Bharat Biotech
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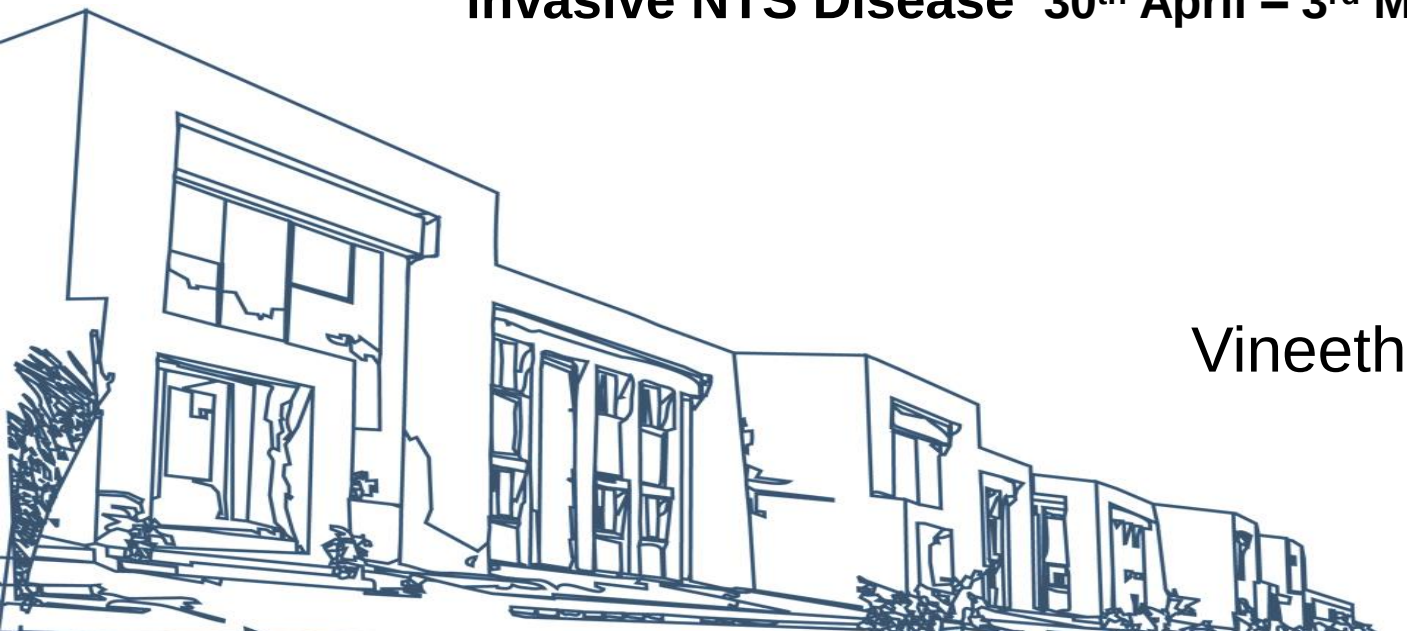
Typbar TCV™

(Typhoid Vi Capsular Polysaccharide-Tetanus Toxoid Conjugate Vaccine)

9th International Conference on Typhoid and invasive NTS Disease 30th April – 3rd May 2015



Vineeth Varanasi

Before the beginning: Typhoid vaccine development at BBIL

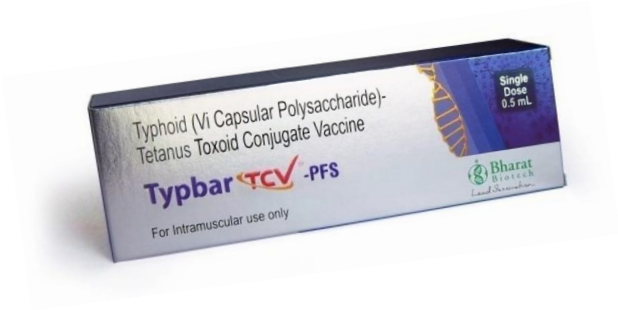
2000: *Salmonella typhi* Ty2 strain generously provided to BBIL by Dr. John Robbins, NIH. Development of Vi capsular polysaccharide vaccine (Typbar)

2002: Phase III study, multi center randomized, active controlled immunogenicity trial with 185 subjects comparing Typbar to Vactyph (Cadilla)

2003: Typbar licensure

2009-2010: Phase IV post-licensure, multi center, randomized, 534 subject comparator controlled non-inferiority study comparing Typbar to Typherix (GSK)

Typbar-TCV Development-Milestones



2014 - Post-Licensure studies

- TCV Measles Interference
- Passive Surveillance
- Active Surveillance

2013 Licensure

2012 Phase III Clinical Trial

2010 Phase II Clinical Trial

2007

2006
Non-clinical Toxicity
Stability testing

2005
R&D scale Vi conjugation to TT

Studies at NIBSC & BBIL
Characterization of conjugate
Mouse immunogenicity

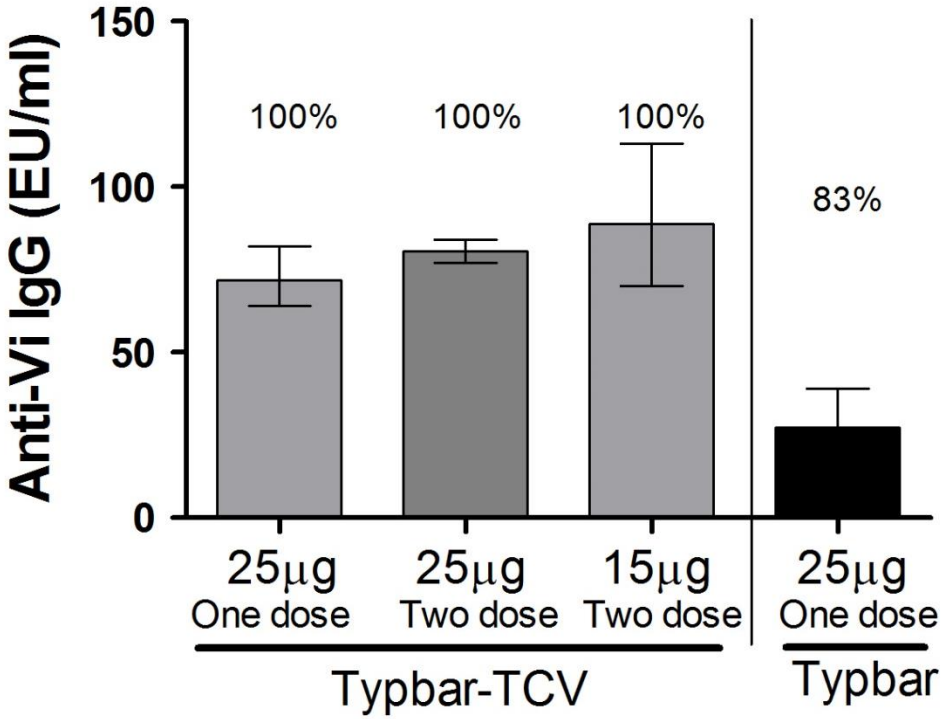
Clinical Trial Phase-IIa/IIb

Open label active controlled Phase IIa / IIb study to evaluate the safety and immunogenicity of BBIL's Typhoid VIPs – TT Conjugate Vaccine *Vs* Reference Typhoid Vi Capsular Polysaccharide Vaccine in healthy teenagers (17-13 yrs) and children (12–2 yrs old).

Protocol Number: BBIL/CTP/02/2008

- Number of subjects enrolled: **100**
- Number of subjects who completed study and were analyzed: **95**

Phase IIa /IIb- Immunogenicity



Single dose of 25µg Typbar-TCV is as immunogenic as two separated doses of 25µg or 15µg Typbar-TCV.

Typbar-TCV Product Characteristics

Description	Presentation
Formulation	Liquid Vaccine
Storage	5ºC ± 3ºC
Dose volume	0.5 ml (Intramuscular injection)
Shelf life	24 months @ 5ºC ± 3ºC
O-Acetyl content (Hestrin)	NLT 0.085 ± 25% (25 µg of Vi Polysaccharide)
Vi Content	NLT 25 µg of Vi Polysaccharide
Free Vi-PS	NMT 20%

Phase-III Clinical Trial

A Phase III, randomized, multicentric, controlled study to evaluate the immunogenicity and safety of BBIL's Typhoid Vi Capsular Polysaccharide Tetanus Toxoid Protein Conjugate Vaccine (Typbar – TCV™) vs. Reference Vaccine (Typbar®) in healthy subjects.

CTRI Registration No : CTRI/2011/08/001957

Trial Initiation Date : 22nd August 2011

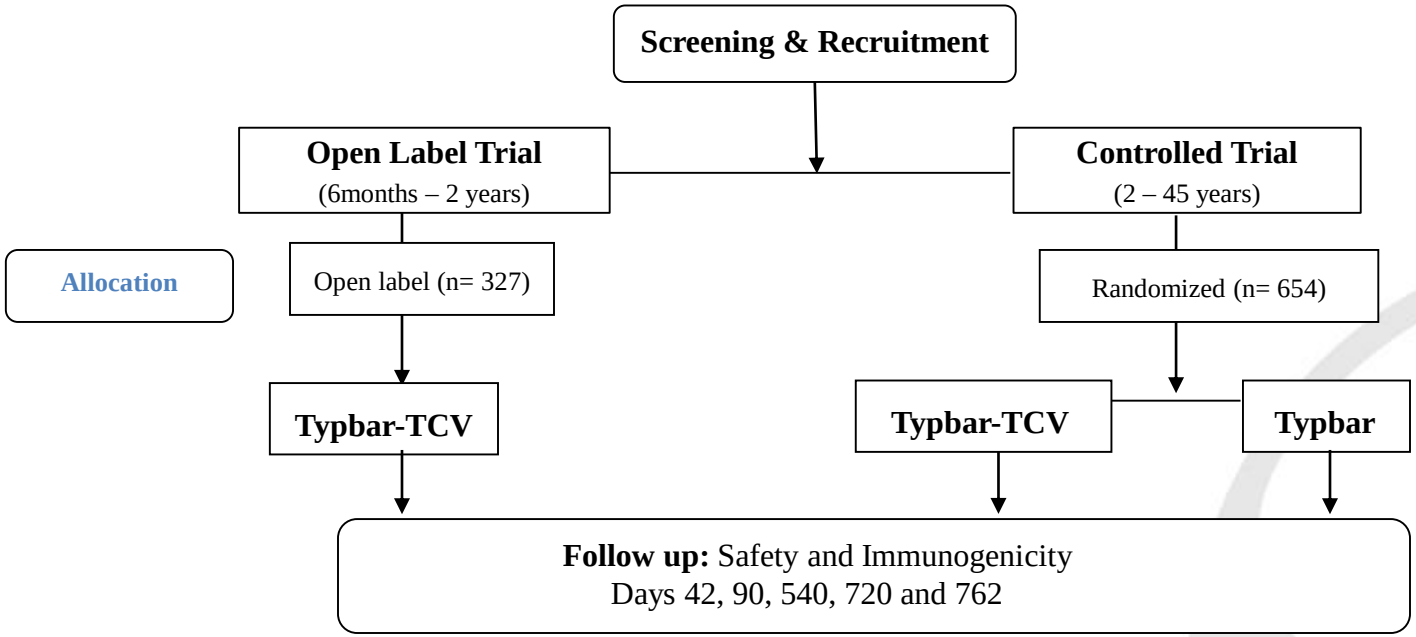
Trial Completion Date : 07th February 2012

Mohan VK et. al, **Clin Infect Dis.** 2015 Apr 13. pii: civ295. [Epub ahead of print]

Trial profile

Test Vaccine: Typbar-TCV™ (TCV); 25 µg/0.5 ml *S.*Typhi (Ty2) Vi capsular polysaccharide Tetanus Toxoid conjugate vaccine. Single dose, I.M injection.

Reference Vaccine: Typbar®; 25 µg/0.5 ml *S.*Typhi (Ty2) Vi capsular polysaccharide vaccine. Single dose, I.M injection.



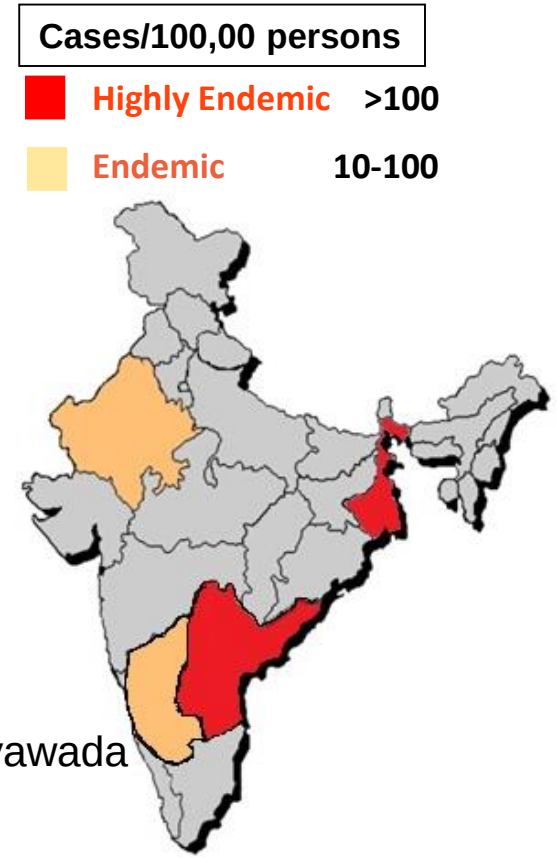
Study objectives

- Comparative assessment of the immunogenicity of typhoid conjugate (TCV) with Vi polysaccharide (comparator).
  - Primary endpoint: anti-Vi IgG response, 6 wks post vaccination.
- Evaluate safety of TCV across all age groups (6 months – 45 years).

- Long-term persistence of anti-Vi IgG.
- Booster responses
- Qualitative assessment of anti-VI response: Avidity, IgG subclasses.

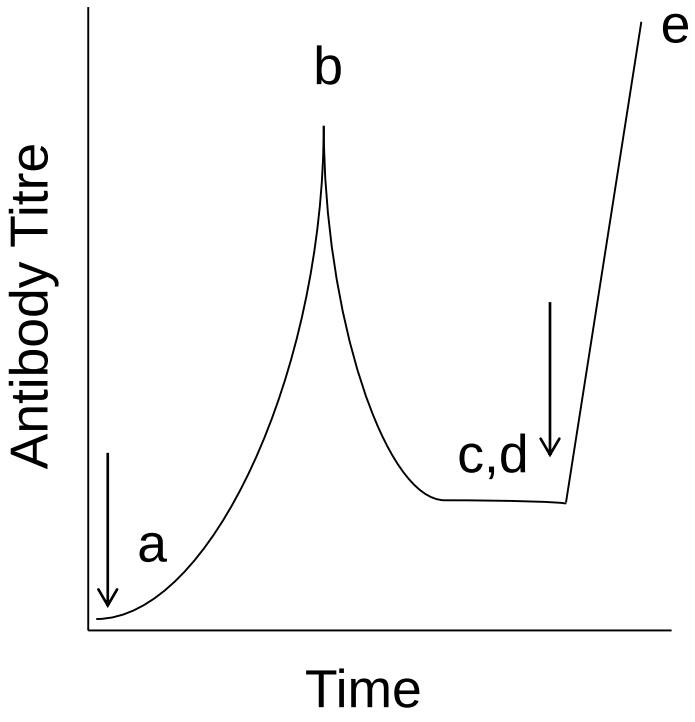
Study investigators and sites

- **Dr. Monjori Mitra**, Institute of Child Health, Kolkata
- **Dr. G. Sampath**, Institute of Preventive Medicine, Hyderabad.
- **Dr. P. Venugopal**, King George Hospital, Visakhapatnam.
- **Dr. Mukesh Gupta**, Soumya Child Clinic, Jaipur
- **Dr. Sudhakar**, Priya Children's Hospital, Vijayawada
- **Dr. S.N. Mahantashetti**, JNMC, Belgaum
- **Dr. Sri Krishna**, Mahavir Hospital, Hyderabad
- **Dr. Bhuvaneswar Rao**, Sri Srinivasa Children's Hospital, Vijayawada



Study was conducted in highly endemic or endemic areas of India

Expectations from typhoid vaccines



a. Safe in all ages, including children.

b. Immunogenic
   - High titre IgG response.
   - Immune response in children < 2 years.

c. Persistence of Vi specific antibodies.

d. Antibody avidity and IgG subclasses.

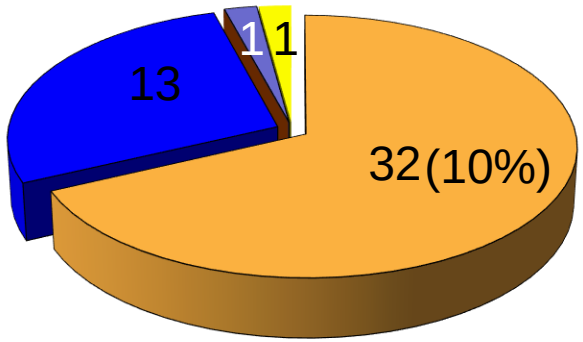
e. Immunological memory- Booster response

WHO. ECBS Guidelines on the quality, safety and efficacy of typhoid conjugate vaccines. **2013**

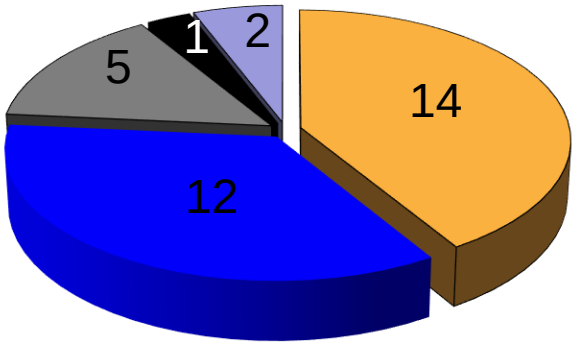
Clinical Safety results

Fever
Pain at injection site
Swelling
Arthralgia
Tenderness
Myalgia
Febrile convulsion

Open Label Trial – TCV (n=332)

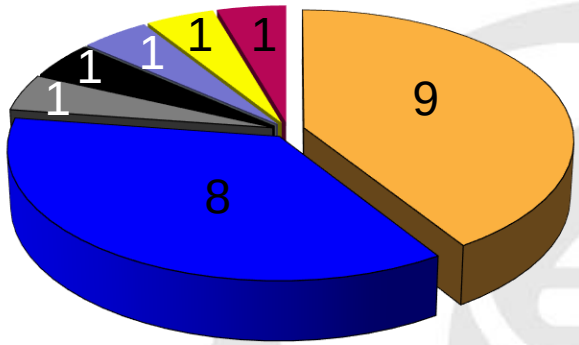


Controlled Trial– TCV (n=332)



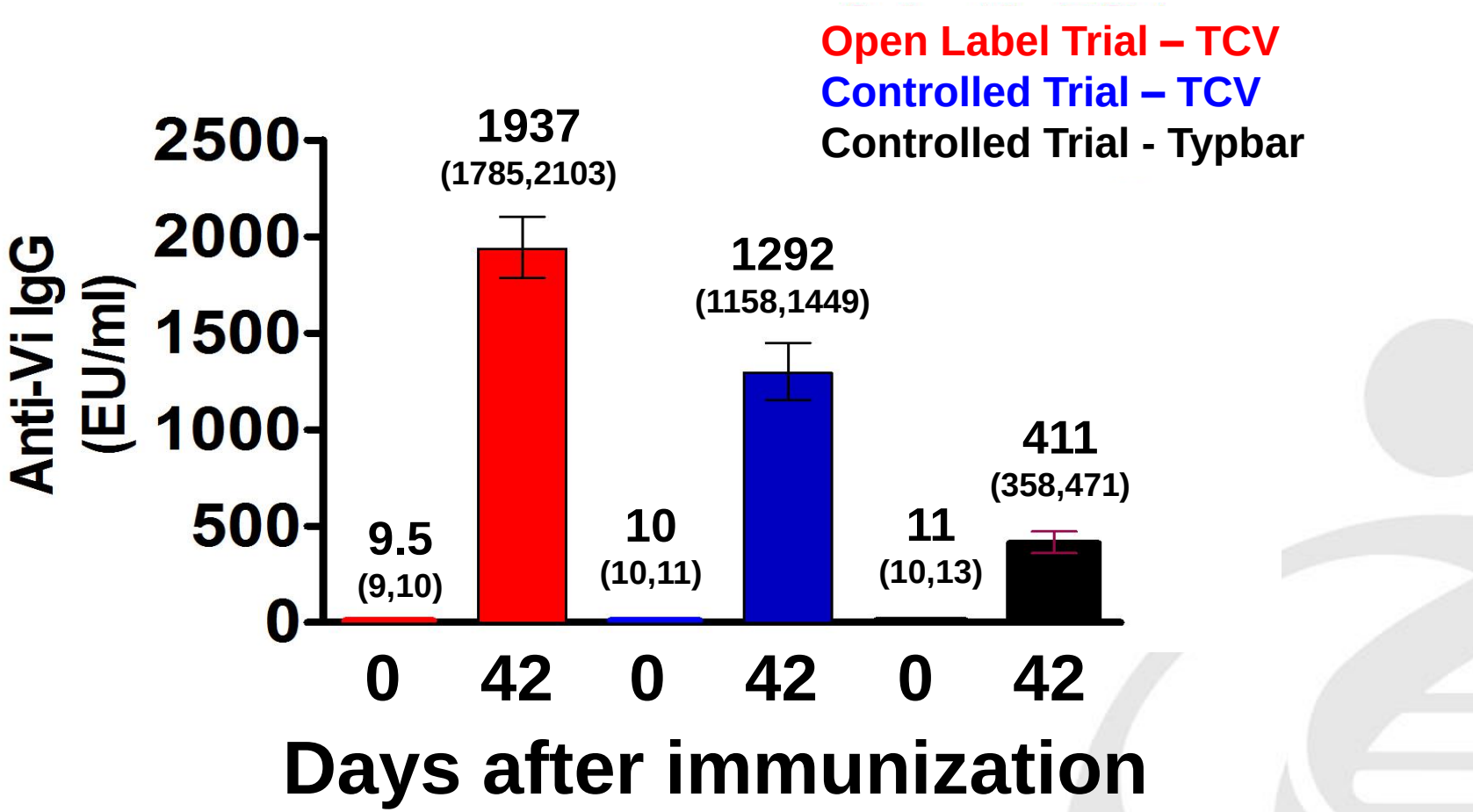
p=0.52
p=0.56
p=0.21
p=1.0

Controlled Trial – Typbar (n=305)



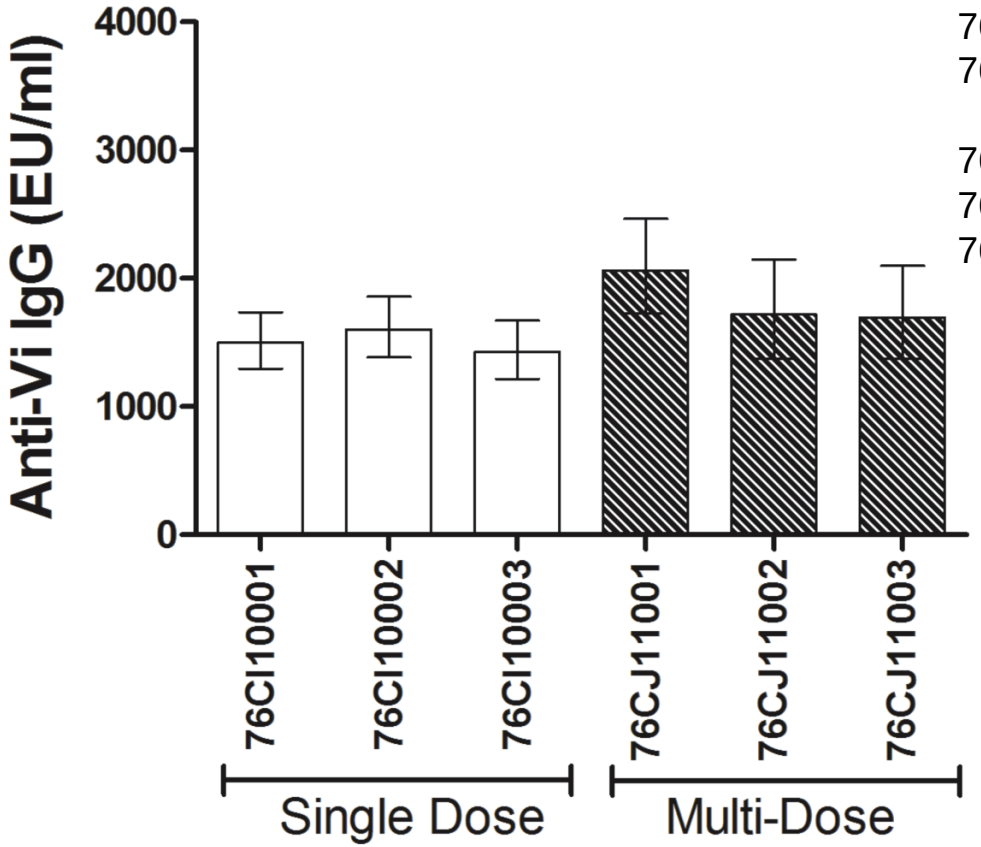
Typbar-TCV is safe in all age groups and is comparable to existing vaccines

High titre anti-Vi IgG response – 6 wks



Typbar-TCV is significantly more immunogenic than Vi polysaccharide.

Vaccine lot consistency



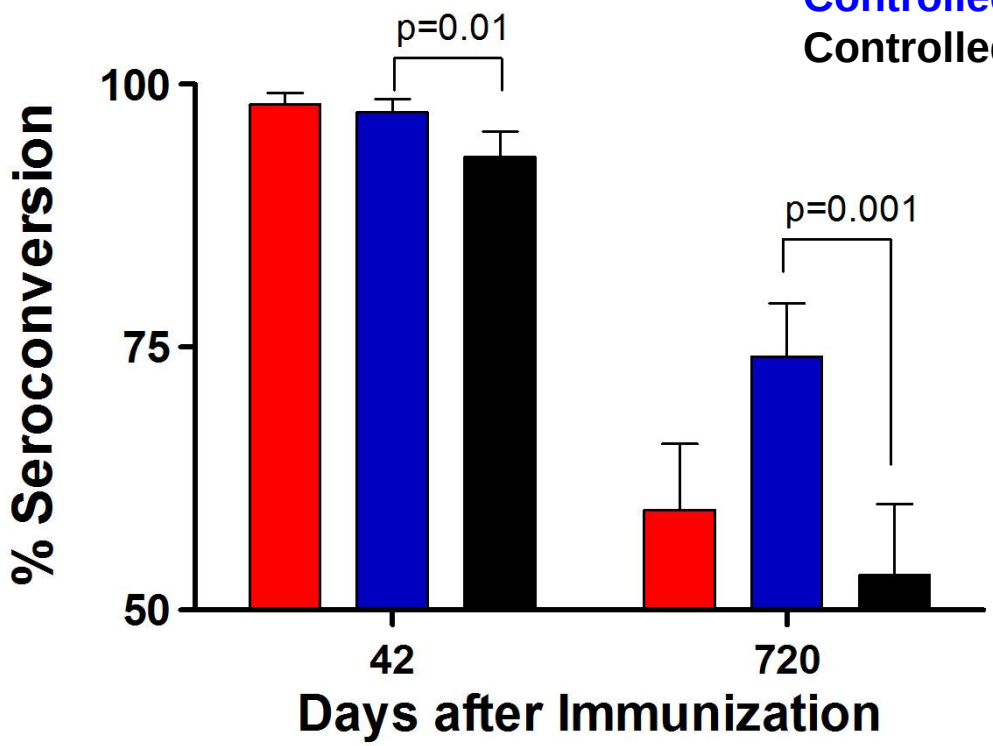
76CI10001 (n=169)
76CI10002 (n=165)
76CI10003 (n=169)
Single Dose

76CJ11001 (n=46)
76CJ11002 (n=46)
76CJ11003 (n=45)
Multi-Dose

High degree of lot-to-lot consistency of both single and multi-dose presentations

Seroconversion

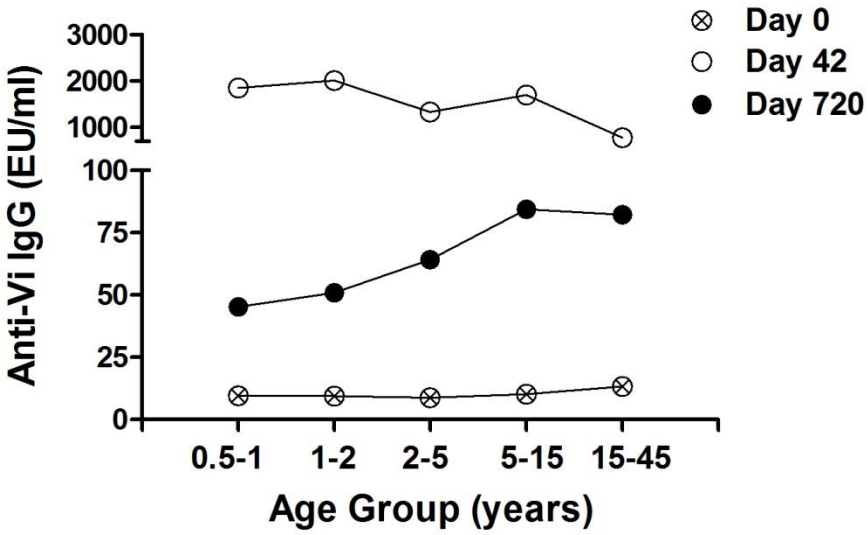
Open Label Trial – TCV
Controlled Trial – TCV
Controlled Trial - Typbar

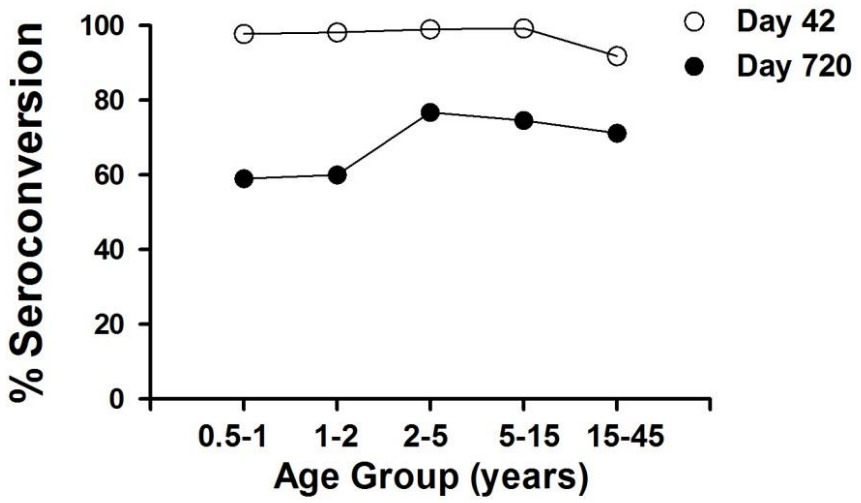


Antibody Persistence

		Day 0	Day 42	Day 720
Open Label Trial	**Typbar-TCV**			
	No. of subjects	307	307	220
	GMT EU/ml (95% CI)	9.5 (9,10)	1937.4 (1785,2103)	48.7 (43,56)
	Fold change		205	5.2
Controlled Trial	**Typbar-TCV**			
	No. of subjects	332	332	243
	GMT EU/ml (95% CI)	10.4 (9.6,11.3)	1292.5 (1153,1449)	81.7 (73,92)
	Fold change		124	7.8
	Typbar			
	No. of subjects	305	305	197
	GMT EU/ml (95% CI)	11.6 (10.5,12.9)	411.1 (359,471)	45.8 (40,53)
	Fold change		35	3.8

Immune response across age groups





Typbar-TCV is immunogenic in all age groups

Greater antibody persistence in older age groups (>15 years)

2 years after a single dose GMT rise over baseline in all ages is ≥ 5 fold

Comparative immunogenicity

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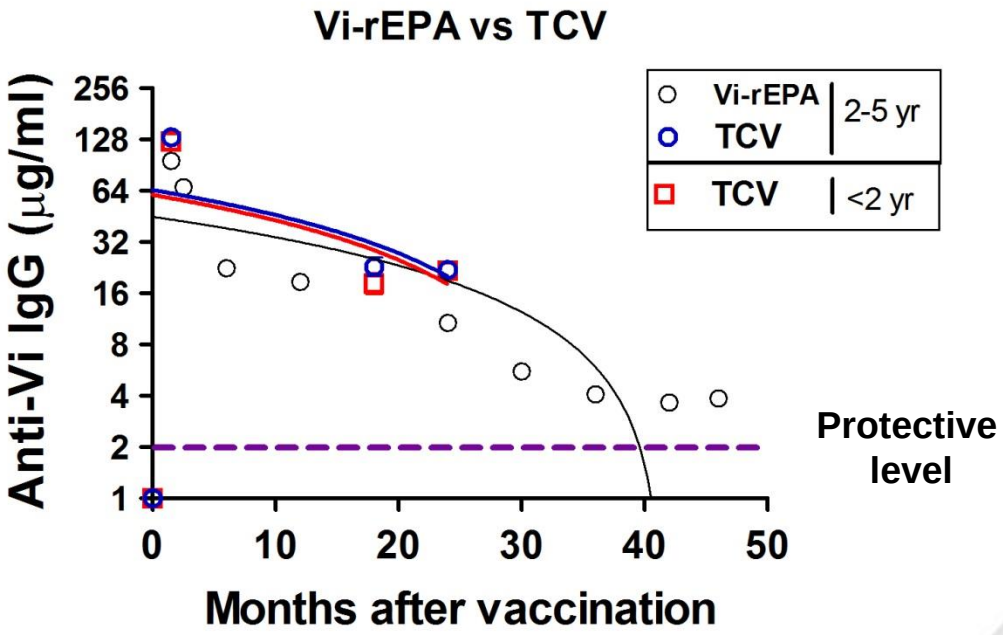
NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development



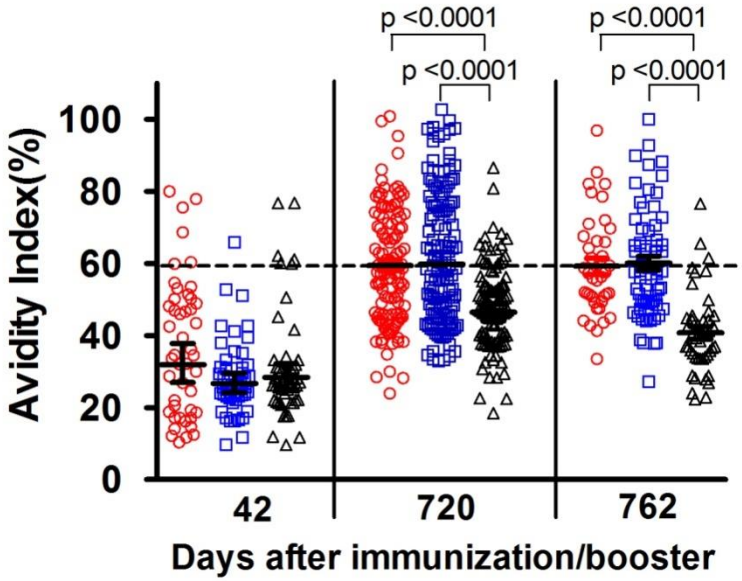
Anti-Vi antibodies likely to persist over the protective level for up to 4 years after vaccination

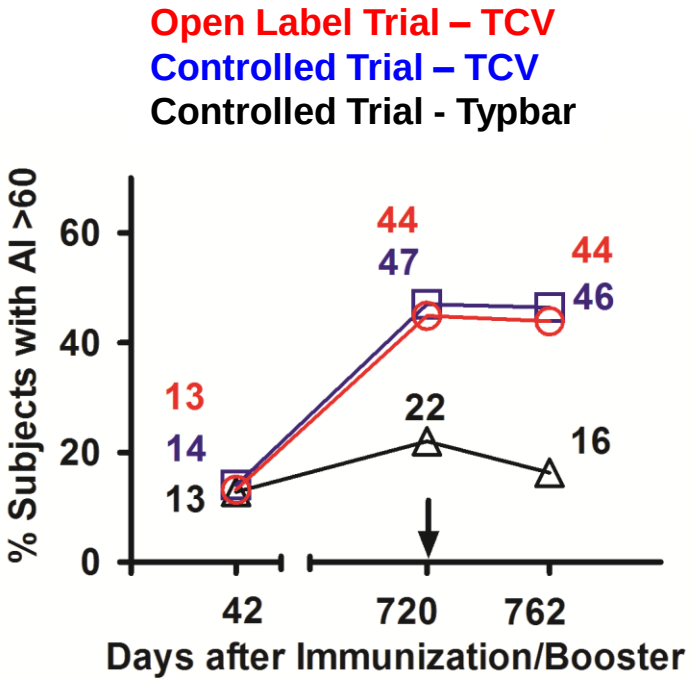
Szu S Expert Rev. Vaccines 2013.12(11):1273-1286.
Mohan VK, et al. Clin Infect Dis. 2015 Apr 13. [Epub ahead of print]

Booster responses – 2 years

		Day 0	Day 42	Day 720	Day 762 (42 days post booster)
Open Label Trial	**Typbar-TCV**				
	No. of subjects	307	307	220	187
	GMT EU/ml (95% CI)	9.5 (9,10)	1937.4 (1785,2103)	48.7 (43,56)	1721.9 (1503,1972)
	Fold change		205	5.2	178 **36**
Controlled Trial	**Typbar-TCV**				
	No. of subjects	332	332	243	175
	GMT EU/ml (95% CI)	10.4 (9.6,11.3)	1292.5 (1153,1449)	81.7 (73,92)	1685.3 (1468,1797)
	Fold change		124	7.8	162 **20**
	Typbar				
	No. of subjects	305	305	197	57
	GMT EU/ml (95% CI)	11.6 (10.5,12.9)	411.1 (359,471)	45.8 (40,53)	445.6 (323,615)
	Fold change		35	3.8	38 **10**

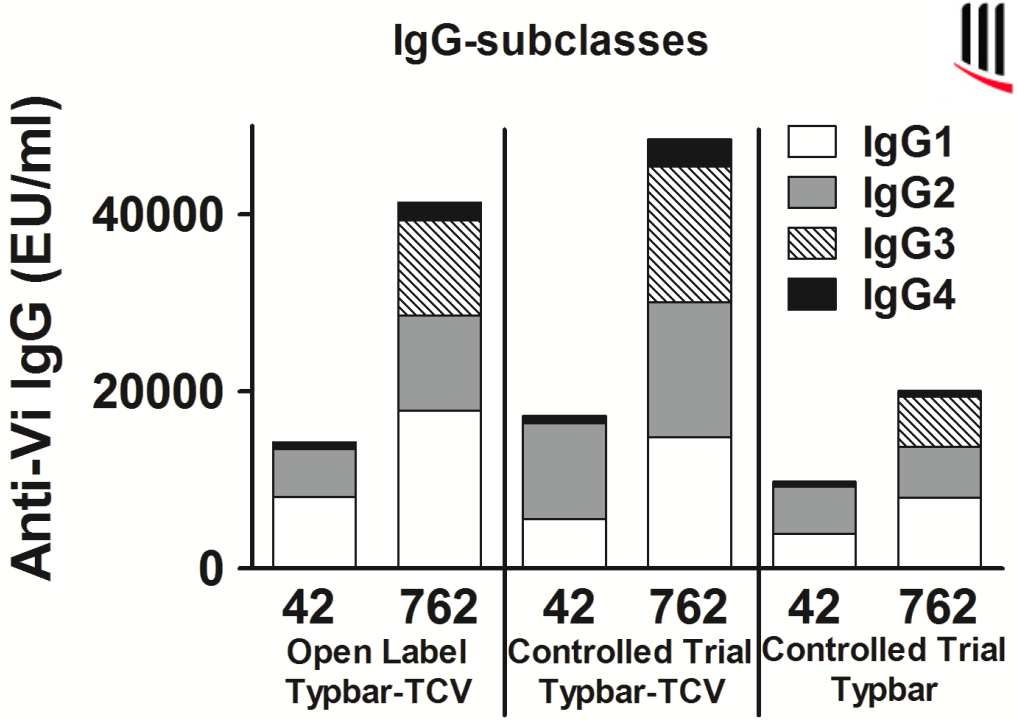
Qualitative assessment of vaccine response - Avidity





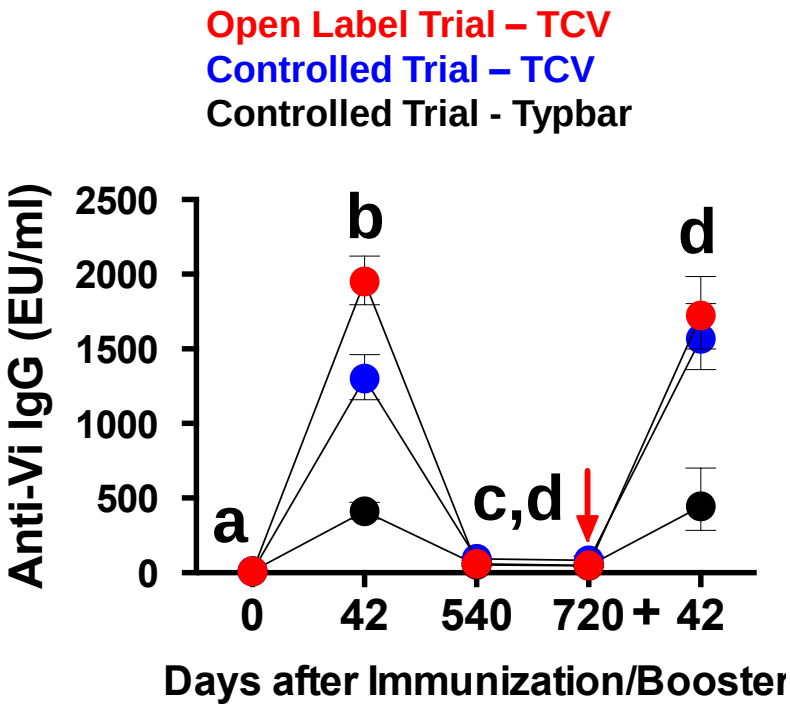
Typbar-TCV potentiates high-avidity antibody responses, that persist after a second dose of the vaccine

Qualitative assessment of vaccine response – IgG Subclass



Typbar-TCV immune response included all sub-classes of IgG

Typbar-TCV conjugate vaccine



a. Safe in all ages, including infants and children.

b. Highly Immunogenic

- High titre IgG response.
- Immune response in children < 2 years.

c. Persistent, Vi specific antibody response.

d. High avidity anti-Vi IgG, including multiple IgG subclasses

e. Potentiates booster responses.

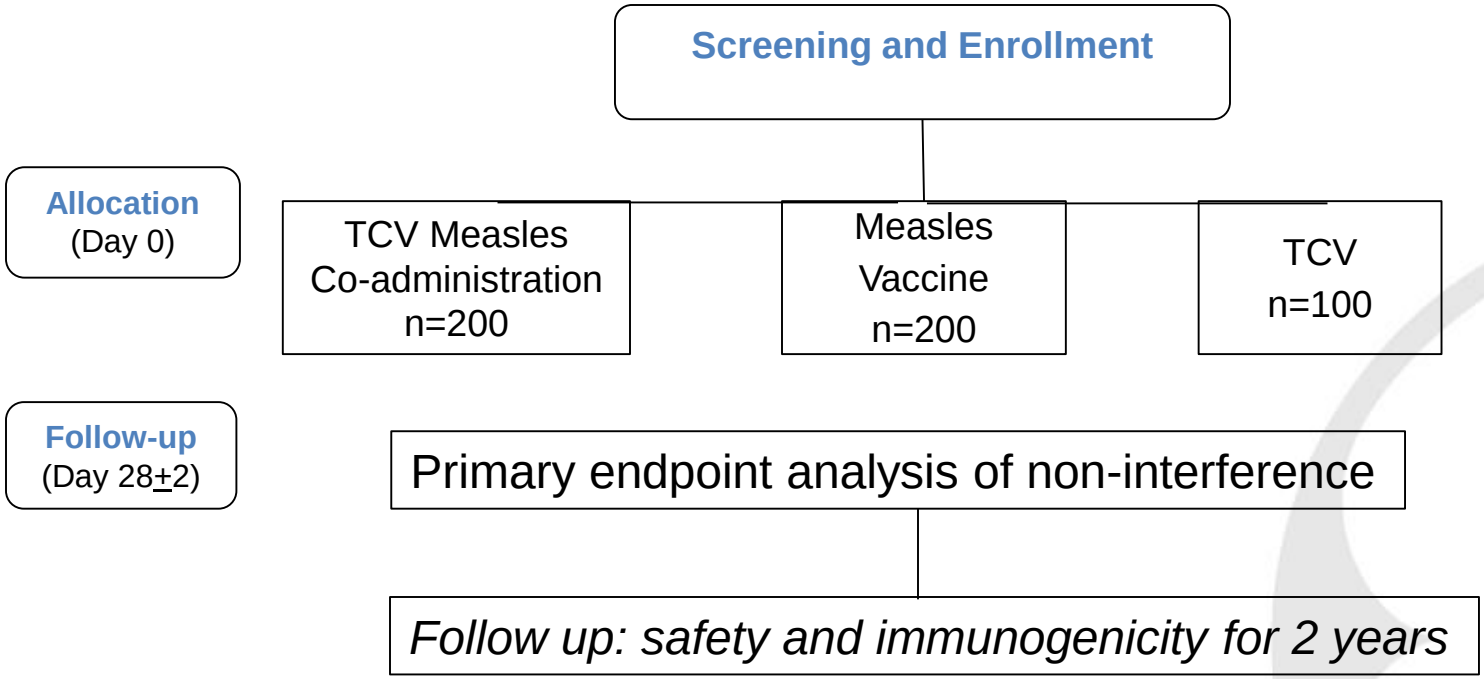
Post-licensure studies

- Long-term follow-up underway for Phase III subjects.
  - ✓ 3-year follow up and data analysis is ongoing.
- TCV-Measles interference study
  - ✓ Enrollment complete: study ongoing
- Passive Surveillance: continuing
- Active Surveillance: Awaiting regulatory approval
- Human Challenge Study in collaboration with Oxford University: Regulatory approvals completed

TCV Measles Interference – Study design

A Phase IV, Randomized, factorial assigned, Open labelled, study to evaluate the non-interference in immune response of Typhoid Vi Capsular Polysaccharide - Tetanus Toxoid Conjugate Vaccine (Typbar-TCV™) administered to children at 9 months, to measles vaccine given concomitantly.

CTRI 2014/04/004532



TCV Measles Interference – preliminary data

Serum anti-Vi and anti-measles IgG antibodies elicited 28 days post-vaccination.

	Measles + Typbar-TCV (n=70)	Measles (n= 25)	Typbar-TCV (n= 20)	p- value
Measles IgG (mIU/ml) GMT (95% CI)	465.6 (388, 558)	507 (369, 697)	-	0.86
Measles IgG % Seroconversion (95% CI)	91.4 (82, 96)	84.0 (65, 94)	-	0.93
Anti- Vi IgG (EU/ml) GMT (95% CI)	1801.0 (1118, 2903)	-	1609 (689, 3756)	0.49

Measles seroconversion: Post vaccination titres >150 mIU/ml
P values for GMT calculated by student's t-test.
P value for proportions calculated by two-tailed Chi-square test with Yates correction.

TCV Measles Interference- Secondary objectives

Safety: Assessed at primary endpoints and long-term follow up.

Dose schedules : Single dose, single dose followed by booster at 6 months or 2 separated doses at 4 week interval.

Long term follow up: Subjects will be tracked for 2 years to test for persistence of anti-Vi titres in the 3 different TCV dose schedules.

Post-market passive surveillance

- Since the Product launch we have marketed close to one million doses of Typbar TCV

- PMS forms are being collected as part of the Passive Post Marketing Surveillance system

- No serious adverse reaction related to vaccine have been reported so far. Surveillance is ongoing.

- Active surveillance protocol submitted and pending regulatory approval. Surveillance expected to start in Q4 2015

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Thank you!

"Team BHARAT Typbar-TCV"

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