants and children as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine. 2004 Jan;22(5–6):569–74.

[32] Das M, Arora N, Bonhoeffer J, Zuber P, Maure C. Intussusception in Young Children: Protocol for Multisite Hospital Sentinel Surveillance in India. Methods Protoc. 2018 Mar 22;1(2):11.

5. Findings/ Result

5.1. Periodic Safety Update Reports

The firm BBIL has conducted PMS studies from Feb 2015 to Aug 2018 and the study is reported to be an ongoing activity with active surveillance for detection and reporting of adverse events (AE). In each visit, vaccine was administered, followed by observation in the clinic for 30 minutes for any immediate adverse events. Diary cards were filled up by parents/caregivers for 07 days following vaccine administration. PMS forms were filled out by doctors/designees and were collected by marketing team of BBIL at periodic intervals for transmission to central database and analysis. So far, during the reporting periods of these PSUR, there have been no regulatory actions or manufacturer actions related to Vaccine safety and no changes made in RSI.

Table 4: ADRs reported in PSURs

S.No.	PSUR interval	Patient Exposure
1	April 2015 to October 2015	4,36,982
2	November 2015 to April 2016	3,78,752
3	May 2016 to October 2016	7,84,053
4	Nov 2016 to April 2017	8,274,079
5	May 2017 to April 2018	3,871,182
6	May 2018 to April 2019	30,027,683

So far, the following data have been summarized in Table 5:

Table 5: Summary of Adverse Events reported in PSURs (2016-2018)

	Total	**1st dose**	**2nd dose**	**3rd dose**
SAEs	0	0	0	0
Case surveyed	4345	-	-	-
AEs (overall)	960 (22.12 %)	382 (8.80%)	322 (7.42 %)	256 (5.90%)
Fever	638 (14.7 %)	261 (6.01%)	204 (4.70 %)	173 (3.99 %)
Irritability	102 (2.35 %)	26 (0.60 %)	42 (0.97 %)	34 (0.78 %)
Vomiting	109 (2.51 %)	50 (1.15 %)	35 (0.81 %)	24 (0.55%)
Diarrhoea	65 (1.5 %)	30 (0.69 %)	21 (0.48 %)	14 (0.32 %)
Other (Spitting)	17 (0.39 %)	5 (0.12 %)	7 (0.16 %)	5 (0.12 %)
Other (Rash)	19 (0.44 %)	9 (0.21 %)	5 (0.12 %)	5 (0.12 %)
Urticaria	1 (0.02 %)	0 (0.00 %)	0 (0.00 %)	1 (0.02 %)
Headache	2 (0.05 %)	0 (0.00 %)	2 (0.05 %)	0 (0.00 %)
Pain	7 (0.16 %)	1 (0.02 %)	6 (0.14 %)	0 (0.00 %)

Conclusion: Based on the available information, it can be concluded that the *Rotavac* (Live Attenuated, Oral) Rotavirus Vaccine appears to be safe, well tolerated in healthy infants. Based on this review of post-licensure safety information; the benefits of vaccination to prevent the majority of *Rotavac* cases continue to far outweigh its risks.

5.2. Adverse Event Following Immunization Surveillance

Two cases of intussusception were reported following *Rotavac* vaccination. The summary of the two cases is as follows:

Case 1: A three and half months old male child received second dose of Pentavalent, *Rotavac* and Oral Polio vaccine on 8th Dec 2016 at 11 am. After 6 days of vaccination (on 14th Dec

2016), the child developed abdominal distension and excessive crying. The child was admitted to a hospital on 15th Dec 2016 where the child was diagnosed as a case of intussusception complicated with intestinal obstruction using real-time ultrasonography of the abdomen. The child was also found to have hypothyroidism. Intussusception was treated with hydrostatic reduction. Child recovered and discharged and started on thyroxine.

Past history: The child had constipation since one month of age and was prescribed syrup lactulose.

Birth history: Full term normal delivery at hospital, birth weight - 2.5 kg

Valid diagnosis: Intussusception

Causality classification: A1

Case 2: A five months old female child received third doses of Penta, *Rotavac*, Oral Polio Vaccine (OPV) and Inactivated Polio Vaccine (IPV) on 21st April 2018 at 10 am. Next day morning child developed vomiting initially followed by vomiting and blood in stool. Child was hospitalized on 24th April 2018. An ultrasound of the abdomen showed ileocolic intussusception. Reduction of intussusception was done under General Anaesthesia (GA). Child recovered and has been discharged.

No significant past history.

Valid diagnosis: Intussusception

Causality classification: A1

5.3. Sentinel Surveillance by CHRD SAS

Figure 4: Flowchart of intussusception cases among infants

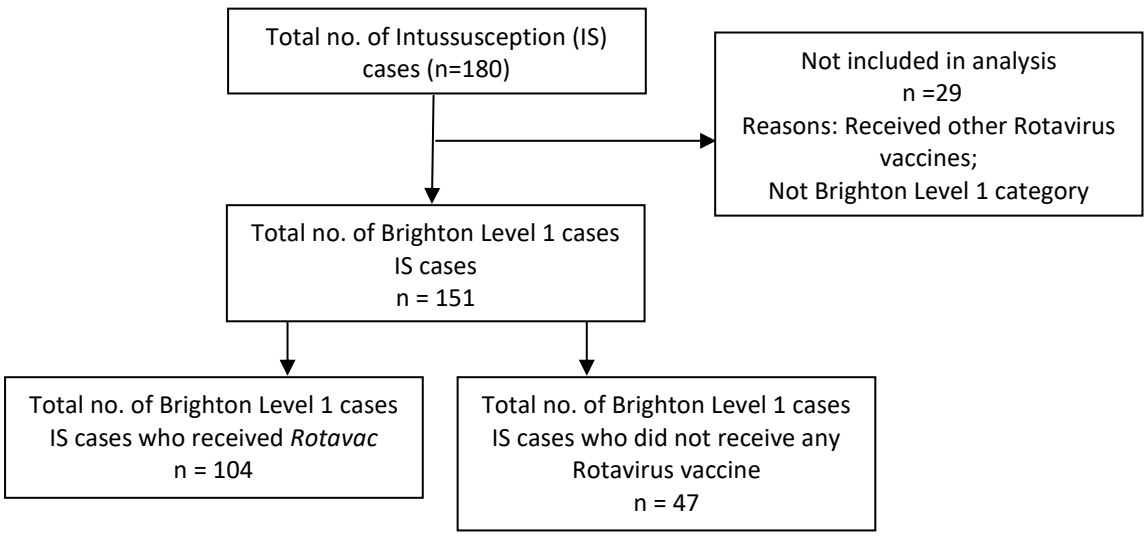


Table 6. Baseline Characteristics of Infants with Brighton Level 1 Intussusception

Variables	All Brighton level 1 IS cases n = 151
Age of onset in days: Median (IQR)	227 (78, 364)
Gender: Female: n (%)	36 (23.8%)
Location of the Intussusceptum	
Ileo-colic	89
Colo-colic	4
Ileo-caecal	1
Ileo-ileal	3
Ileo-colo-colic	1
Not defined	6

Table 7. Cases of intussusception in relation to first, second and third *Rotavac* vaccine doses

Doses and Interval periods	**Total No. of Brighton Level 1 IS cases who received *Rotavac*/*Rotasure* (N = 104)**
1st Dose	
1-7 days	0
1-21 days	1
Additional IS cases after 21 days of 1st dose and before 2nd dose	7
2nd Dose	
1-7 days	0
1-21 days	2
Additional IS cases after 21 days of 2nd dose and before 3rd dose	7
3rd Dose	
1-7 days	1
1-21 days	10
Additional IS cases after 21 days of the 3rd dose	77

Interpretation of analysis: Our analysis using the SCCS methodology showed no significant risk of IS in any of the risk windows (1-7 days or 1-21 days following immunization) after each dose individually or doses 1 and 2 combined or all three doses combined.

5.4. Sentinel Surveillance by THSTI

Table 8: Site-wise enrolment details of Intussusception cases among children less than two years from April 2016 to June 2019

Hospital name	City, state	Vaccine introduction date	Surveillance period	No. of cases enrolled in surveillance	No. of cases included in the SCCS analysis
Kurnool Medical College	Kurnool, Andhra Pradesh	20 Apr 2016	01 Jun 2016-30 Jun 2019	22	13
Government General Hospital and Rangaraya Medical College	Kakinada, Andhra Pradesh	20 Apr 2016	01 Aug 2017-30 Jun 2019	8	8
King George Hospital and Andhra Medical College	Vishakhapatnam, Andhra Pradesh	20 Apr 2016	01 Jul 2016-30 Jun 2019	12	11
Sri Venkateshwara Medical College	Tirupati, Andhra Pradesh	20 Apr 2016	01 Jul 2016-30 Jun 2019	20	13
Sardar Valla Bhai Patel Post Graduate Institute of Paediatrics	Cuttack, Odisha	26 Mar 2016	15 Apr 2016-30 Jun 2019	80	58
Kalinga Institute of Medical Sciences	Bhubaneswar, Odisha	26 Mar 2016	01 Oct 2016-30 Jun 2019	27	14

Institute of Medical Sciences and SUM Hospital	Bhubaneswar, Odisha	26 Mar 2016	1 Dec 2016-30 Jun 2019	11	6
Hi-Tech Hospital	Bhubaneswar, Odisha	26 Mar 2016	02 Feb 2017-30 Jun 2019	5	2
Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences	Rohtak, Haryana	11 Apr 2016	02 Jul 2016-30 Jun 2019	21	16
Shaheed Hasan Khan Mewati Government Medical College	Mewat, Haryana	11 Apr 2016	20 Feb 2016-30 Jun 2019	5	2
Post Graduate Institute of Medical Education and Research	Chandigarh	11 Apr 2016	19 Sept 2016-30 Jun 2019	198	101
Malankara Orthodox Syrian Church Medical College Hospital	Kolencherry, Kerala	No vaccine	1 Aug 2016-30 Jul 2018	29	18
Christian Medical College	Vellore, Tamil Nadu	20 Sep 2017	20 Sept 2017-30 Jun 2019	36	20
Government Vellore Medical College	Vellore, Tamil Nadu	20 Sep 2017	20 Sept 2017-30 Jun 2019	2	1
Kanchi Kama Koti Child Trust Hospital	Chennai, Tamil Nadu	20 Sep 2017	20 May 2017-30 Jun 2019	77	26
Institute of Child Health	Chennai, Tamil Nadu	20 Sep 2017	20 Jul 2017-30 Jun 2019	93	61
Coimbatore Medical College	Coimbatore, Tamil Nadu	20 Sep 2017	21 Aug 2017-30 Jun 2019	18	12
Government Rajaji Hospital and Madurai Medical College	Madurai, Tamil Nadu	20 Sep 2017	26 Dec 2017-30 Jun 2019	23	18
Jawaharlal Nehru Institute of Post-graduate Medical Education & Research (JIPMER)	Puducherry	No Vaccine	27 Sept 2017-30 Jun 2019	38	26
Sawai Man Singh Medical College	Jaipur, Rajasthan	23 Mar 2017	17 Aug 2017-30 Jun 2019	98	73
Rabindranath Tagore Medical College	Udaipur, Rajasthan	23 Mar 2017	25 Aug 2017-30 Jun 2019	20	12
Dr. Sampurnanand Medical College	Jodhpur, Rajasthan	23 Mar 2017	01 Aug 2017-30 Jun 2019	46	23
Mahatma Gandhi Memorial Medical College	Indore, Madhya Pradesh	03 Apr 2017	24 Aug 2017-30 Jun 2019	24	17
Mangala Hospital & Research Centre	Bijnor, Uttar Pradesh	16 Jul 2018	01 Nov 2018-30 Jun 2019	0	0
King George Medical College	Lucknow, Uttar Pradesh	16 Jul 2018	20 Jul 2017-30 Jun 2019	28	16
Institute of Medical Sciences, Banaras Hindu University	Varanasi, Uttar Pradesh	16 Jul 2018	21 Apr 2018-30 Jun 2019	10	6
Government Medical College	Guwahati, Assam	14 Jun 2017	15 Mar 2018-30 Jun 2019	19	16
Total				970	589

Table 9: Socio-demographic and clinical characteristics of infants with Brighton Level 1 Intussusception

Variable	Category	Frequency (%)
Age	1-5 months	219 (37%)
	6-11 months	370 (63%)
Gender	Female	196 (33%)
	Male	393 (67%)
Clinical features	Fever	202 (34%)
	Vomiting	438 (74%)
	Diarrhoea	240 (41%)
	Blood in stools	481 (82%)
	Constipation	55 (9%)
	Abdominal pain	481 (82%)
Location of Intussusception	Ileo-colic	498 (84%)
	Ileo-ileal	33 (6%)
	Colo-colic	22 (4%)

	Compound	17 (3%)
	Unknown	19 (3%)
Treatment modality	Hydrostatic/pneumatic reduction	200 (34%)
	Surgical reduction	321 (54%)
	Intestinal resection	68 (12%)
Treatment outcome	Survived (Discharged home)	583 (99%)
	Died	6 (1%)

Figure 5: Cases of intussusception occurring in the 1-60 days after dose 1, dose 2 and dose 3 of *Rotavac* vaccine in India from April 2016 through June 2019

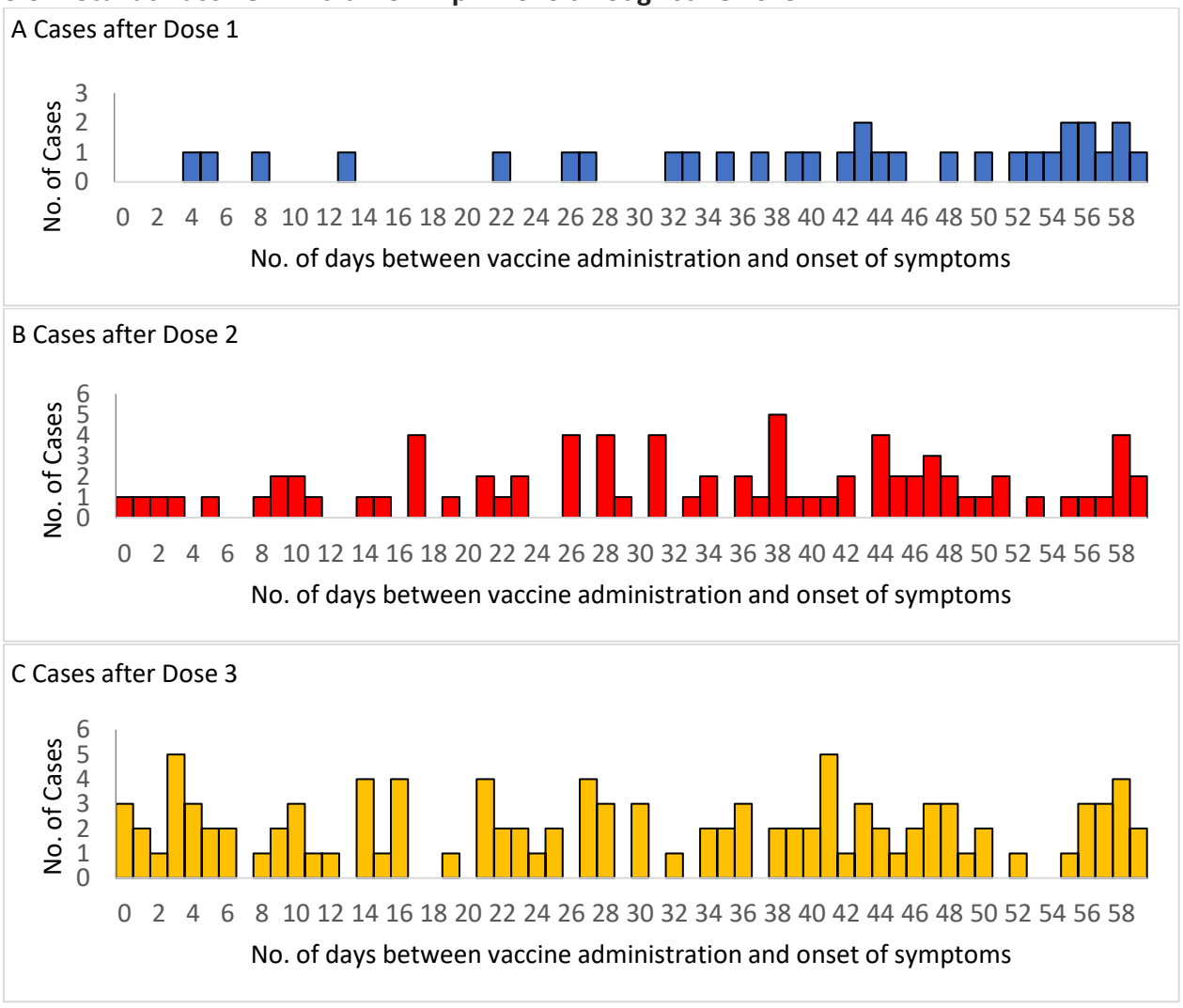


Table 10: Cases of intussusception in relation to first, second and third *Rotavac* vaccine doses

Doses and Interval periods	Total No. of Brighton Level 1 IS cases who received *Rotavac*/*Rotasure*(N = 589)
1st Dose	
1-7 days	2
1-21 days	4
Additional IS cases after 21 days of 1st dose and before 2nd dose	61
2nd Dose	

Doses and Interval periods	Total No. of Brighton Level 1 IS cases who received *Rotavac*/*Rotasure*(N = 589)
1-7 days	4
1-21 days	15
Additional IS cases after 21 days of 2nd dose and before 3rd dose	47
3rd Dose	
1-7 days	15
1-21 days	22
Additional IS cases after 21 days of the 3rd dose	181

The analysis using the SCCS methodology showed no significant risk of IS in any of the risk windows (1-7 days or 1-21 days following immunization) after each dose individually or doses 1 and 2 combined or all three doses combined.

5.5. INCLEN Intussusception Surveillance Network Study

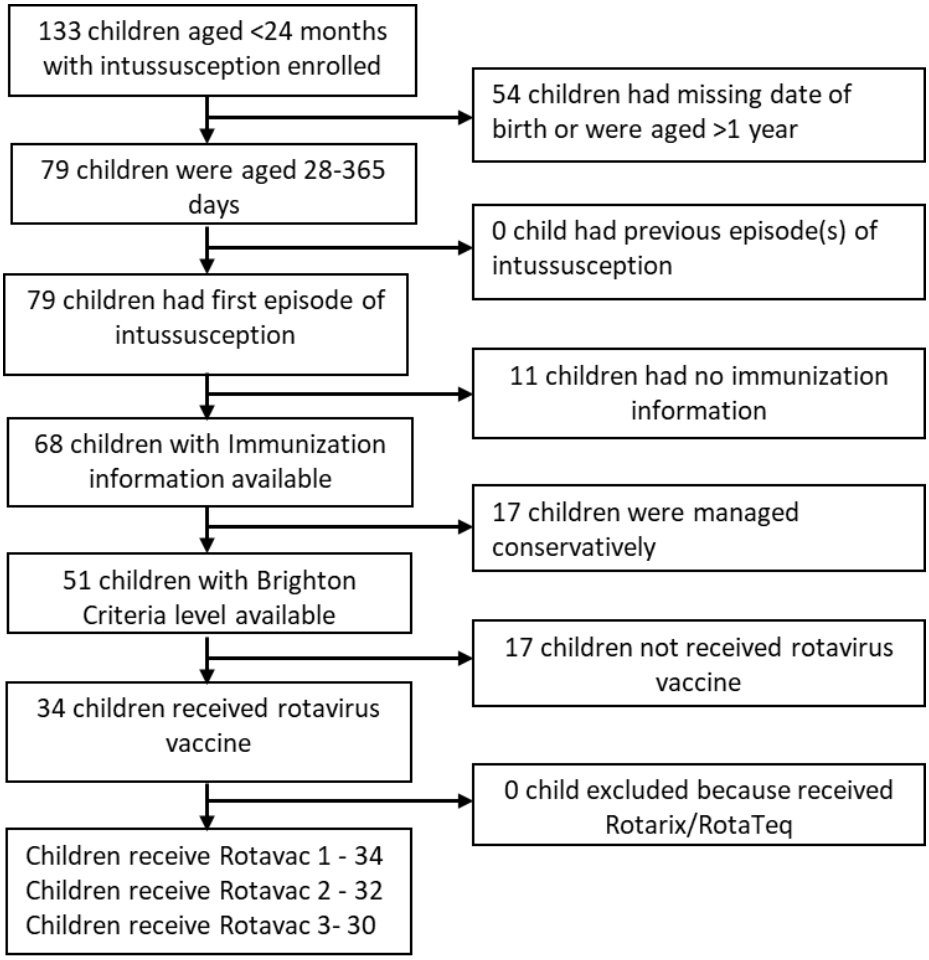
We present the data from the five sites in the states where *Rotavac* was introduced under the UIP.

Brief demographics (ages, gender and location of IS): At the five sites in the states with RVV under UIP, a total of 133 children aged less than two years with intussusception diagnosis were recruited. The male-female ratio was 2:1. The children aged 2-6 months, 7-12 months, 13-18 months and 19-24 months were 46, 51, 24 and 12 respectively. The overall median age was 8 months (Interquartile Range - IQR 5, 13). There was some seasonal variation observed with higher number of intussusception cases during March to June months or the year.

Clinical, management and outcome: The median interval of symptoms was 2 days. Passage of blood-stained stool was the commonest symptom (66.9%), followed by vomiting (65.4%; bilious in 24.1%), abdominal pain (61.7%), excessive crying (51.1%), abdominal distention (24.8%) and fever (18.7%). The classical symptoms triad of intussusception (abdominal pain, vomiting and blood in stools) was observed in 25.5% cases. On examination at the hospitals, blood on per-rectal examination (35.3%), abdominal distention (23.3%), abdominal mass (13.5%), and abdominal tenderness (9.8%) were observed. Ultrasound was the commonest mode of diagnosis (97%) and few (3%) were diagnosed on laparotomy. Ileocolic (88%) was the commonest intussusception site. Pathological lead point was documented in 4.5% cases and lymph nodes were the commonest. Half of the cases (51.9%) were managed by surgery, 30% cases by reduction and 18% were conservatively managed. Out of the cases underwent surgery, 20.3% required resection of bowel. The median interval to presentation for surgical cases (2 days; IQR 1, 3) was longer than those who had reduction (1 day; IQR 1, 3). The indications for surgery were failed reduction (7.2%), late presentation (79.7%) and associated complications (13.1%). Most of the cases recovered and only 2 cases (1.5%) died. The causes of death were post-surgical sepsis, shock and multiorgan failure. The median periods of hospital stay for cases who underwent surgery, reduction and conservative management were 7 days (IQR 5, 9), 2 days (IQR 1, 2) and 3 days (IQR 2, 5), respectively. According to the Brighton diagnostic criteria, 89.1% cases were labelled as Level 1 followed by 7.6% as Level 2. No case was categorised as Level 3 and 3.4% cases did not fit into any level.

Immunization exposure status (flowchart): Definite vaccination documentation was available for 100 (75.2%) children and 84 (63.1%) children had no RVV exposure. For documentation of the intussusception during different risk periods after vaccine exposure, we considered the children aged >1 month and <12 months. The flow chart of selection of cases for analysis is shown in figure 6.

Figure 6: Flow diagram for children included in the analysis



IS after rotavirus vaccine exposure: There were no cases observed within the risk period after dose 1. After dose 2, only one case occurred in the 8-21 days window. After dose 3, one and seven cases were observed in the 1-7 and 8-21 window periods. It is to be noted that the median age of third dose was 115 days (IQR 109-125), which overlaps with the age of natural occurrence of intussusception (Refer to Table 11).

Table 11: Cases of intussusception in relation to first, second and third *Rotavac* vaccine doses

Doses	No. of IS cases
1st Dose	
1-7 days	0
1-21 days	0
Additional IS cases after 21 days	2
2nd Dose	
1-7 days	0
1-21 days	1
Additional IS cases after 21 days	1
3rd Dose	
1-7 days	1
1-21 days	7
Additional IS cases after 21 days	21

6. Discussion

Intussusception is a rare event and occurs in children, mainly during the first year of life, even without exposure to rotavirus vaccine. So far, post-marketing surveillance studies with the multi-national manufacturers' products have shown a low-level risk of intussusception with both products. However, a recent study from several sites and countries in Africa reported that no risk was seen with *Rotarix*, the monovalent vaccine manufactured by GlaxoSmithKline.

While medical records in most high income countries are patient based, thus making analysis of safety events more easily feasible, surveillance for rare AEFIs or those with low level of risk can be challenging in settings where medical records are not electronic, where there are multiple sources of care or access is poor and events following immunization may not linked in time or by healthcare facility. Where strong linked information is not available, the WHO has recommended establishment of sentinel surveillance for linked to new vaccine introduction, such that safety of the vaccine can be evaluated after implementation. India has conducted sentinel surveillance for intussusception using multiple approaches to document *Rotavac* vaccine safety. Collaborative efforts and the Smart Safety Surveillance allowed synthesis of multiple datasets which provide reassurance on *Rotavac* safety.

The key points in consideration of the collated data are:

- Intussusception is a rare event and when presumed to be causally linked to rotavirus vaccination occurs 3-14 days after the first dose, which is outside the immediate window usually reported for AEFIs and PSURs.
- Intussusception is a surgical emergency and is usually managed at healthcare facilities which do not provide immunization and are unlikely to recognise or collect data relating the event in time to the immunization. Hence active efforts to collect immunization data collection is required in sentinel surveillance.
- Individual causality assessment is challenging, since the timing of the later doses of rotavirus vaccination overlaps with the period when intussusception is commonly seen in infancy in the absence of rotavirus vaccination. There are no biological tests that distinguish vaccination-related and unrelated cases of intussusception.
- Smart safety surveillance allowed synthesis of multiple datasets, with high data quality from the sentinel surveillance systems which provide reassurance regarding the safety of the *Rotavac* vaccine. Two studies (SAS and THSTI) were powered to conduct the self-controlled case series analysis and have reported that there is no increase in cases in the 1-7 days, 8-21 days and 1-21 days windows.

The clinical case definition for the diagnosis of acute intussusception in infants and children was developed following recommendations of a meeting organised by the World Health Organization, Geneva, and through consensus of the Brighton Collaboration Intussusception Working Group (Bines et al., 2004). This definition provided a case definition that is suitable for use in studies conducted in different geographical regions with different health-care facilities and resources and was validated in a developed and developing country setting (Bines et al., 2006). The Brighton clinical case definition for intussusception has been endorsed by the CIOMS/WHO Working Group on Vaccine Pharmacovigilance (Brighton

Collaboration, 2007), and formed the basis of the safety assessment of the *Rotavac* vaccine during the efficacy studies and during the post-marketing surveillance reported here.

Causality assessment requires consideration of the strength of association, consistency, specificity, biologic plausibility, coherence, experimental evidence and analogy (WHO, 2001). The clearest and most reliable way to determine whether an adverse event is causally related to vaccination is by comparing rates of the event in vaccinated and non-vaccinated groups in a randomized clinical trial. It is important to note that causality associations cannot usually be confirmed from reports of individual cases without definitive laboratory studies; nonetheless causation may be suspected if there is definite evidence of an increased risk of the event in vaccinated persons.

In many countries where baseline (pre-introduction of rotavirus vaccines) rates of intussusception are available, countries have tracked rates of intussusception in vaccinated and unvaccinated individuals as well as against historical rates. However, in countries where no baseline data are available, this is not feasible, and hence observational studies, such as the self-controlled case series, are helpful in assessing risk in a vaccinated population (Murphy et al., 2001). However, establishing a systematic review of serious adverse events to determine the likelihood of a causal association between an event and the vaccine received can contribute to the analysis of data collected in routine post-marketing surveillance. It can assist in distinguishing true adverse reactions from coincidental events, increase credibility in the surveillance programme, and assist in making decisions on further action needed.

In view of the past experience with rotavirus vaccines, both with respect to the risk of adverse effects and varying efficacy in different settings, countries planning to introduce rotavirus vaccines are encouraged to develop a system of post-marketing surveillance for these vaccines. Such a system requires coordination between the national regulatory authority, the national immunization programme, and the relevant vaccine manufacturer(s), and may also involve collaboration with academic partners. Since there is substantial variability in the quality of post-marketing surveillance systems in different countries and in data regarding vaccine safety obtained from routine surveillance systems, making data difficult to interpret and inadequate to guide vaccination policy. In recognition of these issues, the WHO Global Advisory Committee on Vaccine Safety and other expert groups recommended a standardized approach to address potential safety issues to accompany the introduction of rotavirus vaccines, particularly in developing countries where the capacity to support post-marketing surveillance activities may be limited. Under the Smart Safety Surveillance project, all the routine reporting systems as well as those established for the purpose of sentinel surveillance as recommended by WHO were brought together to evaluate safety signals through all data sources to enhance the quality of safety data available at the population level.

In all studies, over 1500 cases of intussusception were analysed. The majority of the intussusception cases were observed during 4-10 months of age, a part of the period overlaps with the age of primary doses of rotavirus vaccination. Nonetheless, self-controlled case series analysis demonstrated no increased risk of intussusception associated with *Rotavac* vaccination in two separate analyses. The synthesis of routine data and systematically

designed studies adopting sound methodology in India has brought together all stakeholders in immunization safety to demonstrate that Smart Safety Surveillance can leverage multiple data sources to provide reassurance on the safety of a new vaccine.

7. Annexure

Annexure 1

Date of Introduction of rotavirus vaccine in 36 States and UTs of India.

S. No.	State Name	Date of Introduction	Phases
1	Himachal Pradesh	15th March 2016	**Phase 1**
2	Odisha	6th April 2016	
3	Haryana	13th April 2016	
4	Andhra Pradesh	22nd April 2016	
5	Tripura	18th February 2017	**Phase 2**
6	Rajasthan	23rd March 2017	
7	Madhya Pradesh	2nd April 2017	
8	Assam	14th June 2017	
9	Tamil Nadu	17th September 2017	
10	Jharkhand	7th April 2018	**Phase 3**
11	Uttar Pradesh	4th September 2018	
12	Manipur	22nd June 2019	**Phase 4**
13	Daman & Diu	26th June 2019	
14	Gujarat	1st July 2019	
15	Bihar	3rd July 2019	
16	Sikkim	3rd July 2019	
17	Arunachal Pradesh	6th July 2019	
18	Chhattisgarh	11th July 2019	
19	Maharashtra	20th July 2019	
20	Goa	25th July 2019	
21	Dadra & Nagar Haveli	25th July 2019	
22	Chandigarh	31st July 2019	
23	Nagaland	2nd August 2019	
24	Delhi	6th August 2019	
25	Punjab	7th August 2019	
26	Uttarakhand	7th August 2019	
27	Mizoram	7th August 2019	
28	Andaman & Nicobar Island	8th August 2019	
29	Meghalaya	16th August 2019	
30	West Bengal	21st August 2019	
31	Karnataka	26th August 2019	
32	Jammu & Kashmir	28th August 2019	
33	Puducherry	29th August 2019	
34	Lakshadweep	4th September 2019	
35	Telangana	5th September 2019	
36	Kerala	6th September 2019	