ROTAVAC 5D®

NEONATAL · NATURALLY ATTENUATED
ORAL HUMAN ROTAVIRUS (116E) VACCINE

WHO-PREQUALIFIED

WORLD'S 1ST ASSURED 5D PROTECTION

PROVEN EFFICACY • UNPARALLELED SAFETY

BHARAT BIOTECH

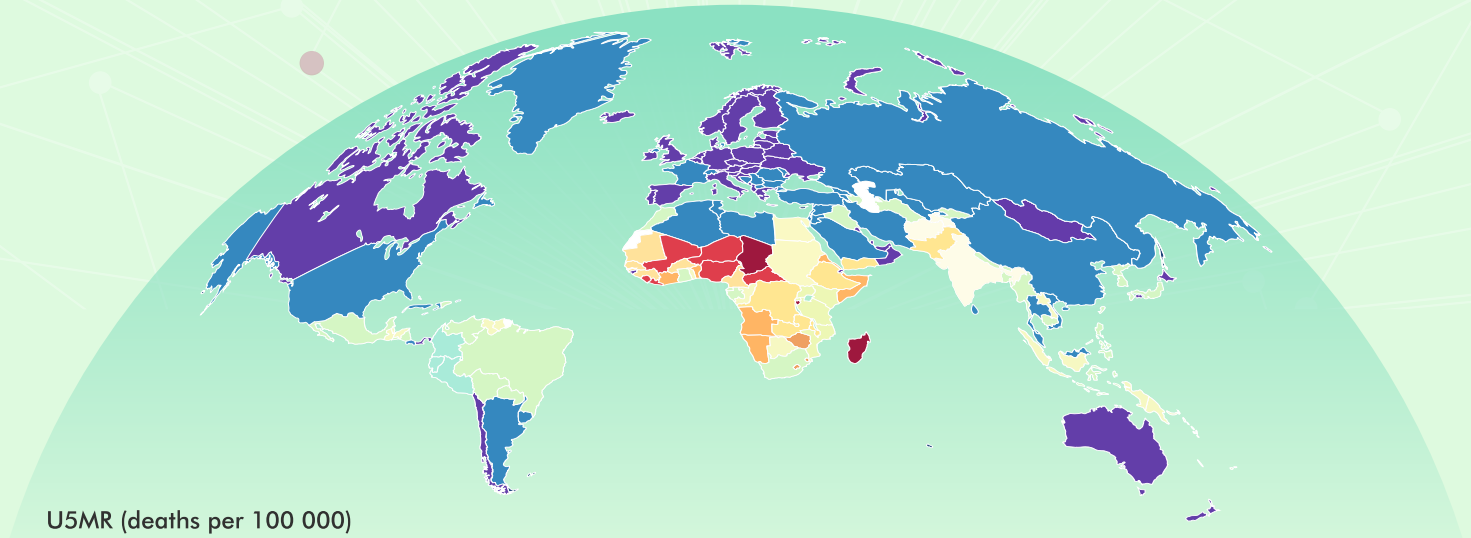
Introducing

ROTAVAC 5D®

Proven Efficacy · Unparalleled Safety

DIARRHEA
COMMON ILLNESS - GLOBAL KILLER

Globally diarrhea is the 5th leading cause of death amongst children <5 years with ~446 000 deaths annually.[1]



U5MR (deaths per 100 000)

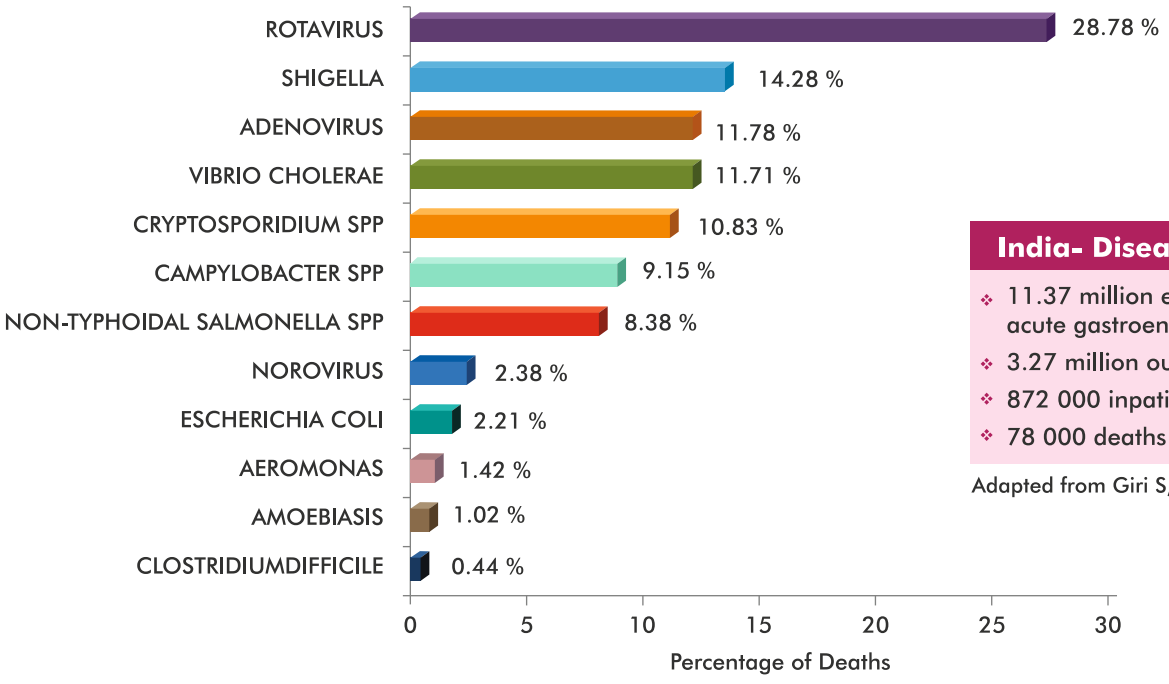
<1	1-4	5-9	10-24	25-49	50-99	100-149	150-199	200-299	300-499	≥500

U5MR, Under-Five Mortality Rate.

Adapted from GBD 2016 Diarrhoeal Disease Collaborators, (Revised 2018).[1]

ROTAVIRUS - THE LEADING CAUSE OF DIARRHEAL MORTALITY (<5 YEARS OF AGE)

GLOBAL ROTAVIRUS IMPACT



India- Disease Burden[2]

- 11.37 million episodes of acute gastroenteritis (AGE)
- 3.27 million outpatient visits
- 872 000 inpatient admissions
- 78 000 deaths

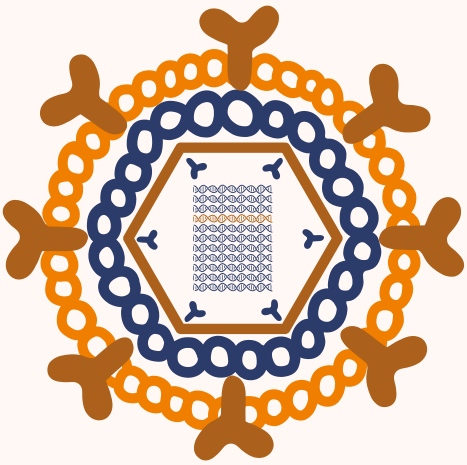
Adapted from Giri S, et al. 2019.[2]

Adapted from GBD 2016 Diarrhoeal Disease Collaborators, (Revised 2018).[1]

VACCINATION - THE BEST TOOL TO PREVENT ROTAVIRUS INFECTION

ROTAVAC 5D®- THE G9P[11] STRAIN (116E)

neonatal Human Rotavirus Vaccine (nHRV)[3]



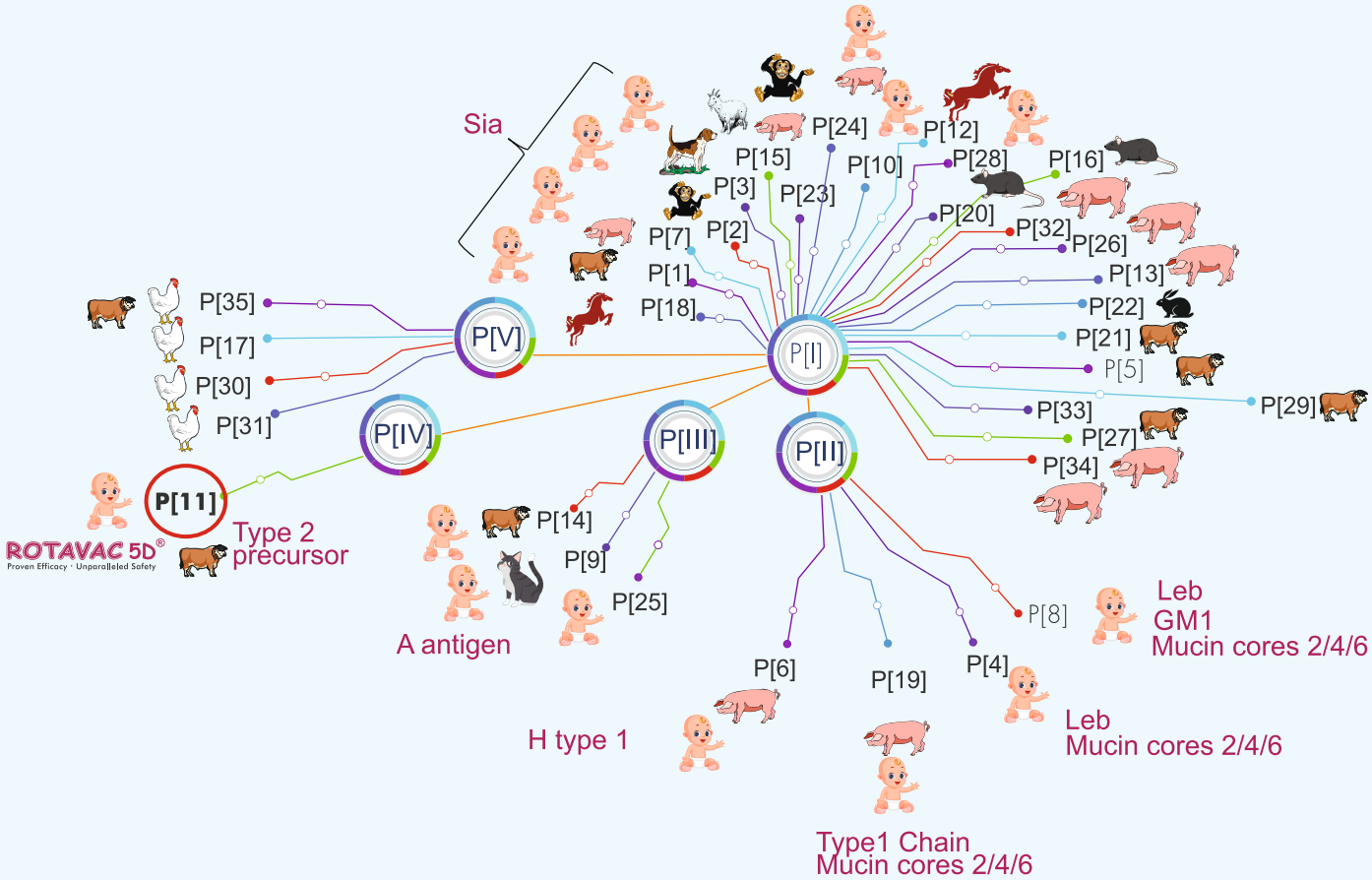
VP4
VPI/VP3
VP2
VP6
VP7
dsRNA — Human origin
dsRNA — Bovine origin

Naturally reassortant, attenuated & asymptomatic[3]

Adapted from Das BK, et al. 1994.[3]

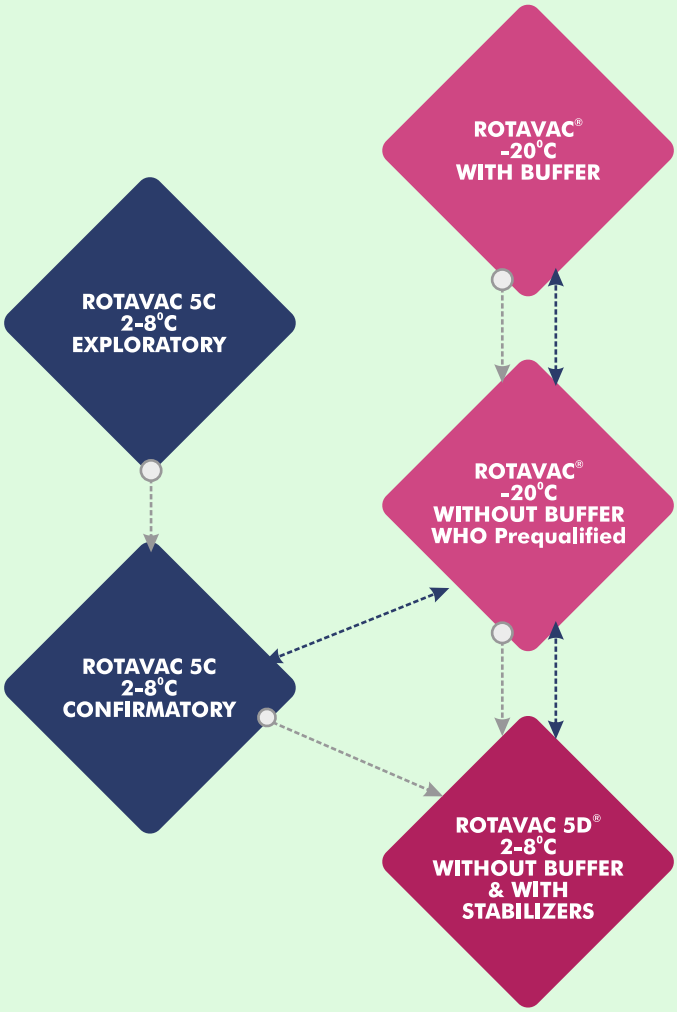
ROTAVAC 5D® - PROTECTS FROM BIRTH

ROTAVAC 5D® protects against rotavirus infection from birth (i.e. neonates and infants) since P[11] serotype binds to developmentally regulated Histo Blood Group Antigen (HBGA) Type 2 precursor.[4]



Adapted from Jiang X, et al. 2017.[4]

ROTAVAC 5D® - DEVELOPMENTAL PATHWAY

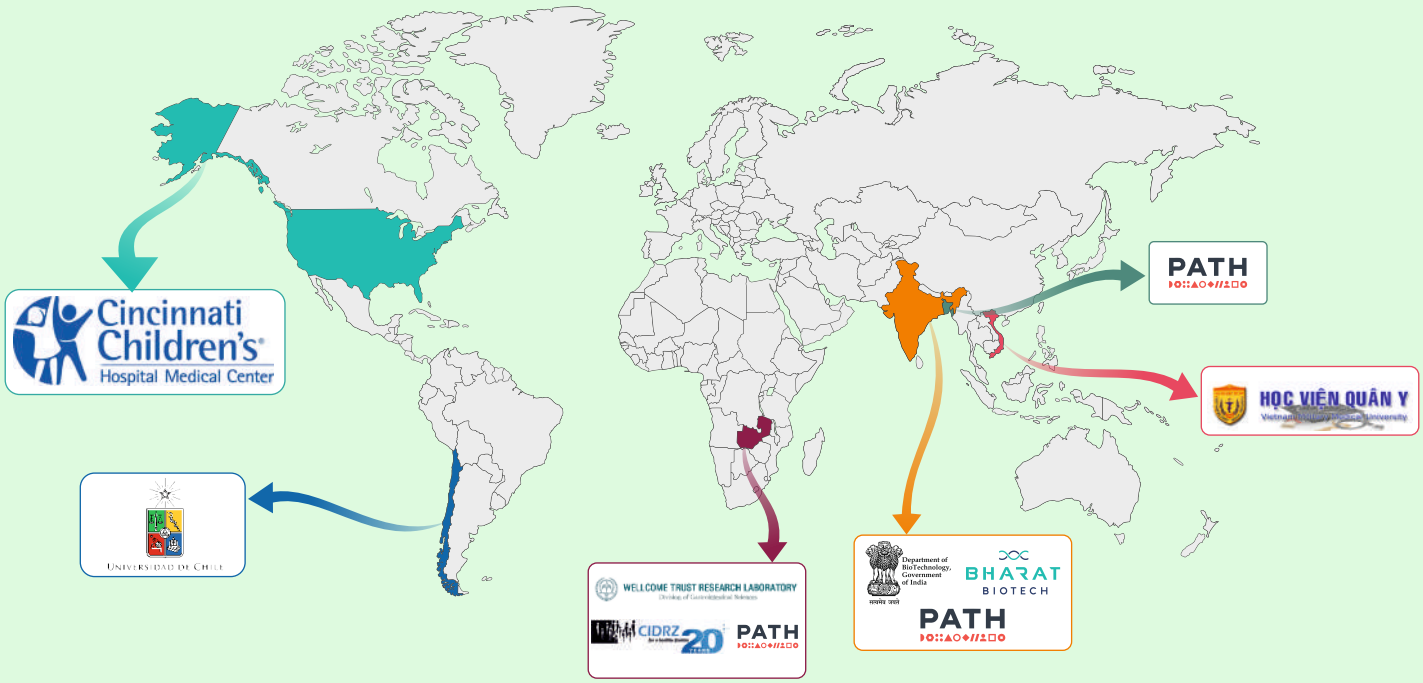


ROTAVAC 5D® is developed based on ROTAVAC® and ROTAVAC 5C formulations, is found to be equally efficacious when compared to the WHO Prequalified ROTAVAC®.

Product Development

Compared in Clinical Trials

ROTAVAC® - STUDIES ACROSS THE WORLD



ROTAVAC 5D® - ALLIED CLINICAL TRIALS

Clinical Trial	Country	Formulation	Subjects		Endpoint
Phase 3	India	ROTAVAC 5C[5] (Exploratory Phase)	Infants	675	Safety & Immunogenicity
		ROTAVAC 5C[6] (Confirmatory Phase)		1300	Lot-to-Lot Consistency
Phase 3	India	ROTAVAC 5D®[7]	Infants	360	Safety & Immunogenicity
Phase 3	India	ROTAVAC 5D®[8]	Neonates & Infants	450	Safety & Immunogenicity (Birth Dose Study)
Phase 4	India	ROTAVAC 5D®[9]	Infants	384	Lot-to-Lot & EPI Non-interference
Phase 2b	Zambia	ROTAVAC 5D®[10]	Infants	450	Safety & Immunogenicity
Phase 4	India	ROTAVAC 5D®	Infants	15000	Safety (Ongoing)

ROTAVAC 5D® - UNIQUE FEATURES

- World's first and only liquid formulation with low dose volume of 0.5 mL.
- Novel vaccine, with naturally reassortant and attenuated G9P[11] neonatal strain.
- Easy to administer with no spit-ups.
- Highly stable at 2 to 8°C.
- Easy vaccine logistics and cold chain management.
- Low biomedical waste disposal post-vaccination.
- Safe to administer concomitantly with other childhood vaccines.[11]
- Excellent efficacy in children from Rotavirus diarrhea – clinically proven through first and largest vaccine trial in India (two years efficacy study).[12, 13]
- Exhibits potential protection against RV infection from birth (i.e. neonates and infants) since P[11] serotype binds to the developmentally regulated Histo Blood Group Antigen (HBGA) precursor.[4]
- Broad heterotypic protection against global Rotavirus genotypes (G1P[8], G1P[4], G2P[4], G12P[6], G12P[8], G9P[4], G9P[8], G1P[6], G2P[6], G12P[11]).[12, 13]
- Prevents severe Rotavirus diarrhea requiring hospitalization.[12, 13]
- Infectivity/immunogenicity of ROTAVAC 5D® is enhanced with breast milk interaction (HMOs) that is specific to P[11] Rotaviruses.[14]
- A pre-filled syringe (PFS) with single dose and multi-dose glass vial presentations aiding decision making in different countries.
- Most convenient and easy to adapt under universal immunization programs by countries.
- Smart Safety Surveillance (3S) approach promoted by WHO demonstrated no increased risk of intussusception associated with ROTAVAC® in a self-controlled case series analysis.[15]

World Health Organization

ROTAVAC 5D® RECEIVES WHO PREQUALIFICATION

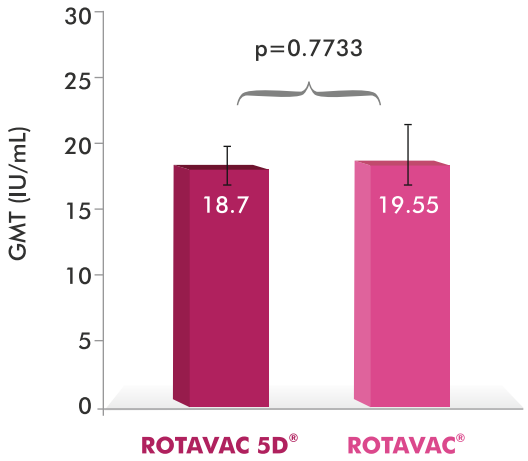
- **World's 1st** and only liquid formulation
- **Low dose** volume of 0.5mL
- Highly stable at **2-8°C**
- A **pre-filled syringe** with single dose
- First and **Largest Efficacy** trial in India

ROTAVAC 5D® - PHASE 3 CLINICAL TRIALS

ROTAVAC 5D® confers similar clinical safety and immunogenicity profiles when compared to the WHO Prequalified ROTAVAC®.[7]

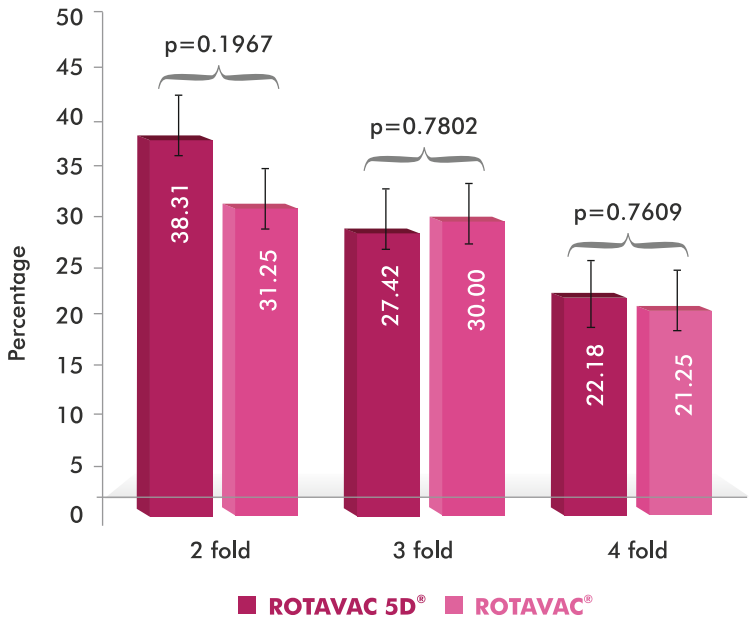
IMMUNOGENICITY

Geometric Mean Titer (GMT)*

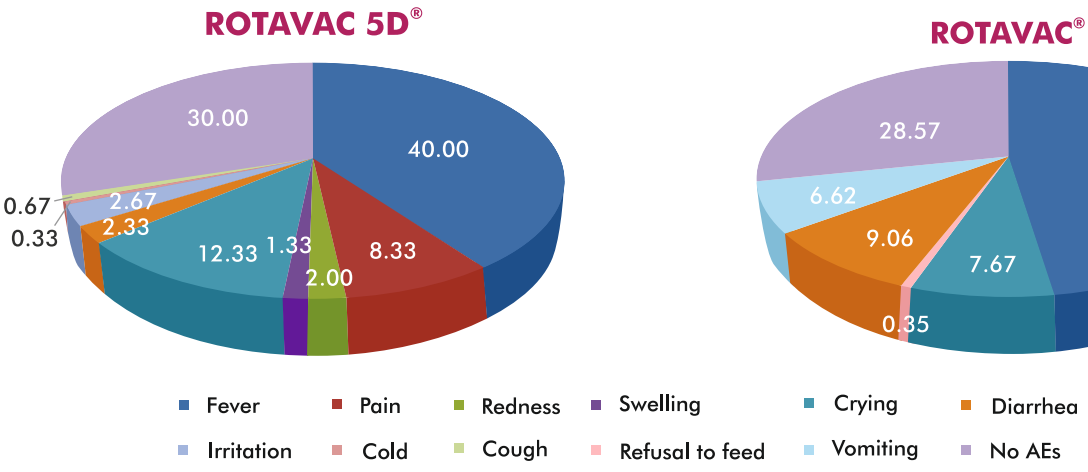


*Post-vaccination

Seroconversion



SAFETY



Note: Possibly due to concomitantly administered vaccines.

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ROTAVAC® PUBLICATIONS

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PUBLICATIONS

Vaccine 39 (2021) 36333640

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Immunogenicity and safety of two monovalent rotavirus vaccines, ROTAVAC and ROTAVAC 5D® in Zambian infants

R. Chilengi [a], K. Mwila- Kazimbaya [a], M. Chirwa [a], N. Sukwa [a], C. Chipeta [a], R.M. Velu [a], N. Katanekwa [a], S. Babji [b], G. Kang [b], M.M. McNeal [c], N. Meyer [c], G. Gompana [d], S. Hazra [d], Y. Tang [e], J. Flores [e], N. Bhat [e], N. Rathi [d,*]

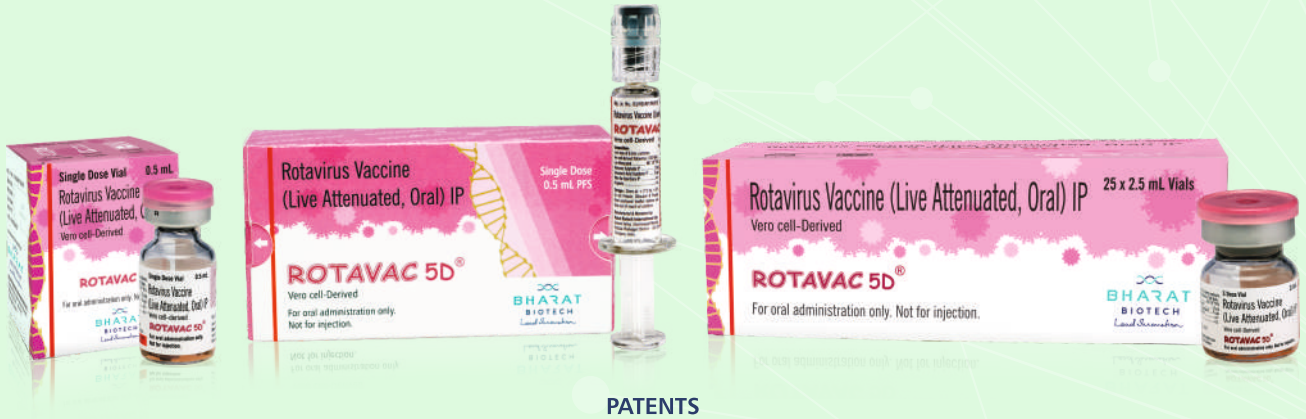
The Journal of Infectious Diseases

MAJOR ARTICLE

Human Neonatal Rotavirus Vaccine (RV3-BB) Produces Vaccine Take Irrespective of Histo-Blood Group Antigen Status

Karen Boniface,[1] Sean G. Byars,[2] Daniel Cowley,[3] Carl D. Kirkwood,[3] and Julie E. Bines[3]

[1]Enteric Diseases Group, Murdoch Childrens Research Institute, [2]Melbourne School of Population and Global Health and [3]Department of Pediatrics, University of Melbourne, and [4]Bill and Melinda Gates Foundation, Seattle, Washington; and [5]Department of Gastroenterology and Clinical Nutrition, Royal Childrens Hospital, Parkville, Australia



PATENTS

A Composition Useful as a Vaccine - PCT/IN2007/000190
A Composition Useful as Rotavirus Vaccine and a Method therefor - PCT/IN2010/000041
Novel Rotavirus vaccine compositions and processes for preparing the same - PCT/IN2013/000272
A buffer free, acid stable, low dose volume rotavirus vaccine - PCT/IN2017/050237

ABRIDGED PRESCRIBING INFORMATION

Therapeutic Indications: For prophylactic use only. ROTAVAC 5D® is indicated for active immunization of infants from the age of 6 weeks for the prevention of gastroenteritis due to Rotavirus infection when administered as a 3-dose regimen. **Dosage and Method of Administration:** ROTAVAC 5D® should be administered as a 3-dose regimen, 4 weeks apart, beginning at 6 weeks of age. ROTAVAC 5D® can be co-administered with other routine childhood immunizations (i.e. Diphtheria, Tetanus and Pertussis [DTwP], Haemophilus Influenzae type B [Hib], Hepatitis B vaccine and Oral/Injectable Polio Vaccine [OPV & IPV]). Based on recommendations from the World Health Organization (WHO) (Rotavirus vaccines WHO Position Paper, January 2013 in Weekly Epidemiological Report No.5, 2013, 88, 49-64), if the routine childhood immunizations are initiated later than 6 weeks of age and/or at a longer dose interval than 4weeks, ROTAVAC 5D® can still be co-administered with DTwP. It is recommended that infants who receive ROTAVAC 5D® as the first dose should complete the 3-dose regimen with ROTAVAC 5D®. There is no data on safety, immunogenicity or efficacy when ROTAVAC 5D® is administered interchangeably with other Rotavirus vaccines. **Pediatric Population:** All doses of Rotavirus vaccine should be administered to children by the age of 8 months (34 weeks). **Method of Administration:** ROTAVAC 5D® is for oral use only and should not be injected. In case, an incomplete dose is administered (the baby spits up or regurgitates most of the vaccine), a single replacement dose may be administered at the same vaccination visit*. The baby may continue to receive the remaining doses as per schedule. However, in clinical trials, the reported incidence of spitting or vomiting is <0.5%. *Physician's discretion is advised. **Contraindications:** Hypersensitivity to any component of the vaccine. Individuals with Severe Combined Immunodeficiency Disease (SCID). Cases of gastroenteritis associated with live rotavirus vaccines have been reported in infants with SCID. History of intussusception (IS). Ongoing gastroenteritis. **Special Warning/Precautions:** Administration of ROTAVAC 5D® may be considered with caution in immune-compromised infants and infants in close contact with immune-deficient persons, if in the opinion of the physician, withholding the vaccine entails greater risk. Similarly, acute infection or febrile illness may be a reason for delaying the administration of ROTAVAC 5D®, unless in the opinion of the physician, withholding the vaccine entails greater risk. Low-grade fever and mild upper respiratory tract infection are not contraindications to ROTAVAC 5D®. Available data shows a small increased incidence of intussusception (IS) following the first dose of Rotavirus vaccines especially after the first dose (WHO position paper, January 2013). The safety data from the clinical trials of ROTAVAC 5D® did not show an increased risk or incidence of IS. However, it is advised that health care providers follow-up on any symptom suggestive of IS e.g., continuous vomiting, blood in stools and abdominal lump or distension of the abdomen. Similar to other vaccines, vaccination with ROTAVAC 5D® may not result in complete protection against Rotavirus induced gastroenteritis or gastroenteritis due to other pathogens. In the clinical trial, OPV, IPV, and Pentavalent (DTwP, HepB, and Hib) vaccines were administered concurrently with ROTAVAC 5D®. Three doses of ROTAVAC 5D® can be safely administered with three doses of pentavalent vaccines and three doses of OPV as well as IPV without diminishing the antibody response to each component of these vaccines. It is well tolerated when administered concomitantly with routine childhood vaccines. **Pregnancy and Lactation:** ROTAVAC 5D® is a pediatric vaccine and should not be administered to adults including pregnant women. There are no restrictions on the infant's liquid consumption including breast-milk, either before or after vaccination with ROTAVAC 5D®. **Adverse Reactions:** Clinical Trial Experience commonly reported adverse events during the clinical trial including fever, diarrhea, cough, and others like running nose and irritability. No vaccine-related SAEs were reported. There was no vaccine-related case of intussusception observed/reported. Fever could be due to the concomitant injectable vaccines. **Overdose:** No case of overdose has been reported. **Pharmacological Properties - Pharmaco-therapeutic Group:** Rotavirus diarrhea vaccines. **Pharmacodynamic Properties:** Protective efficacy **Efficacy:** In total 12 clinical trials, approximately 15000 subjects were vaccinated with different formulations of ROTAVAC® vaccines consisting of ORV116E as the active ingredient. These ORV116E strain containing ROTAVAC® formulations (ROTAVAC®, ROTAVAC 5C & ROTAVAC 5D®) were tested for their safety, immunogenicity, and non-inferiority. The adverse reaction profile and immunogenicity profile observed in subjects administered with these formulations were similar. ROTAVAC 5D® formulation is evaluated equally safe and immunogenic as ROTAVAC® and ROTAVAC 5C. **ROTAVAC 5D® (ORV 116E):** There were no statistically significant differences in the pre and post-vaccination IgA titers between the ROTAVAC 5D® and ROTAVAC® (mean baseline titer 10.31 and 11.57 U/mL respectively (p=0.29 comparing all arms); and post-vaccination titer 18.70 and 19.55 U/mL, respectively (p=0.77). Four-fold seroconversion occurred by day 84 in 22.18% of the ROTAVAC 5D® arm, and 21.5% of the ROTAVAC®. There was no significant difference in seroconversion rates between the ROTAVAC® and ROTAVAC 5D® (p=0.86). **Post-marketing Surveillance Data:** It is carried out for the Rotavirus 116E strain-based vaccine ROTAVAC® and no SAEs were observed thus far. **Pharmacokinetic Properties:** Evaluation of pharmacokinetic properties is not required for vaccines. **Pharmaceutical Particulars – Incompatibilities:** This product should not be mixed in same syringe with any other medicinal products/active immunizing agents. **Special Precautions for Storage:** The vaccine should be stored at +2°C to 8°C. Do not freeze. Keep out of reach of children. Do not use the vaccine after the expiration date shown on the label. **Presentation:** ROTAVAC 5D® is presented in USP type I glass PFS- Single-dose 0.5 mL, single and multi-dose glass vial.

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