

Rotavirus vaccine Development at Shantha

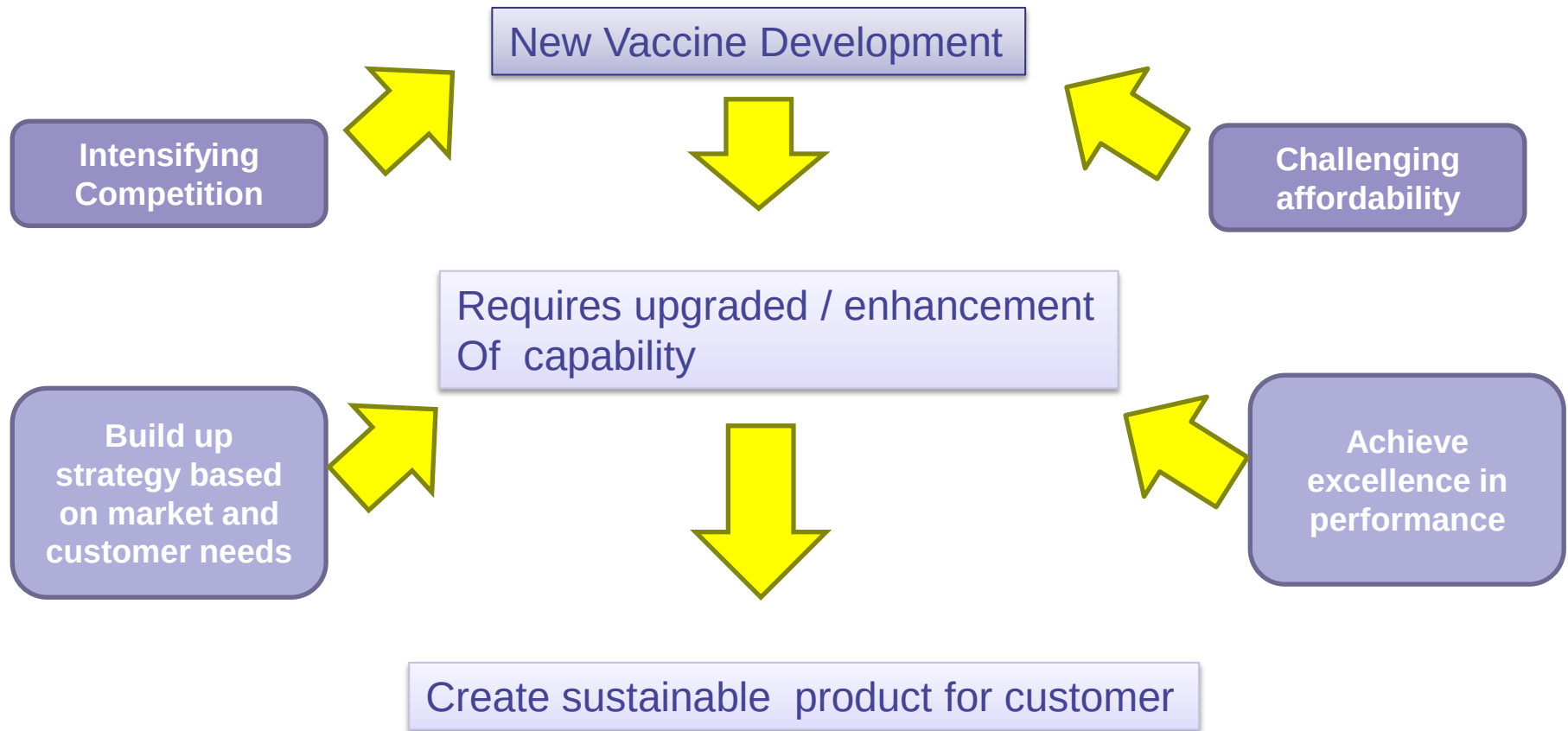
8th Indo-Global Summit and Expo on “Vaccines,
Therapeutics and Healthcare”, Nov 02 – 04 2015, HICC,
Hyderabad, India

Lopa Adhikary
Shantha Biotechnics Private Limited
(A Sanofi Company)

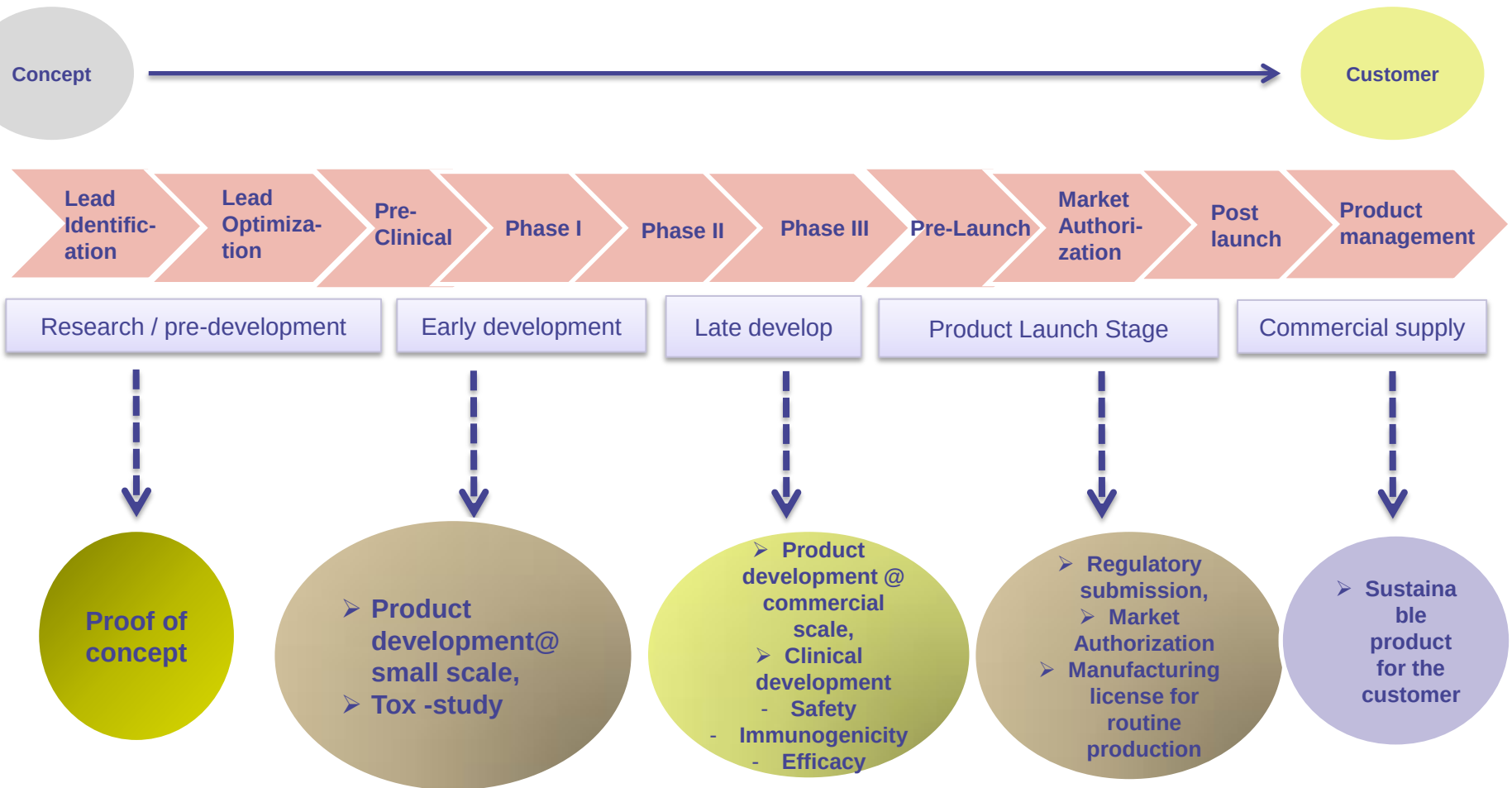
Snap Shot of Rota Vaccine

- New Vaccine Development Path
- Rotavirus – Burden of Disease and Vaccine Demand
- Rotavirus Program at Shantha Biotechnics Private Limited
 - About Shantha
 - Rota Vaccine Program at Shantha
 - Product development
 - Clinical Development

New Vaccine Development in changing Scenario



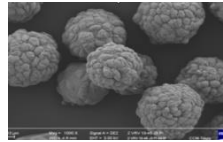
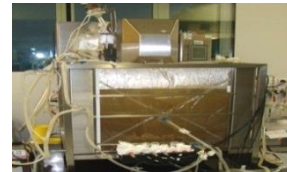
New Vaccine Development Path



Development Stages for Rotavirus Vaccine (1/4)

● Process Development

- Cell bank, Virus bank preparation, testing and characterization as per regulatory need
- Platform technology (cell Factory, Cell cube, Roller bottle, Bio-fermenter)



- Feasibility to scale up of upstream and down stream process
- Capacity build up to meet business need at competitive COGM
- Identify and finalize critical process parameters
- Inbuilt quality for routine production with robustness and batch consistency
- Clinical batch manufacturing
- Successful transfer of process from development to production

Development Stages for Rotavirus Vaccine (2/4)

- **Analytical development**

- To be designed to address the requirements for National Regulatory Authority and compliance with WHO TRS 841 and ICH guidelines
- Finalize the list of Batch Release tests, In Process Control Tests, Process Monitoring Tests for Bulk and Finished Product
- Develop specifications for all the tests as per guideline
- Develop, qualify and validate test methods
- Stability study program
 - @ Real Time, Accelerated, Stress stability, Cumulative
 - With development / clinical / validation batches/ production batches of bulk and finished product
 - To assign shelf life of bulk and finished product

Development Stages for Rotavirus Vaccine (3/4)

● Formulation Development

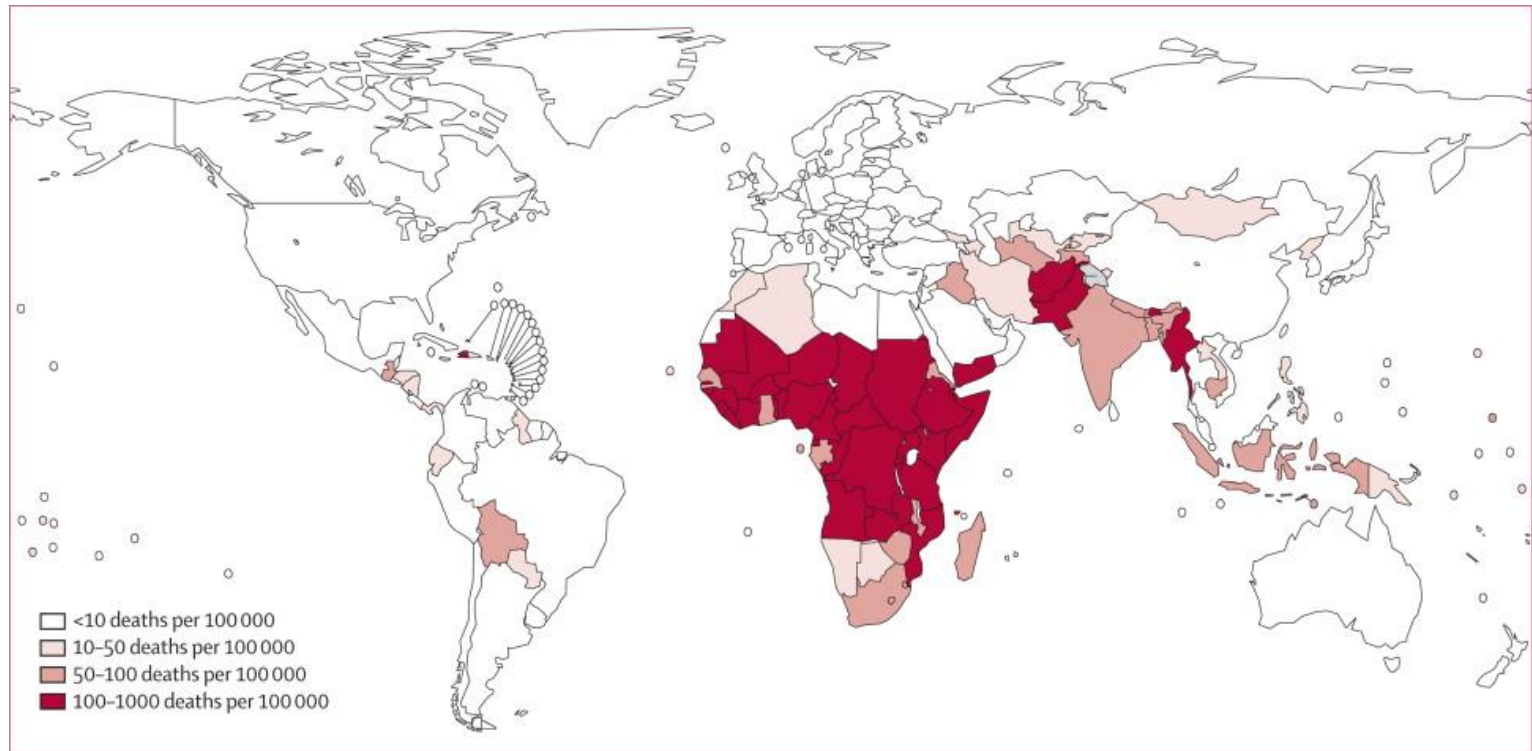
- **Administration: Oral**
- **Presentation : Liquid / Lyophilized etc**
 - Composition: With or without animal origin
 - Stabilization of virus
 - Neutralization of acid
 - Stability of vaccine
 - Storage Temperature
- **Container:**
 - Operation: easy to operate, quality and HSE compliance
 - Market feasibility, competitive advantage
 - Easy to handle, open and administer
 - Product compatibility
 - Impact on COGM



Development Stages for Rotavirus vaccine (4/4)

- Clinical Development to address
 - Safety of the vaccine
 - Immunogenicity
 - To select the dose
 - Efficacy
- Product Launch
 - Regulatory Submission
 - Market authorization
 - Product Launch

Rotavirus Burden of Disease



Rotavirus mortality in children younger than 5 years

Lancet Infectious Diseases 2012; 12: 136-141

Vaccine Demand and Licensure of New Vaccine

- Rotavirus is one of the leading cause of viral diarrhea in children under the age of 5 years resulting in ~80% death in low income Asian and Sub-Saharan African countries
- Affordable vaccine is still a significant medical need
- Global demand for Rota vaccine will reach to ~ 270 million doses (post 2020) based on internal estimate
- Currently available rotavirus vaccines (RotaTeq™, Rotarix™ & Rotavac™) can only partially satisfy the increasing rotavirus vaccine demand
- Need to introduce more new vaccines into the market to avoid supply constrain for the global demand

Rotavirus Vaccine program at Shantha

About Shantha

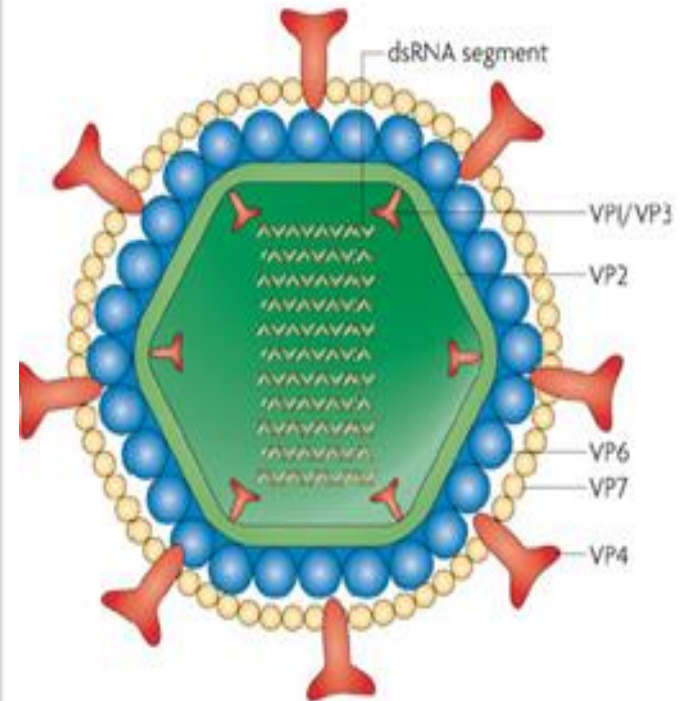


- The first Indian company to develop, manufacture & market a recombinant human healthcare product in India – Shanvac™ B
- The first Indian company to develop, manufacture & market in India an Oral Cholera Vaccine – Shanchol™
- 2009: Acquisition by Sanofi



Rota vaccine Program at Shantha

- Shantha has collaborated with National Institutes of Health (NIH), USA for Rota vaccine program.
- The main objective of Rota vaccine program at Shantha is to develop and license a cost effective Rotavirus vaccine in India.
- Live attenuated Bovine Human reassortant rotavirus vaccine is currently being developed by Shantha.
- The vaccine includes 4 serotypes (G1, G2, G3 and G4) currently responsible for major outbreaks worldwide.



Nature Reviews Microbiology 2007; 5: 529-539

Rota Vaccine program at shantha

Product Development

● Process

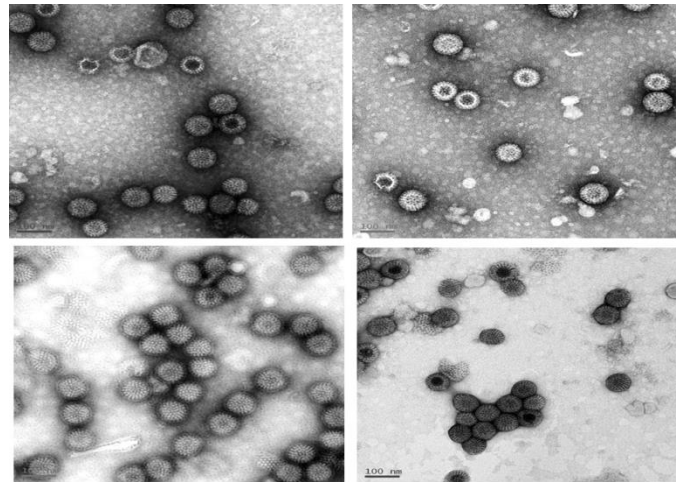
- Raw Material tested
- Cell bank, virus bank made , tested and characterized
- Upstream and down stream process optimized and validated
- Individual viral strains are cultured on Vero cells
- The monovalent harvest pools are stabilized and stored till formulated as tetravalent vaccine
- Phase III clinical batches manufactured, tested and characterized

Rota Vaccine program at shantha

Product Development

● Analytical

- All batch release tests, in process control tests and process monitoring tests were identified, developed and qualified and validated
- Specification developed as per regulatory need
- Viral Characterization
 - The viral strains were extensively characterized during the production of rotavirus vaccine and found to be physically and genetically stable



Electron Micrographs of the four Rotavirus Vaccine strains

Rota Vaccine program at shantha

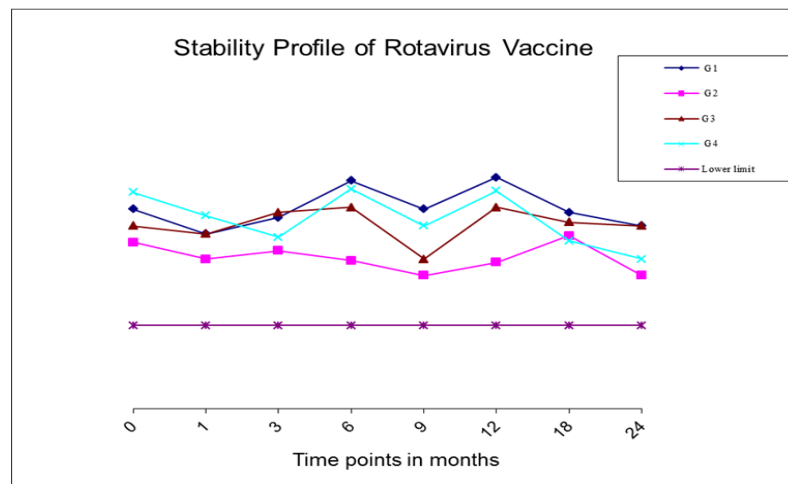
Product Development

● Formulation

- The final vaccine is presented as a ready to use tetravalent liquid formulation of 2 mL/dose.
- The formulation contains necessary stabilizers to maintain viral stability
- It also contain antacids for resisting acidic environment of the stomach.

● Stability profile of rotavirus vaccine

- The Liquid Formulation of the rotavirus tetravalent vaccine is stable for at least 24 months at real time storage conditions



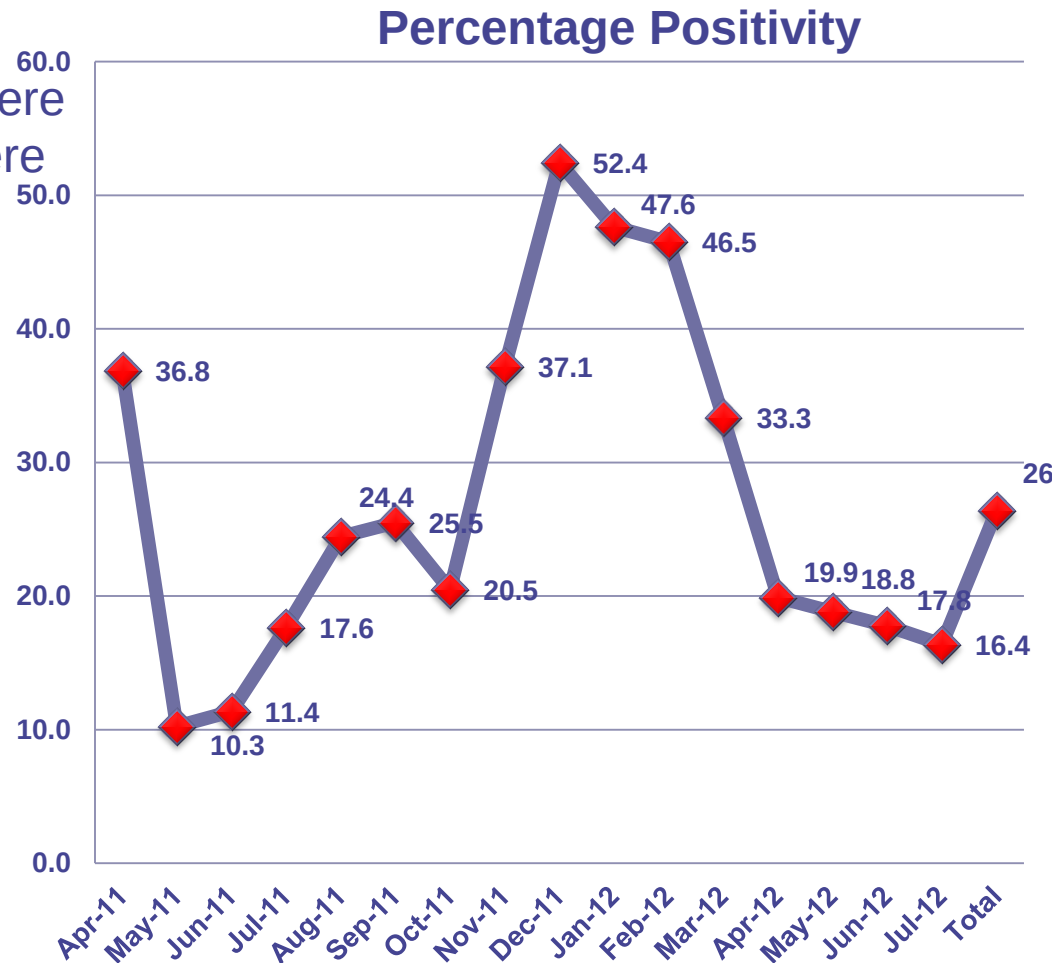
Representative stability plot of the Rotavirus Vaccine at real time storage conditions

Rota Vaccine Program at Shantha

Clinical Development - Rotavirus epidemiology study

- A total of 4,711 Diarrheal cases severe enough requiring hospitalization were studied
- Stool samples were collected from 2,051 & were subjected to ELISA testing
- 541(26.4%) turned out to be positive for Rotavirus
- Reported winter seasonality

Ref: Vaccine 32S (2014) A13–A19



Rota Vaccine Program at Shantha

Clinical Development - Phase I Safety study

Phase I, Randomized, prospective, double blind, Placebo controlled safety evaluation study

Study Visit	D0	D10
Gr 1	*BRV-TV (High dose)	Follow up
Gr 2	Placebo	Follow up

*BRV-TV: Rota vaccine manufactured, tested and released by Shantha Biotechnic Pvt. Ltd.

- **Result:** During 10 days safety follow up period no AE/SAE was reported.

Vaccine 2014; 32S: A117–A123

Rota Vaccine Program at Shantha

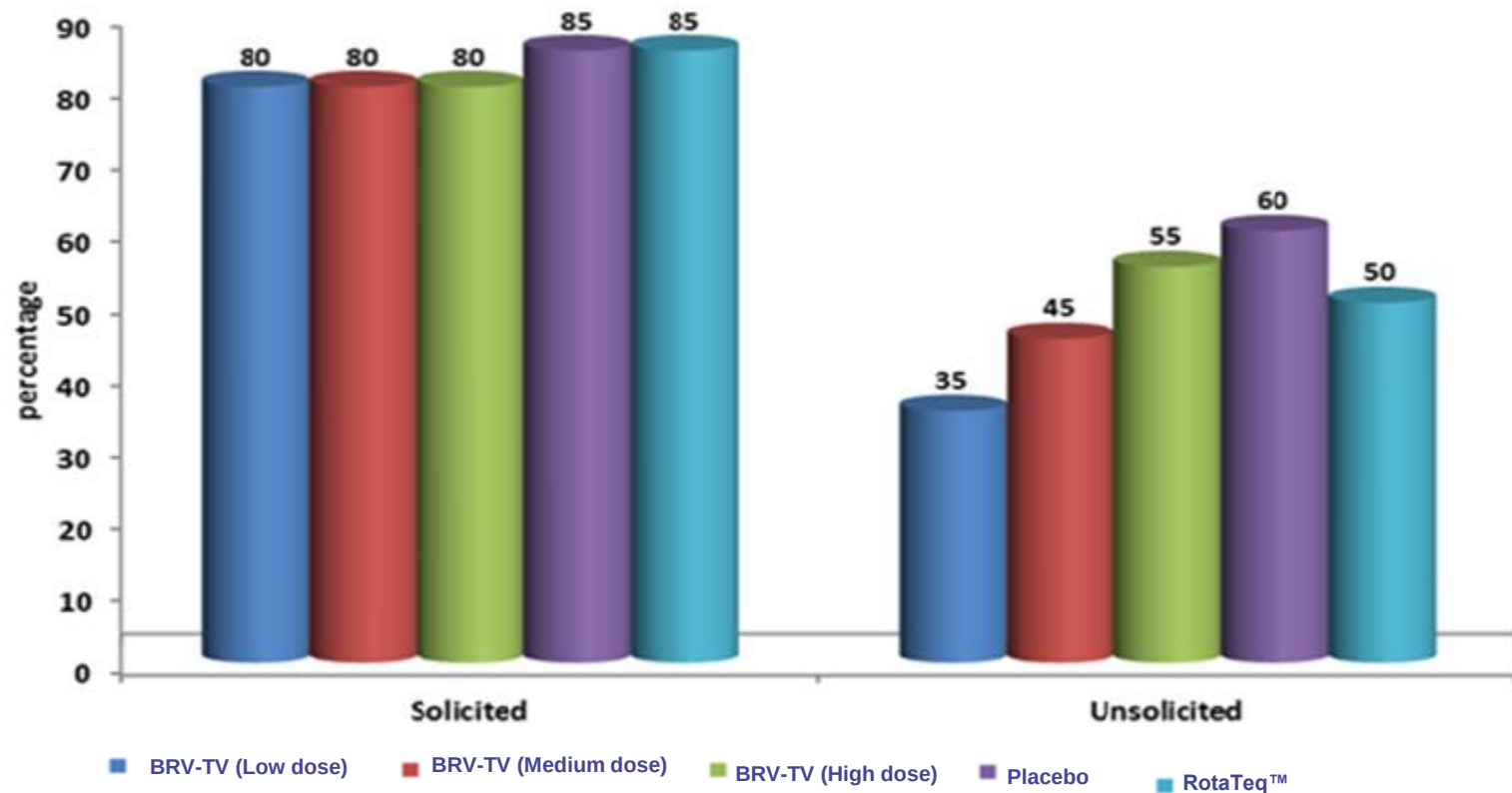
Clinical Development - Phase II Clinical study

Age Study visit	W6 D0	W10 D28	W14 D56	W18 D84
Gr 1	BRV-TV (Low dose)	BRV-TV (Low dose)	BRV-TV (Low dose)	
Gr 2	BRV-TV (medium dose)	BRV-TV (medium dose)	BRV-TV (medium dose)	
Gr 3	BRV-TV (high dose)	BRV-TV (high dose)	BRV-TV (high dose)	
Gr 4	RotaTeq™	RotaTeq™	RotaTeq™	
Gr 5	Placebo	Placebo	Placebo	
All infants	Pentavalent vaccine OPV Blood Sample Stool for viral shedding 3,5 and 7 days after vacc	Pentavalent vaccine OPV [Blood Sample] Stool for viral shedding 3,5 and 7 days after vacc	Pentavalent vaccine OPV Blood Sample Stool for viral shedding 3,5 and 7 days after vacc	Blood Sample Stool for viral shedding 3,5 and 7 days after vacc

Vaccine 2014; 32S: A117–A123

Rota Vaccine Program at Shantha

Phase I/II study - Solicited and Unsolicited Adverse Events



Conclusion: BRV-TV has a safety profile as good as placebo and the licensed vaccine

Vaccine 2014; 32S: A117–A123

Rota Vaccine Program at Shantha

Clinical Development - Phase I/II study: Immunogenicity Results

- All doses tested were immunogenic resulting in an increase in anti-rotavirus IgA
- Increasing doses resulted in a greater proportion of children seroconverting
- Highest immune response was observed with BRT-TV (High dose)
- Immune response against RotaTeq™ was found to be lower than with BRV-TV (High dose)
- Lowest immune response was observed in placebo group

Vaccine 2014; 32S: A117–A123

Rotavirus phase III immune non-inferiority study (CTRI/2014/08/004893)

- Multi-center, randomized, single blind, parallel arm, study
- Total number of infants divided equally into two groups:

	6 Weeks	10 Weeks	14 Weeks	18 weeks
All Infants	Pentavalent vaccine & OPV	Pentavalent vaccine & OPV	Pentavalent vaccine & OPV	-
Group 1	BRV-TV	BRV-TV	BRV-TV	-
Group 2	RotaTeq™	RotaTeq™	RotaTeq™	-
	<i>Blood sample</i>	-	-	<i>Blood sample</i>

- Study planned to be conducted at all sites (Pediatric and Public Health) attached to Medical Schools in India

Rotavirus Vaccine program at shantha

Conclusion

- A fully liquid, stable, having good safety profile and immunogenic live attenuated Rotavirus vaccine has been developed by Shantha Biotechnics Private Limited



Thank you