BHARAT BIOTECH

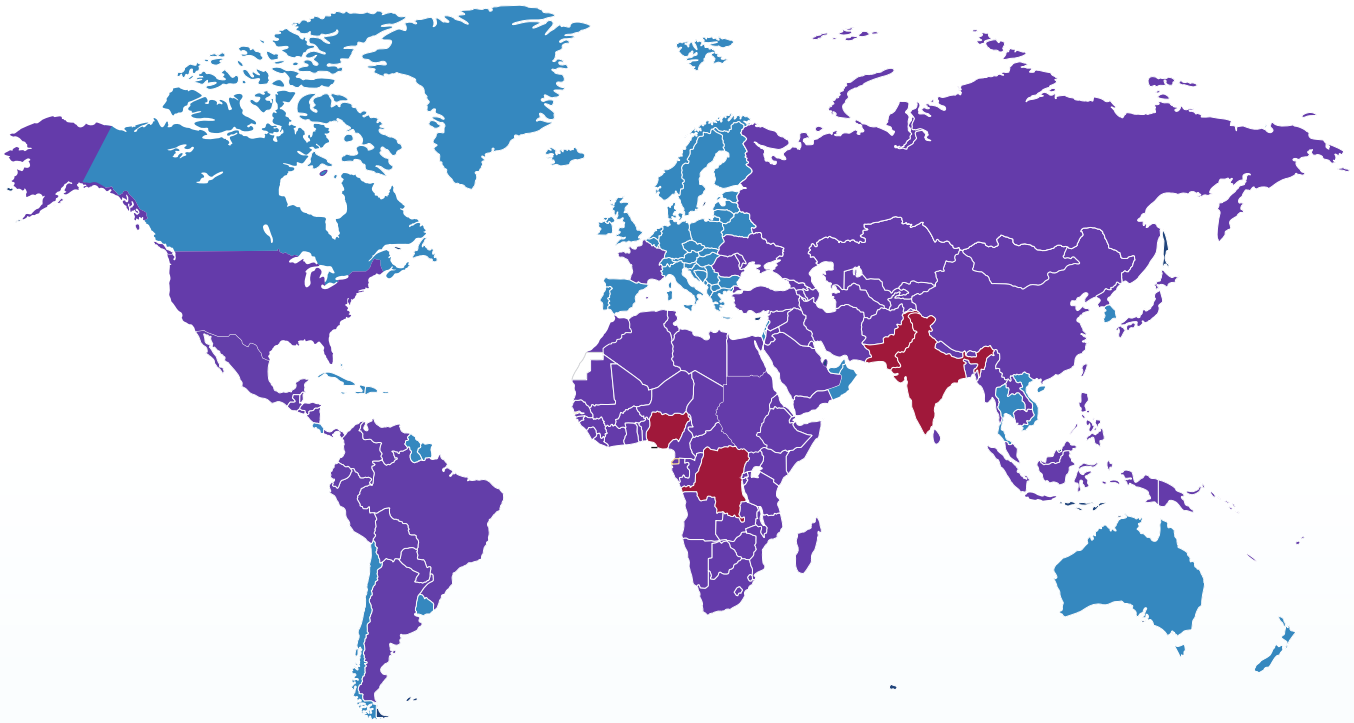
# ROTAVAC®

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

## EPIDEMIOLOGY

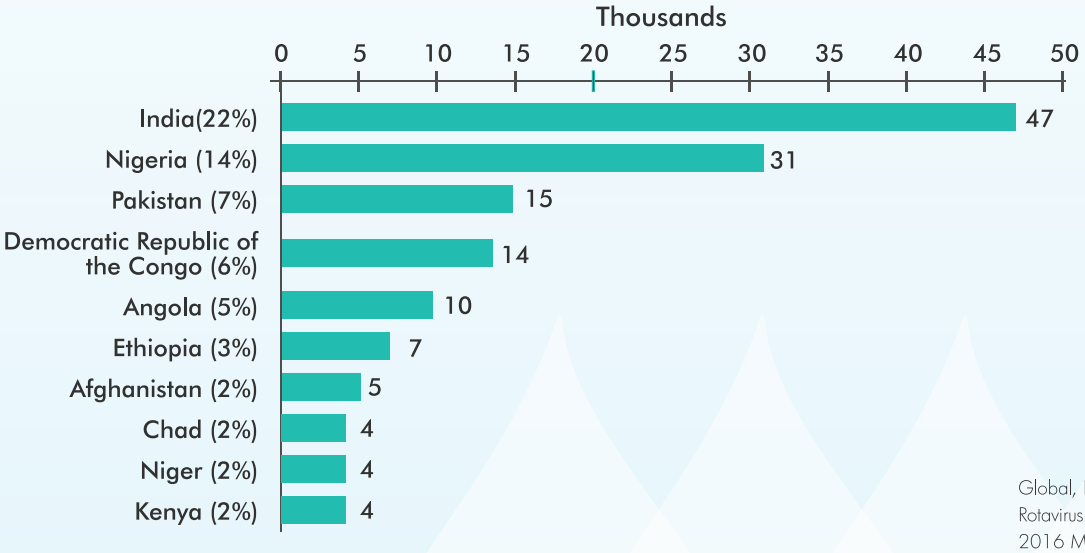
# GLOBAL DISTRIBUTION OF ROTAVIRUS MORTALITY

**WHO estimated rotavirus deaths for children under 5 years of age**
As of April 2016, the WHO estimates that globally 215,000 (197,000 – 233,000) child deaths occurred during 2013 due to rotavirus infection compared to 528,000 (465,000 – 591,000) in 2000.




- Date source: WHO/IVB Rotavirus diseases burden estimates, April 2016.
- Map production: Immunization Vaccines and Biologicals, (IVB), World Health Organization.

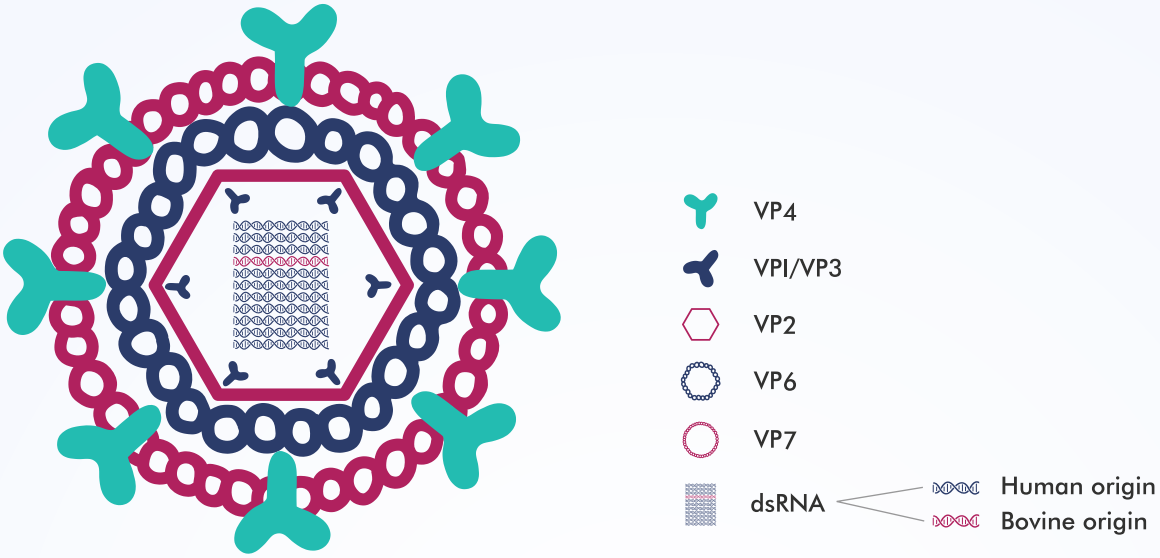
## COUNTRIES WITH HIGHEST NUMBER OF ROTAVIRUS DEATHS IN CHILDREN UNDER 5 YEARS OF AGE




Global, Regional, and National Estimates of Rotavirus Mortality in Children. Clin Infect Dis. 2016 May 1:62 Suppl 2:S96-S105.

## ROTAVAC® - THE G9P[11] STRAIN, nHRV 116E

ASYMPTOMATIC
NEONATAL
NATURALLY
ATTENUATED




nHRV, neonatal Human Rotavirus Vaccine.

- Characterization of Rotavirus Strains from Newborns in New Delhi, India. J clin microbial, July 1994, Vol. 32, No. 7, p. 1820-1822.
- Complete genome sequence analysis of candidate human rotavirus vaccine strains RV3 and 116E. Virology 2010 Sep 15; 405 (1): 201-13.

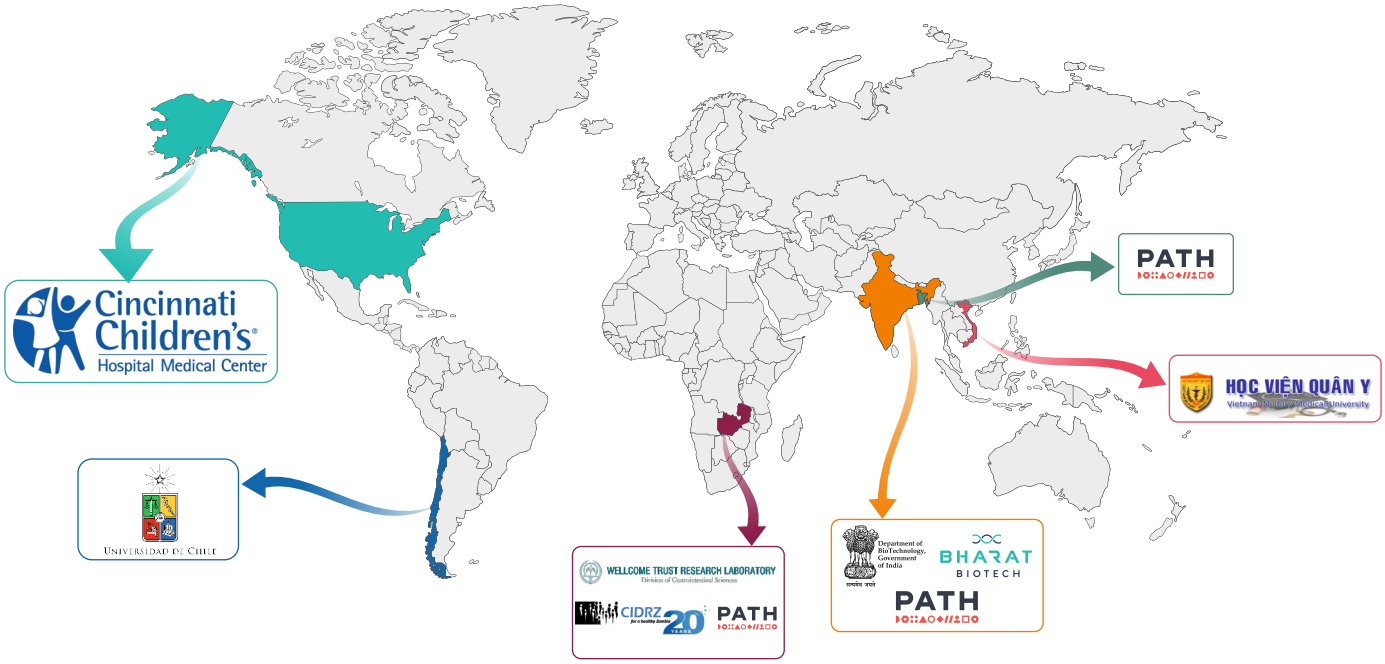
## ROTAVAC® – UNIQUE FEATURES

| | ROTAVAC® | Other RV vaccines |
|---|---|---|
| Parent rotavirus strain | Monovalent neonatal human naturally attenuated G9P[11] strain | Artificially attenuated, reassortant Monovalent to Multivalent strains* |
| Volume per dose | 0.5 mL | Up to 2.5 mL |
| Formulation | No reconstitution required | Require reconstitution* |
| Residues | No residues present | Fragments of DNA from Porcine Circovirus (PCV) Type 1 & 2 were detected* |
| Administration | Easy administration | Tedious administration* |
| Cold chain space | ~3.0 $cm^3$/dose | ~ 4x space required |
| VVM | Yes | Yes* |

*Exceptions for some RV vaccines

# ROTAVAC® – CLINICAL TRIALS

## GLOBAL CLINICAL TRIALS - ESTABLISHING SUPERIOR EFFICACY

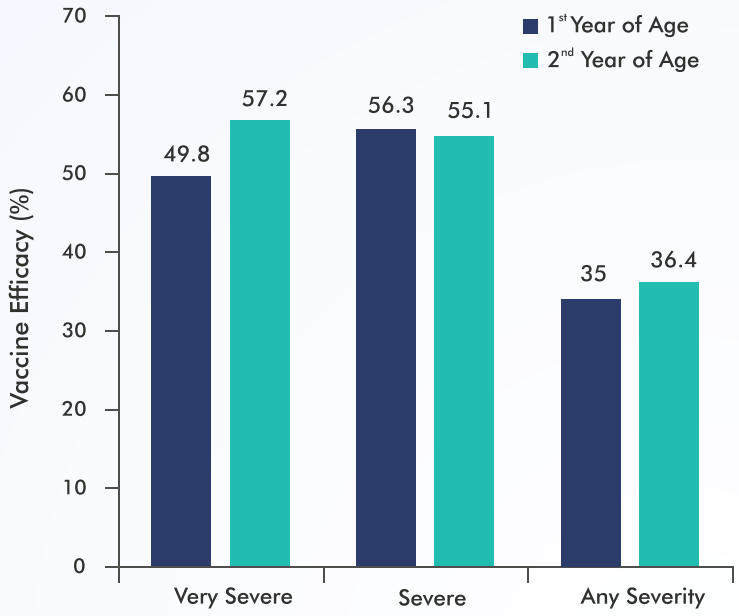



| NO. | CLINICAL STAGE | AGE GROUP | SUBJECTS | LOCATION | END POINT |
|---|---|---|---|---|---|
| 1 | Phase I: Adults/ Children | 18-45 years/ 2-12 years | 90 | USA | Safety |
| 2 | Phase 1: Adults/ Children | 18-45 years /2-12 years | 90 | India | Safety |
| 3 | Phase 1: Infants[1] | 8-12 weeks | 90 | India | Dose Escalation |
| 4 | Phase 1b/2a: Infants[2] | 8-20 weeks | 360 | India | Safety / Immunogenicity |
| 5 | Phase 3: Infants[3,4] | 6-8 Weeks | 6799 | India | Efficacy |
| 6 | Phase 3:Non-interference Study[5] | 6-8 Weeks | 1356 | India | Non-interference |
| 7 | Phase 4: Infants[6] | 6-8 Weeks | 900 | India | Immunogenicity/ Safety w & w/o buffer |
| 8 | Phase 4: Comparator Study[7] | 6-8 Weeks | 464 | India | Safety / Immunogenicity |
| 9 | Phase 3 Study (Birth dose study) | 0-14 weeks | 408 | India | Safety / Immunogenicity Neonatal Sch vs. Infant Sch |
| 10 | Post-Marketing Surveillance[8] | 6-8 Weeks | Active Surveillance ~25,000<br>INCLEN Trust Surveillance ~100,000 | India | Safety |
| 11 | Phase 3 Study [9] | 6-8 Weeks | 360 | Vietnam | Safety / Immunogenicity |
| 12 | Phase 2b Study[10] | 6-8 Weeks | 450 | Zambia | Safety / Immunogenicity |
| 13 | Phase 3 Study[11] | | | Palestine | Cost-effectiveness |

# ROTAVAC® – PHASE III TRIALS

## ESTABLISHING SAFETY, EFFICACY & NON-INTERFERENCE

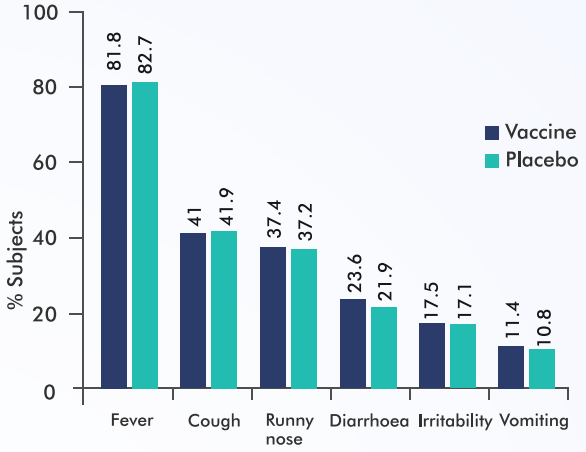
### PROVEN LONG-TERM EFFICACY[3, 4]



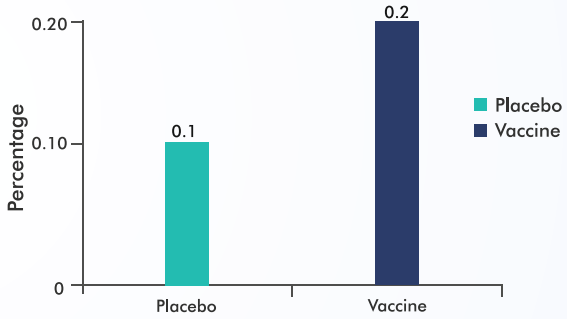

**RVGE Severity**

Vesikari score (> 11) & Very Severe (> 16)

### ADVERSE EVENTS DURING TRIAL[3] 2011-2013

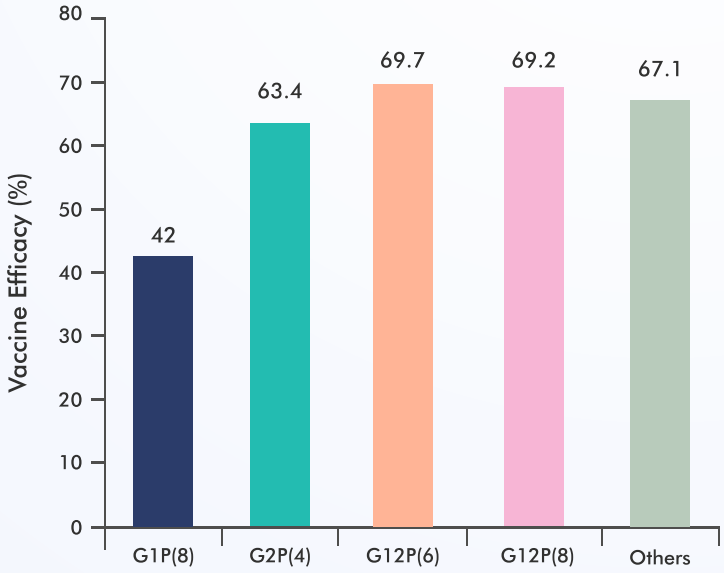



### INTUSSUSCEPTION (IS) - NOT VACCINE ATTRIBUTABLE[4] (Brighton Diagnostic Criteria Level 1)




- No cases of IS related to ROTAVAC®
- All cases of IS occurred after Dose 3
- 1st case of IS was detected 112 days post 3rd dose of ROTAVAC® and 36 days post 3rd dose of Placebo, respectively
- Proportion of IS equivalent in both arms (p>0.05)

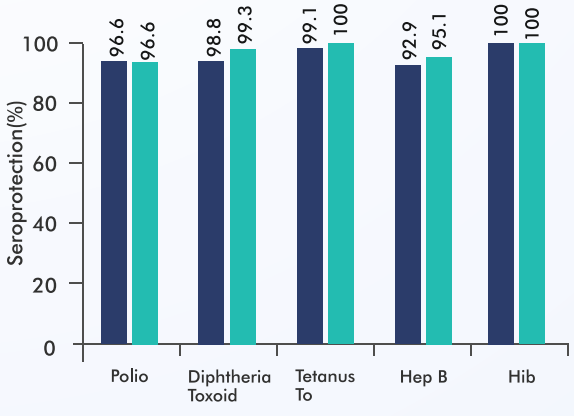
### BROAD HETEROTYPIC CROSS - PROTECTION[4]




**RV Genotypess**

Also protective against G9P[8], G1P[4], G1P[6], G2P[6], G12P[11]

### ROTAVAC® DOES NOT INTERFERE WITH IMMUNE RESPONSE TO CHILDHOOD VACCINES[5]




Pertussis: Geometric mean concentration (GMC) ratio between both groups is 1.0 (0.8, 1.1)

## INFLUENCE OF COINFECTIONS ON ROTAVAC® EFFICACY

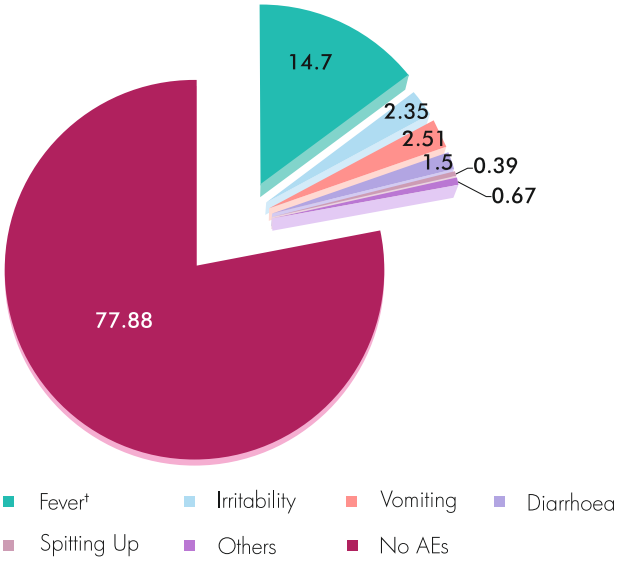
**RV VACCINE EFFICACY INFLUENCED BY COINFECTION WITH OTHER ENTEROPATHOGENS**

**Proven 11.3% Vaccine Efficacy increase in 2 years, in the absence of coinfections.**

Improved adjusted vaccine efficacy for ROTAVAC® after accounting for coinfections.

Diarrheal Etiology and Impact of Coinfections on Rotavirus Vaccine Efficacy Estimates in a Clinical Trial of a Monovalent Human–Bovine (116E) Oral Rotavirus Vaccine, Rotavac, India. Clin Infect Dis. 2019 Jul 2; 69(2):243-250.

## ROTAVAC® POST-MARKETING SURVEILLANCE




†Likely due to concomitant childhood vaccines such as Pentavalent & Inactivated polio vaccine (IPV).

Smart Safety Surveillance (3S) approach promoted by WHO demonstrated no increased risk of intussusception associated with ROTAVAC® in a self-controlled case series analysis.‡

‡White Paper - Safety of Rotavirus Vaccine in India, Smart Safety Surveillance Approach, Nov 2019.

## VACCINES EFFICACY - LOW RESOURCE SETTINGS (HIGH UNDER 5 MORTALITY RATE)

| Countries | Vaccine | Schedule | 1st Year Efficacy | 2nd Year Efficacy | Combined | Relative decline in Efficacy year 2 vs 1 |
|---|---|---|---|---|---|---|
| India | ROTAVAC® | 6,10,14 Weeks | 56% | 49% | 55% | 12% |
| | BRV-PV | 6,10,14 Weeks | 36% | - | 39% | - |
| Bangladesh | RV5 | 6,10,14 Weeks | 46% | 39% | 43% | 15% |
| Ghana | RV5 | 6,10,14 Weeks | 65% | 29% | 56% | 55% |
| Mali | RV5 | 6,10,14 Weeks | 1% | 19% | 18% | - |
| Malawi | RV1 | 10, 14 Weeks | 49% | 3% | 34% | 94% |
| | RV1 | 6,10,14 Weeks | 50% | 33% | 42% | 34% |
| South Africa | RV1 | 10, 14 Weeks | 46% | - | 32% | - |
| | RV1 | 6,10,14 Weeks | 89% | - | 85% | - |


- Vaccines for preventing rotavirus diarrhoea: vaccines in use (Review). Cochrane Database of Systematic Reviews, Issue 3, 2019.
- Efficacy of live oral rotavirus vaccines by duration of follow-up: a meta-regression of randomised controlled trials. Lancet Infect Dis 2019; 19: 717–27.

# HBGAs - POTENTIAL RECEPTORS FOR ROTAVIRUSES

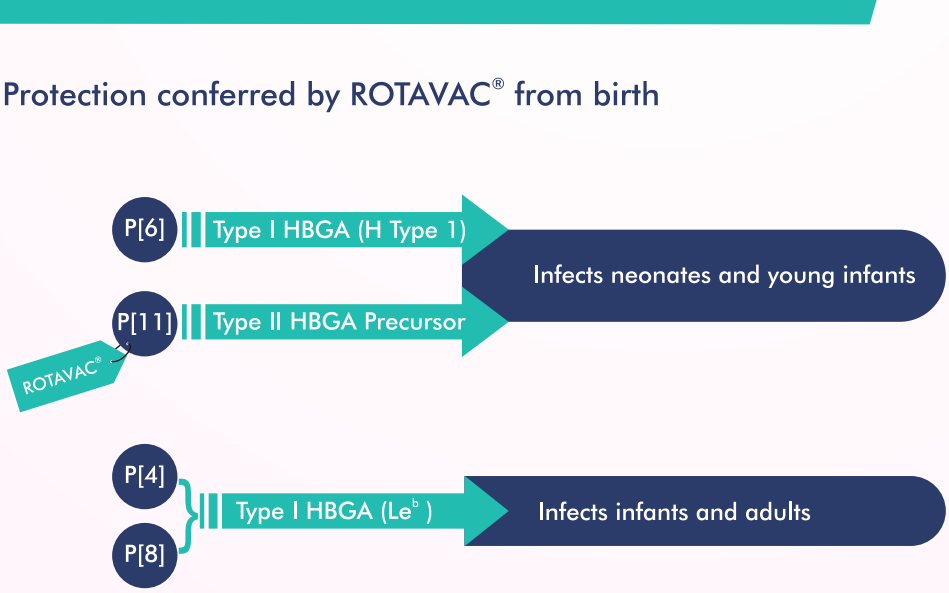
HISTO BLOOD GROUP ANTIGENs (HBGAs) vs ROTAVAC®

## Binding of Rotaviruses to human HBGAs - Essential for effective vaccine performance

| | Vaccine | RV strain used as Vaccine | Receptor | Vaccine Efficacy | |
|---|---|---|---|---|---|
| | | | | High Income Countries | Low & Middle Income Countries |
| 1. | ROTAVAC® | G9P[11] (nHRV) | Type 2 HBGA Precursor | - | Moderate |
| 2. | RV1 | G1P[8] | H Type I & $Le^b$ | High | Moderate |
| 3. | RV5 | G1(Human) P[5] (Bovine)<br>G2 (Human) P[5] (Bovine)<br>G3 (Human) P[5] (Bovine)<br>G4 (Human) P[5] (Bovine) | No known human receptor | High | Moderate |
| | | G6 (Bovine) P[8] (Human) | H Type I & Leb | | |
| 4. | BRV-PV | G1(Human) P[5] (Bovine)<br>G2 (Human) P[5] (Bovine)<br>G3 (Human) P[5] (Bovine)<br>G4 (Human) P[5] (Bovine)<br>G9 (Human) P[5] (Bovine) | No known human receptor | - | Low |

## ROTAVIRUS STRAINS - AGE-SPECIFIC SUSCEPTIBILITY

### Protection conferred by ROTAVAC® from birth




Histo-blood group antigens as receptors for rotavirus, new understanding on rotavirus epidemiology and vaccine strategy. Emerg Microbes Infect. 2017 Apr 12; 6(4):e22.

# IMPACT OF BREAST MILK ON ROTAVAC® EFFICACY

## HUMAN MILK OLIGOSACCHARIDES (HMOs) vs ROTAVAC®

**Rotavirus Infection**

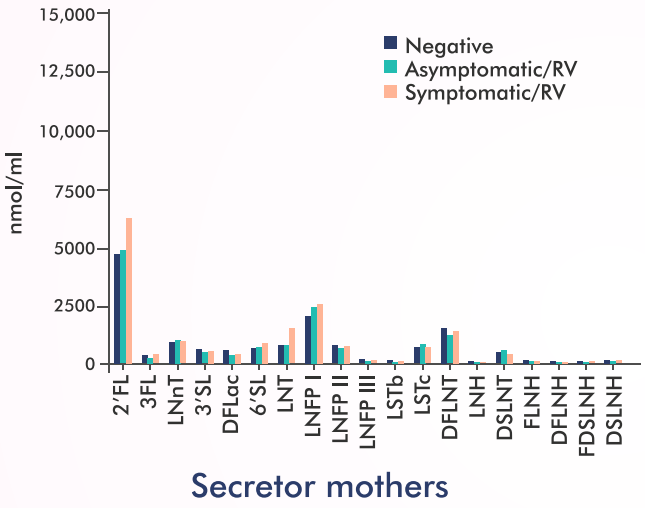
Symptomatic — Older children P[4], P[8]

Asymptomatic/Symptomatic

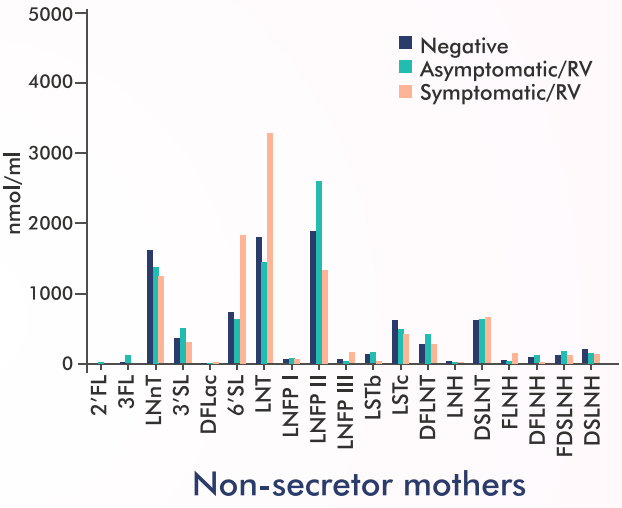
Neonates/newborn P[6], P[11]

**Specific Breast Milk Oligosaccharides enhance the infectivity of neonatal rotavirus strains (116E - ROTAVAC®) and vaccine efficacy.**

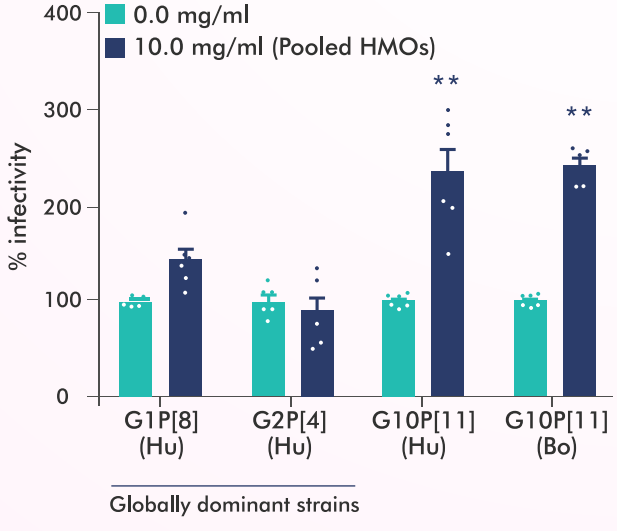
Specific HMOs are associated with symptomatic rotavirus infection

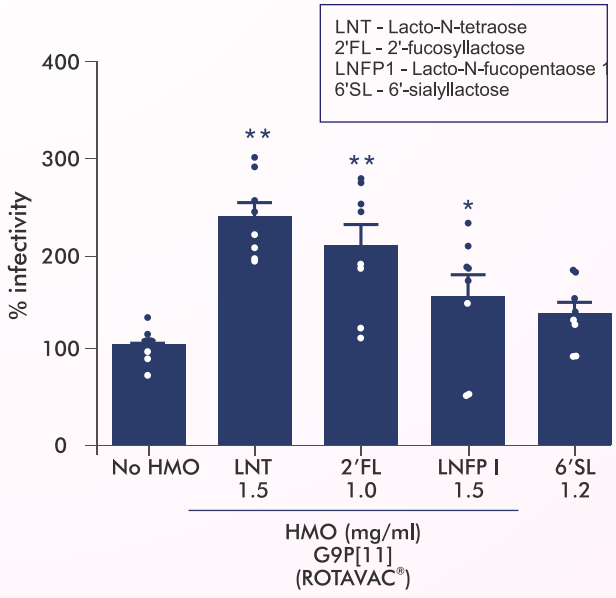



Secretor mothers




Non-secretor mothers




Increase in infectivity in presence of HMOs is specific to P[11] rotaviruses.
No difference is observed with globally dominant rotavirus strains.

Human milk oligosaccharides, milk microbiome and infant gut microbiome modulate neonatal rotavirus infection. Nat Commun. 2018 Nov 27; 9(1):5010.

## UNPARALLELED ROTAVAC®

01 ROTAVAC® (nHRV) naturally attenuated neonatal Human-Bovine reassorted asymptomatic G9P[11] strain.

02 ROTAVAC® is licensed with a low dose volume (0.5 mL) & permits complete vaccine uptake by eliminating infant spit-ups.

03 ROTAVAC® confers protection from birth.

04 Cross protects against most prevalent global rotavirus strains G1P[4], G1P[6], G1P[8], G2P[4], G2P[6], G9P[4], G9P[8], G12P[6], G12P[8], G12P[11].

05 Safe concomitant administration with childhood vaccines.

06 Smart Safety Surveillance (3S) approach promoted by WHO demonstrated no increased risk of intussusception associated with ROTAVAC® in a self-controlled case series analysis.

07 Higher efficacy compared to other RV vaccines in high mortality settings.

08 Breast milk interaction enhances the infectivity/immunogenicity of ROTAVAC®.

09 Increase in efficacy of ROTAVAC® in the absence of coinfections.

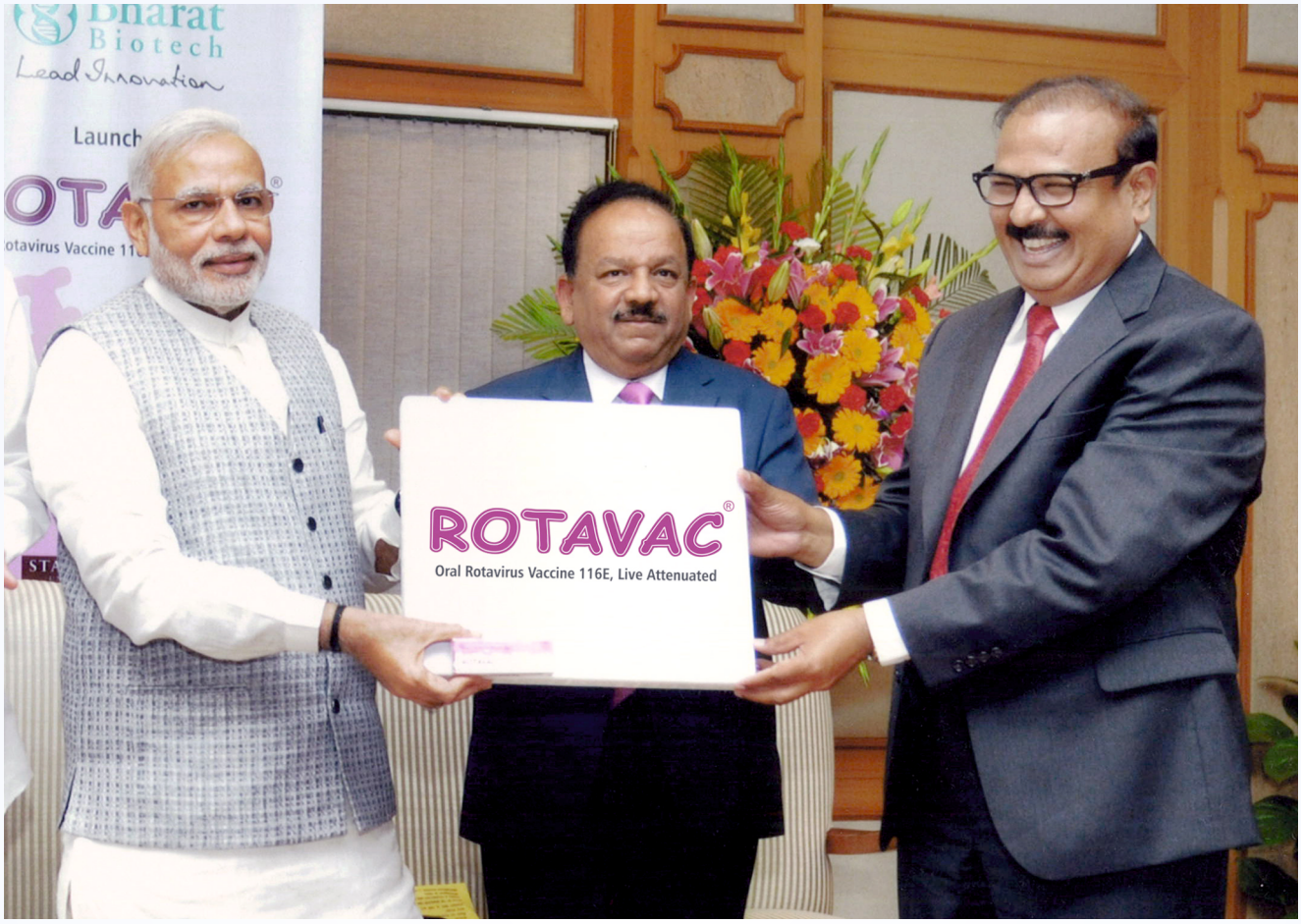
10 Highly stable at -20°C for 60 months and 2-8°C for 6 months during shelf life.

## REFERENCES


1. Safety and immunogenicity of two live attenuated human rotavirus vaccine candidates, 116E and I321, in infants: Results of a randomised controlled trial. Vaccine 24 (2006) 5817–582.
2. A Dose-Escalation safety and Immunogenicity Study of Live Attenuated Oral rotavirus Vaccine 116E in Infants: A Randomized, Double-Blind, Placebo-Controlled Trial. Journal of Infectious Diseases: 2009 (1) 421-429.
3. Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian infants: a randomised, double-blind, placebo-controlled trial. Lancet 2014. (383), 9935, p2136–2143.
4. Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian children in the second year of life. Vaccine, 2014 Aug; 32 Suppl 1:A110-6. ®
5. ROTAVAC® does not interfere with the immune response to childhood vaccines in Indian infants: A randomized placebo controlled trial. Heliyon, 2017,May 16;3(5):e00302.
6. A Phase 4, multicentre, randomized, single-blind clinical trial to evaluate the immunogenicity of the live, ® attenuated, oral rotavirus vaccine (116E), ROTAVAC®, administered simultaneously with or without the buffering agent in healthy infants in India. Hum VaccinImmunother. 2018 Jul 3; 14 (7):1791-1799.
7. 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 Volume 37, Issue 31, 18 July 2019, Pages 4407-4413.
8. INCLEN Intussusception Surveillance Network Study Group. Risk of intussusception after monovalent rotavirus vaccine (ROTAVAC®) in Indian infants: A self-controlled case series analysis. Vaccine. 2021 Jan 3;39(1):78-84. doi: 10.1016/j.vaccine.2020.09.019. Epub 2020 Sep 21. PMID: 32972735; PMCID: PMC7738754.
9. Immunogenicity, safety and reactogenicity of ROTAVAC® in healthy infants aged 6-8 weeks in Vietnam. Vaccine. 2021 Feb 12;39(7):1140-1147. doi: 10.1016/j.vaccine.2020.12.086. Epub 2021 Jan 16. PMID: 33461837.
10. Immunogenicity and safety of two monovalent rotavirus vaccines, ROTAVAC® and ROTAVAC 5D® in Zambian infants. Vaccine. 2021 Jun 16;39(27):3633-3640. doi: 10.1016/j.vaccine.2021.04.060. Epub 2021 May 12. PMID: 33992437; PMCID: PMC8204902.
11. Debellut F, Jaber S, Bouzya Y, Sabbah J, Barham M, Abu-Awwad F, Hjaija D, Ramlawi A, Pecenka C, Clark A, Mvundura M. Introduction of rotavirus vaccination in Palestine: An evaluation of the costs, impact, and cost-effectiveness of ROTARIX and ROTAVAC®. PLoS One. 2020 Feb 5;15(2):e0228506. doi: 10.1371/journal.pone.0228506. PMID: 32023295; PMCID: PMC7001920.

## SOCIAL INNOVATION FROM INDIA

ROTAVAC®




**ROTAVAC® is the first vaccine derived from an Indian strain, identified by an Indian scientist, manufactured by an Indian company, studied in Indian population for the benefit of the world.**

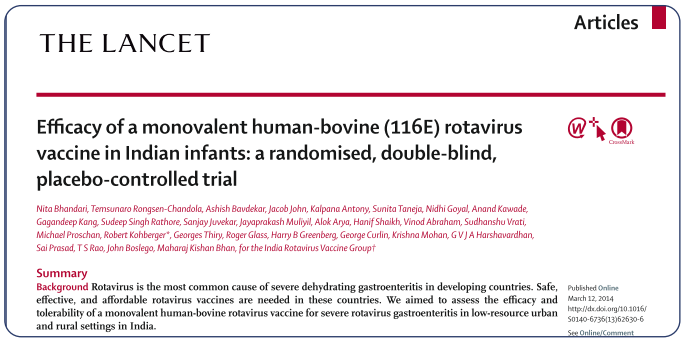
**Achieving WHO Prequalification, ROTAVAC® is a perfect story of Social Innovation and is under public health vaccination programs across the world.**

## ROTAVIRUS VACCINE DEVELOPMENT PROJECT

A 16-Member Worldwide Public Private Partnership Collaboration

Department for International Development
NIH National Institutes of Health
CDC Centers for Disease Control and Prevention
Department of BioTechnology, Government of India
Stanford University
Johns Hopkins University
HRD Centre for Health Research and Development Society for Applied Studies
KEM Hospital PUNE Quality and ethics in patient care
The Research Council of Norway
thsti Translational Health Science and Technology Institute
BHARAT BIOTECH
BILL & MELINDA GATES foundation
PATH

# ROTAVAC® PUBLICATIONS



Articles

THE LANCET

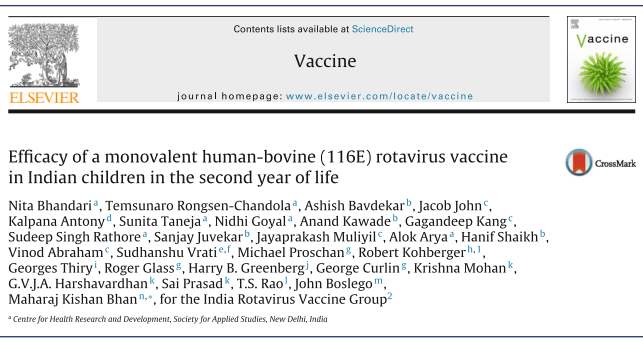
## Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian infants: a randomised, double-blind, placebo-controlled trial

Nita Bhandari, Temsunaro Rongsen-Chandola, Ashish Bavdekar, Jacob John, Kalpana Antony, Sunita Taneja, Nidhi Goyal, Anand Kawade, Gagandeep Kang, Sudeep Singh Rathore, Sanjay Juvekar, Jayaprakash Muliyil, Alok Arya, Hanif Shaikh, Vinod Abraham, Sudhanshu Vrati, Michael Proschan, Robert Kohberger*, Georges Thiry, Roger Glass, Harry B Greenberg, George Curlin, Krishna Mohan, G V J A Harshavardhan, Sai Prasad, T S Rao, John Boslego, Maharaj Kishan Bhan, for the India Rotavirus Vaccine Group†

**Summary**

**Background** Rotavirus is the most common cause of severe dehydrating gastroenteritis in developing countries. Safe, effective, and affordable rotavirus vaccines are needed in these countries. We aimed to assess the efficacy and tolerability of a monovalent human-bovine rotavirus vaccine for severe rotavirus gastroenteritis in low-resource urban and rural settings in India.

Published Online March 12, 2014 http://dx.doi.org/10.1016/S0140-6736(13)62630-6 See Online/Comment



Contents lists available at ScienceDirect

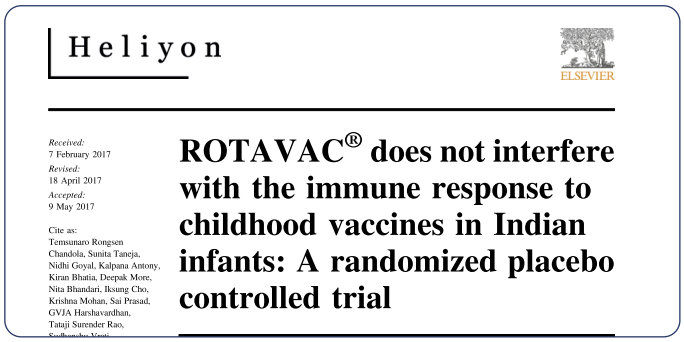
Vaccine

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

## Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian children in the second year of life

Nita Bhandari[a], Temsunaro Rongsen-Chandola[a], Ashish Bavdekar[b], Jacob John[c], Kalpana Antony[d], Sunita Taneja[a], Nidhi Goyal[a], Anand Kawade[b], Gagandeep Kang[c], Sudeep Singh Rathore[a], Sanjay Juvekar[b], Jayaprakash Muliyil[c], Alok Arya[a], Hanif Shaikh[b], Vinod Abraham[c], Sudhanshu Vrati[e,f], Michael Proschan[g], Robert Kohberger[h,1], Georges Thiry[i], Roger Glass[g], Harry B. Greenberg[j], George Curlin[g], Krishna Mohan[k], G.V.J.A. Harshavardhan[k], Sai Prasad[k], T.S. Rao[l], John Boslego[m], Maharaj Kishan Bhan[n,*], for the India Rotavirus Vaccine Group[2]

[a] Centre for Health Research and Development, Society for Applied Studies, New Delhi, India



Heliyon

ELSEVIER

Received: 7 February 2017
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Accepted: 9 May 2017

Cite as: Temsunaro Rongsen Chandola, Sunita Taneja, Nidhi Goyal, Kalpana Antony, Kiran Bhatia, Deepak More, Nita Bhandari, Iksung Cho, Krishna Mohan, Sai Prasad, GVJA Harshavardhan, Tataji Surender Rao, Sudhanshu Vrati

## ROTAVAC® does not interfere with the immune response to childhood vaccines in Indian infants: A randomized placebo controlled trial

HUMAN VACCINES & IMMUNOTHERAPEUTICS
2018, VOL. 14, NO. 7, 1791–1799
https://doi.org/10.1080/21645515.2018.1450709

Taylor & Francis
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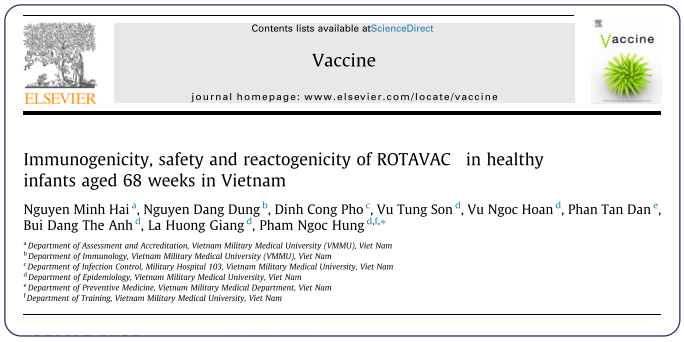
RESEARCH PAPER

OPEN ACCESS Check for updates

## A Phase 4, multicentre, randomized, single-blind clinical trial to evaluate the immunogenicity of the live, attenuated, oral rotavirus vaccine (116E), ROTAVAC , administered simultaneously with or without the buffering agent in healthy infants in India

Raches Ella[a], Radhika Bobba[a], Sanjay Muralidhar[a], Sudhir Babji[b], Krishna Mohan Vadrevu[a], and Maharaj Kishan Bhan[c]

[a]Bharat Biotech International Limited, Genome Valley, Shameerpet, Hyderabad, India; [b]Division of Gastrointestinal Sciences, Christian Medical College, Vellore, Tamil Nadu, India; [c]Indian Institute of Technology, Government of India, Delhi, India



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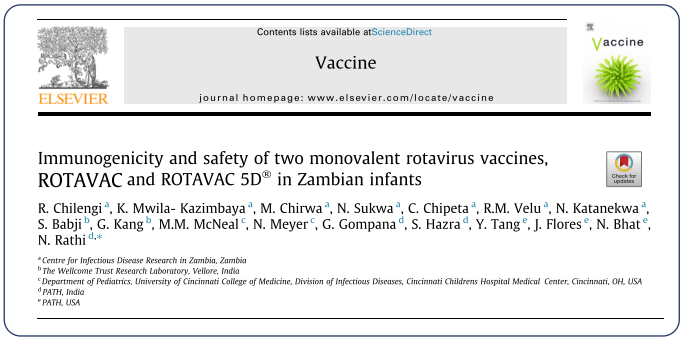
## Immunogenicity, safety and reactogenicity of ROTAVAC in healthy infants aged 68 weeks in Vietnam

Nguyen Minh Hai[a], Nguyen Dang Dung[b], Dinh Cong Pho[c], Vu Tung Son[d], Vu Ngoc Hoan[d], Phan Tan Dan[e], Bui Dang The Anh[d], La Huong Giang[d], Pham Ngoc Hung[d,f,*]

[a] Department of Assessment and Accreditation, Vietnam Military Medical University (VMMU), Viet Nam
[b] Department of Immunology, Vietnam Military Medical University (VMMU), Viet Nam
[c] Department of Infection Control, Military Hospital 103, Vietnam Military Medical University, Viet Nam
[d] Department of Epidemiology, Vietnam Military Medical University, Viet Nam
[e] Department of Preventive Medicine, Vietnam Military Medical Department, Viet Nam
[f] Department of Training, Vietnam Military Medical University, Viet Nam



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

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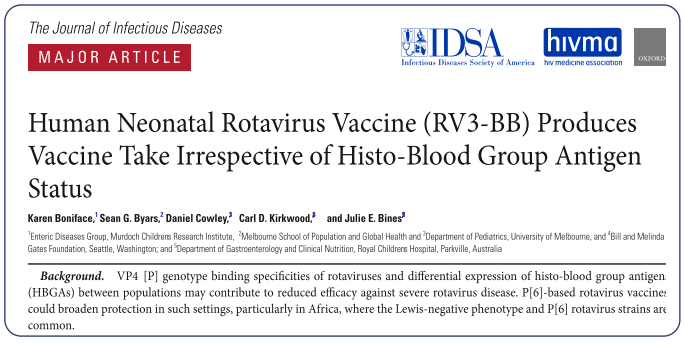

The Journal of Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

## 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]

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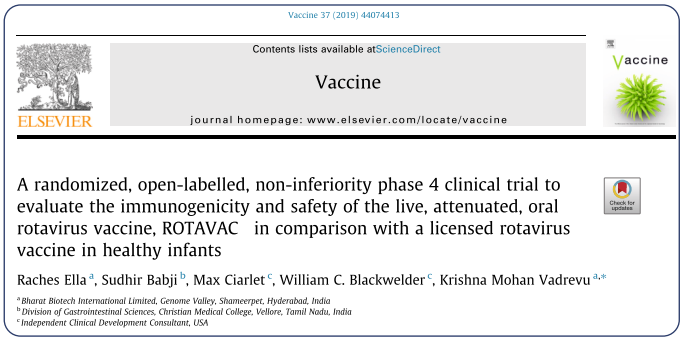
***Background.*** VP4 [P] genotype binding specificities of rotaviruses and differential expression of histo-blood group antigens (HBGAs) between populations may contribute to reduced efficacy against severe rotavirus disease. P[6]-based rotavirus vaccines could broaden protection in such settings, particularly in Africa, where the Lewis-negative phenotype and P[6] rotavirus strains are common.



Vaccine 37 (2019) 44074413

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Vaccine

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

## 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

Raches Ella[a], Sudhir Babji[b], Max Ciarlet[c], William C. Blackwelder[c], Krishna Mohan Vadrevu[a,*]

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The Daily Star

### NEW HOPE FOR ROTAVIRUS VACCINE

Bharat Biotech's rotavirus vaccine gets WHO prequalification. A new, cheaper, and heat-stable rotavirus vaccine could prevent thousands of childhood deaths.

GLOBAL CITIZEN

### THE 10 BIGGEST GLOBAL HEALTH WINS OF 2018

In January, vaccine manufacturer Bharat Biotech announced that the World Health Organization (WHO) had approved the development of a new rotavirus vaccine, ROTAVAC® — which costs only $1 per dose.

A vaccine against rotavirus is a big step forward in ensuring global health as rotavirus and other diarrheal diseases are the second biggest killer of children under 5 years old.

# ROTAVAC®

Recipient of the
**NATIONAL TECHNOLOGY AWARD 2018**
from the Technology Development Board
Department of Science & Technology
Government of India


**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® 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 series. **Dosage and method of administration:** ROTAVAC® should be administered as a 3-dose regimen, 4 weeks apart, beginning at 6 weeks of age. ROTAVAC® may be co-administered with other routine childhood vaccines (i.e., Diphtheria, Tetanus and Pertussis [DTwP], Hepatitis B vaccine and Oral Polio Vaccine [OPV]). Based on recommendations from the World Health Organization (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 4-weeks, ROTAVAC® can still be co-administered with DTwP. **ROTAVAC® vial should be fully thawed (till liquid) prior to administration.** It is recommended that infants who receive ROTAVAC® as the first dose should complete the 3-dose regimen with ROTAVAC® . There is no data on safety, immunogenicity or efficacy when ROTAVAC® is administered interchangeably with other rotavirus vaccines. **Paediatric Population:** All doses of Rotavirus vaccine should be administered to children by the age of 8 months (34 weeks). **Method of administration:** ROTAVAC® 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). **Special warning/ Precautions:** Administration of ROTAVAC® 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®, 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®. 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. The safety data from the clinical trials of ROTAVAC® did not show an increased risk of IS for ROTAVAC® when compared to placebo. However, it is advised that health care providers follow-up on any symptoms 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® may not result in complete protection against rotavirus induced gastroenteritis or gastroenteritis due to other pathogens. The analysis of the immune response for the 3 OPV serotypes was performed by analysing geometric mean titre (GMT) and the proportion of subjects meeting the accepted protective titre (neutralizing antibody ≥1:8) for recipients of OPV plus ROTAVAC® and OPV plus placebo. In summary, the analysis of post-immunization revealed that subjects receiving OPV concurrently with ROTAVAC® generated comparable immune responses to all three polio serotypes compared to those receiving OPV without ROTAVAC®. In phase III clinical trial, subjects received 3 doses of ROTAVAC® or placebo concomitantly with childhood vaccines DTwP, Hepatitis B vaccine and OPV. There was no significant difference in immediate or follow-up adverse events in the ROTAVAC® or the placebo group. **Pregnancy and lactation:** ROTAVAC® is a paediatric 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®. **Adverse Reactions: Clinical Trial Experience** Safety data from phase III trials of ROTAVAC® is discussed below. Overall the events reported are similar to those reported in other rotavirus vaccine clinical trials. Commonly reported adverse events included fever, vomiting, and diarrhoea. In the phase III efficacy study with 6, 799 infants of 6-7 weeks of age, the prevalence of immediate, solicited and serious adverse events was similar in the vaccine and placebo groups. Analyses for solicited adverse events showed a similar prevalence of fever, vomiting, diarrhoea, cough, runny nose, irritability and rash. Commonly observed immediate adverse event within 30 minutes of administration are vomiting and spitting up (<0.5%). No differences were detected between ROTAVAC® and placebo groups in the post-vaccination reactogenicity. In the phase III trial, there were six confirmed cases of IS observed among the 4,532 ROTAVAC® recipients (0.13%), and two among the 2,267 placebo recipients (0.09%). The minor difference in the number of subjects with IS was not statistically significant (p=0.73). There were no reports of IS in the 14-day period following vaccination; the first case identified occurred in a placebo subject, 36 days after the third dose. The first case reported among ROTAVAC® recipients occurred 112 days after the third dose. G1P [8] was identified in the stool from this subject. All IS events were resolved after pneumatic reduction or barium enema; none required surgical intervention and none fatal. As per WHO, on Rotavirus vaccines, "….the benefits of rotavirus vaccination against severe diarrhoea and death from rotavirus infection far exceeds the risk of intussusception." **Preterm infants and infants with human immunodeficiency virus (HIV) infection:** Clinical studies have not been conducted in these groups of population and data are not available **Overdose:** In the phase III trial, one subject received a double dose of ROTAVAC®. This subject was followed daily with home visits for 14 days and no adverse events were identified or reported. **Pharmacological properties - Pharmaco-therapeutic group:** rotavirus diarrhoea vaccines. **Pharmacodynamic properties:** Protective efficacy **Efficacy:** Multi-centre clinical study was conducted in India to evaluate the efficacy of ROTAVAC® to prevent severe rotavirus gastroenteritis. Vaccine efficacy (VE) for severe non- vaccine RVGE was 56.4%, during the first year of life. The VE against severe non-vaccine RVGE in the second year of life was 49%. Non-vaccine RVGE requiring hospitalisation and of any cause ROTAVAC® prevented 47.7% of all hospitalisation ≥24hrs due to severe non- vaccine rotavirus gastroenteritis. **Immune response:** The immunogenicity of ROTAVAC® was assessed by serum anti-rotavirus IgA ELISA. The observed serological response rate after the third dose of ROTAVAC® was 40.3% in comparison to 18.4% in the placebo group. Summary: In the phase III Efficacy clinical trial, ROTAVAC®: • Is efficacious in the prevention of severe non-vaccine RVGE • Is efficacious in the prevention of severe non-vaccine RVGE during the first year and second year of life. • Is efficacious in the prevention of non-vaccine RVGE of any severity during the first and second year of life. • Offers broad protection against the most commonly circulating RV genotypes in India. • Reduced hospitalisations and supervised rehydration therapy due to severe GE of any aetiology. **Pharmacokinetic properties:** Evaluation of pharmacokinetic properties is not required for vaccines. **Pharmaceutical particulars—Incompatibilities:** This product should not be mixed with any other medicinal products/active immunizing agents.

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