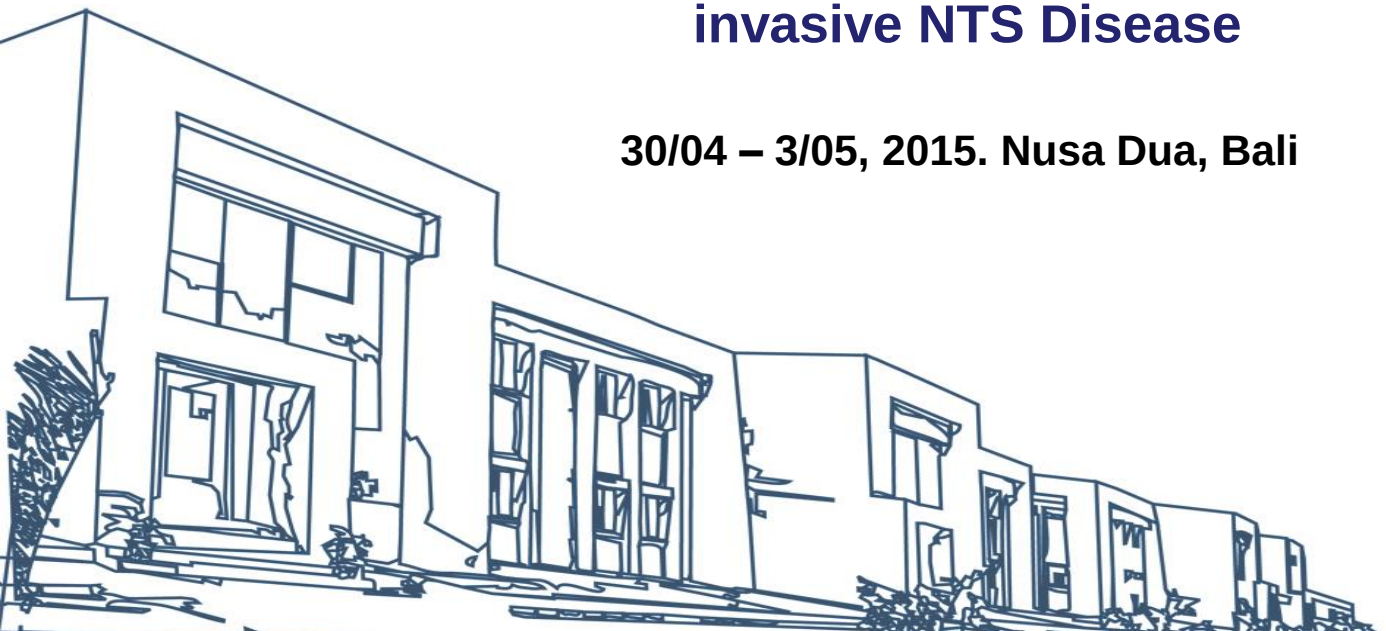
Integration of typhoid conjugate vaccine in national immunization schedules: Opportunities and Challenges.

9th International Conference on Typhoid and invasive NTS Disease

30/04 – 3/05, 2015. Nusa Dua, Bali



Objective

Review the existing clinical data on Vi conjugate vaccines, based on literature and our experience with Typbar-TCV to ascertain data sufficiency to assist global policy formualtion.

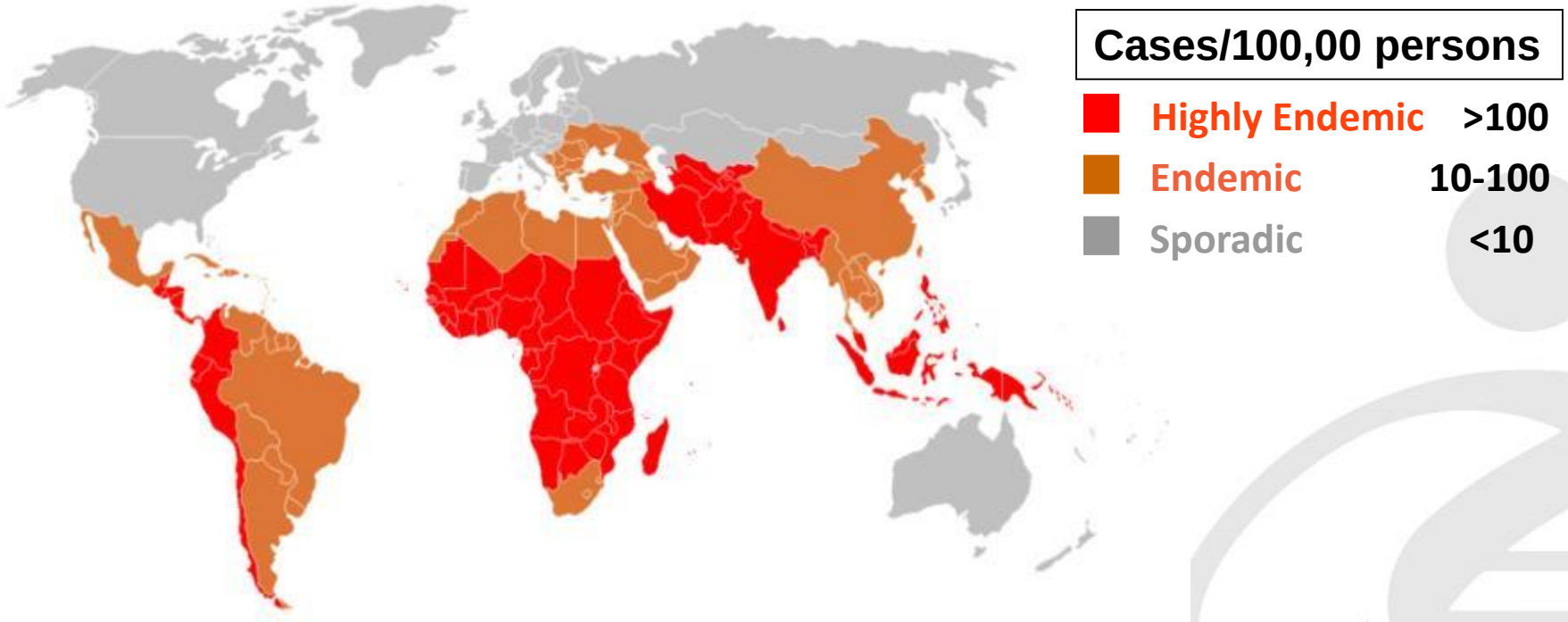
Presentation Outline

- Need for typhoid vaccine – Disease burden
- Typhoid conjugate vaccines – Key considerations
- Available data from typhoid conjugate vaccines (TCV)
- Programmatic considerations
- Integration of TCV into childhood immunization programs

Typhoid epidemiology

Disease Burden

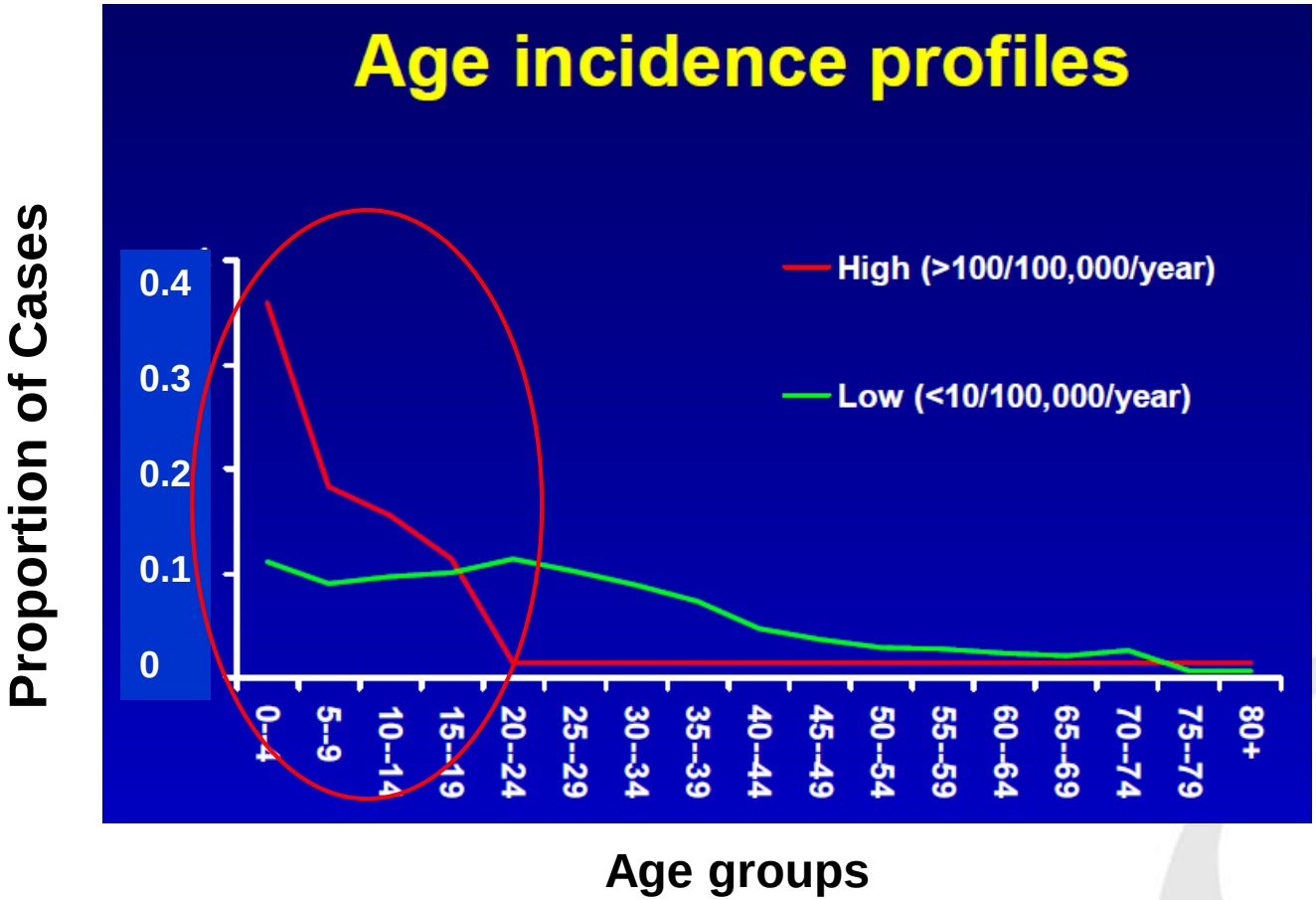
This disease is endemic in most developing countries.



21 million cases worldwide, mortality ***estimates*** of 216,000 to 600,000.

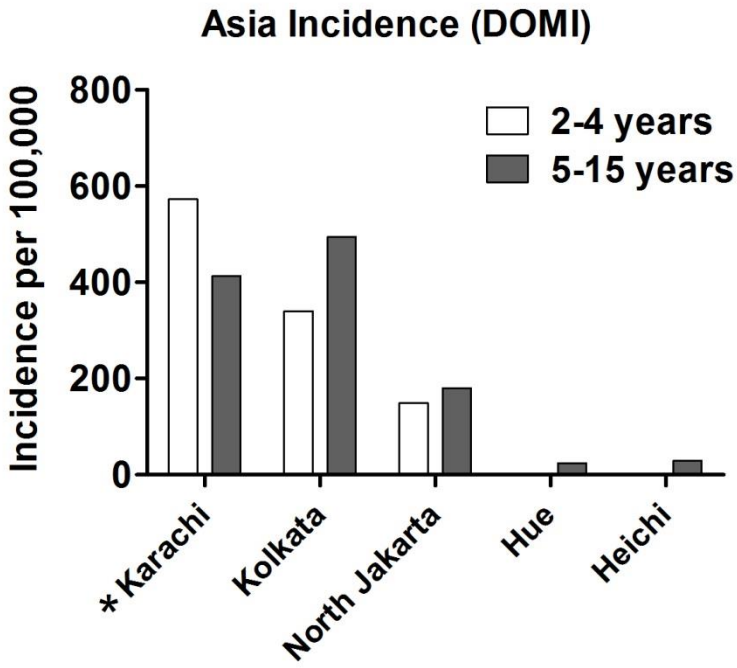
http://www.who.int/immunization/topics/en/
http://www3.chu-rouen.fr/Internet/services/sante_voyages/pathologies/typhoide/

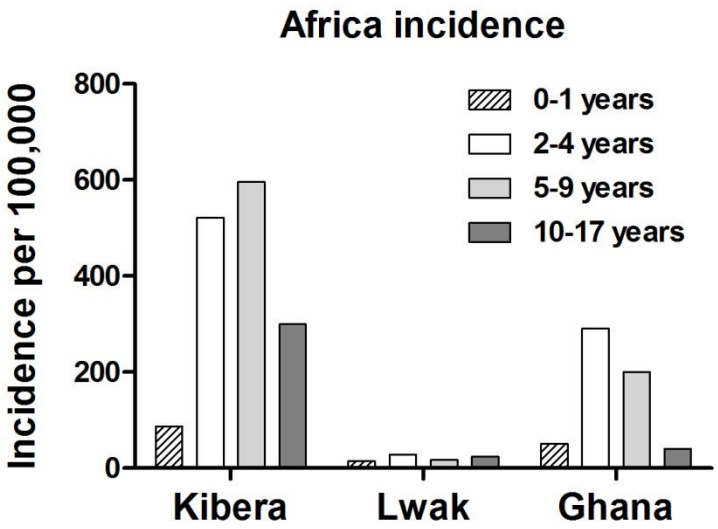
Age stratified disease burden



Crump JA, et al. Bull World Health Organ 2004;82:346-353

Typhoid fever incidence – Asia and Africa





- High incidence of typhoid fever in the region.
- Substantial regional variation in incidence.
- “Modified” Passive srvlnce.

- High incidence in urban slums; rates similar to those from Asia.
- Lower burden in rural children from Ghana (and Lwak, Kenya), compared to urban areas; regional differences
- Active srvlnce.

Ochiai RL, et al. Bull World Health Organ 2008;86:260-268.
Breiman, RF et. al, PLoS One. 2012; 7(1): e29119.
Marks, F et. al, Emerg Infect Dis. 2010; 16(11): 1796–1797.

Typhoid conjugate vaccines

Typhoid conjugate vaccines

TYPBAR-TCV

- Capsular Vi polysaccharide from Ty2 strain–conjugated to carrier protein.
- Approved for use in ages 6 months and above
- Dosing: Single dose, intramuscular injection.

Licensed in India

Vaccines in Development

China (LIBP)/NIH, USA : Vi-rEPA

Italy/India (NVIGH/BE) : Vi-CRM_{197}

IVI/Indonesia PT Bio Farma) : Vi-DT

Key considerations for typhoid conjugate vaccine implementation

Bharat Biotech
Lead Innovation

1. Target age group for TCV immunization in the UIP program
2. Number of vaccine doses in primary vaccination series
3. Age dependency of primary vaccination series
4. Timing of booster dose
5. Immunological basis of protection ; correlates of protection
6. Persistence of protective levels of antibodies
7. Compatibility with Measles and MMR vaccines
8. Post Marketing & Effectiveness Studies
9. Efficacy studies – are they imperative

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

Programmatic considerations

Typhoid Conjugate vaccines: Window of Opportunity (1)

	Age	Birth	6 Weeks	10 Weeks	14 Weeks		9 months	12 Months	15 Months	18 months
Vaccine										
BCG		BCG								
Hep B		Hep B0	Hep B1	Hep B2	Hep B3					
Polio		OPV0	OPV1	OPV2	OPV3					
DTP			DTP 1	DTP 2	DTP 3					
Hib			Hib 1	Hib 2	Hib 3					
Pneumococcal			PCV 1	PCV 2	PCV 3					
Rotavirus			RV 1	RV 2	RV 3					
MCV							MCV1		MCV2	
Hep A								*Hep A1 & Hep A2*		
Typhoid							*TCV*			

MCV- Measles-containing vaccine
MCV1- First dose of MCV
MCV2- Second dose of measles; may be given with rubella

Typhoid Conjugate vaccines: Window of Opportunity (2)

- Typhoid is not a major concern in the < 12 month age infants ; certainly much lower at < 6 months.
- MCV, only vaccines in the 9-18 month window (Measles & MMR).

- Targeting TCV co-administration with Measles vaccines seems ideal and allows flexibility for adoption of one/two dose schedules.
- Co-administration with MCV needs to be studied to allow for this schedule.

- School based programs should also be considered to achieve complete coverage (in many endemic countries, peak incidence is at school age ; DOMI studies & Jakarta data).

Typhoid Conjugate vaccines- Clinical experience

Typhoid Conjugate vaccines under discussion

Vi-rEPA: National Institutes of Health, Single & Two-dose 25µg Vi-rEPA conjugate.

Vi-CRM_{197}: Novartis, Vi-CRM_{197} conjugate

Typbar-TCV: Bharat Biotech Intl Ltd, Single dose 25µg Vi-TT conjugate

Typbar-TCV Results

Detailed Results for Typbar-TCV on:

- Phase III results : Ab titres post vaccination
- Long term persistence
- Avidity results
- IgG sub-classes
- Booster effect
- Measles & MCV interference

would be presented in a separate talk, later.

Dosage

Vi-rEPA

Amt (μg) of Vi as Vi-rEPA	No. of children, GM no. of ELISA U/ml (25th–75th percentiles)[b]		
	Preimmune	10 wk	1 yr
5.0	76, 0.17 (0.10–0.22)	80, 43.0 (29.1–60.8)	75, 6.43 (3.84–10.4)
12.5	80, 0.14 (0.09–0.20)	80, 74.7 (49.9–102)	79, 11.3 (7.15–15.7)
25.0	78, 0.13 (0.08–0.20)	77, 102 (65.1–163)	77, 13.3 (7.87–23.3)

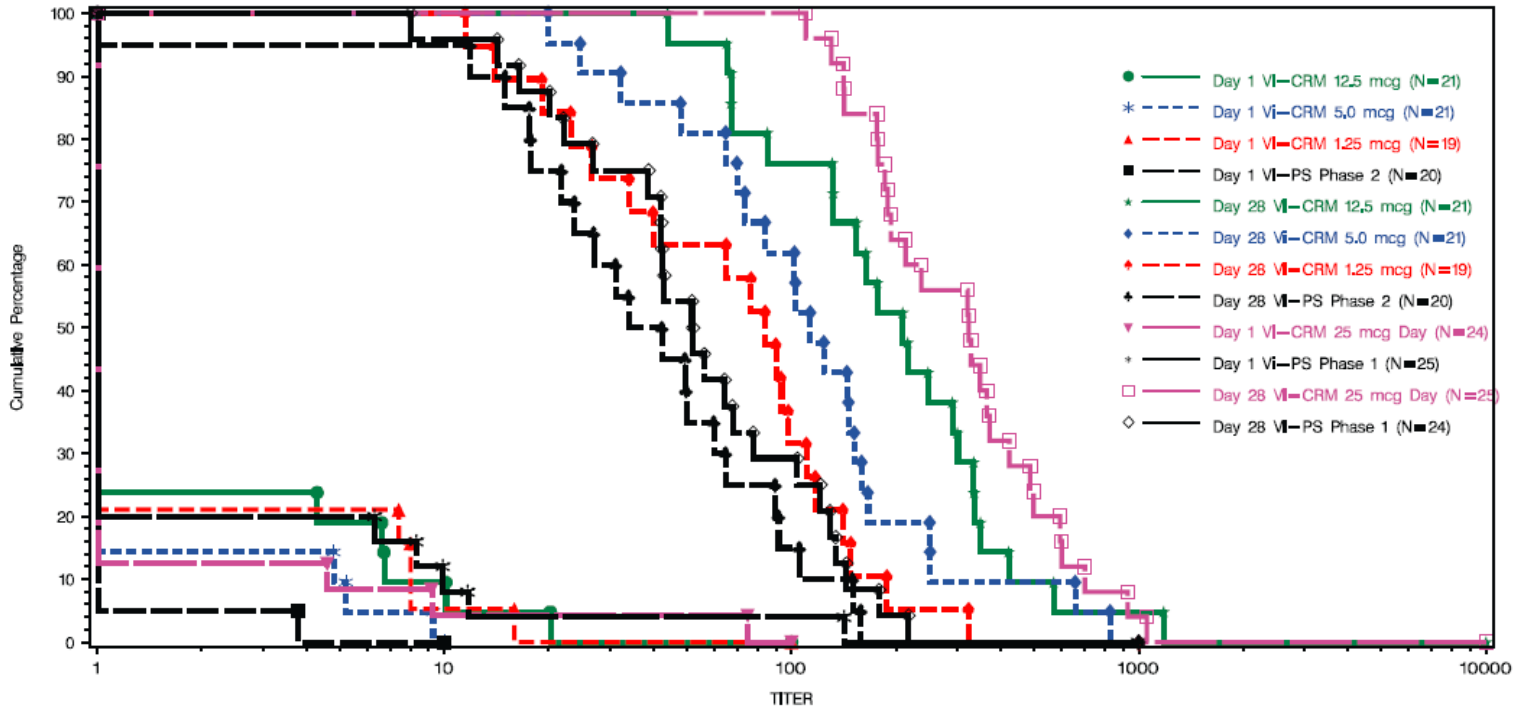
Typbar-TCV : Phase II results

	GMT (U/mL)	**95 CI** (UUL,LL)
25 µg, Single Dose	71.7	82, 64
25 µg, Two Doses	80.4	84,77
15 µg, Two Doses	88.8	113,70

Canh DG, et al. Infect Immun. 2004.72(11):6586-6588.

Dosage

Vi-CRM$_{197}$



Van Damme P, et al. PLoS One 2011. 6 (9): e25398.

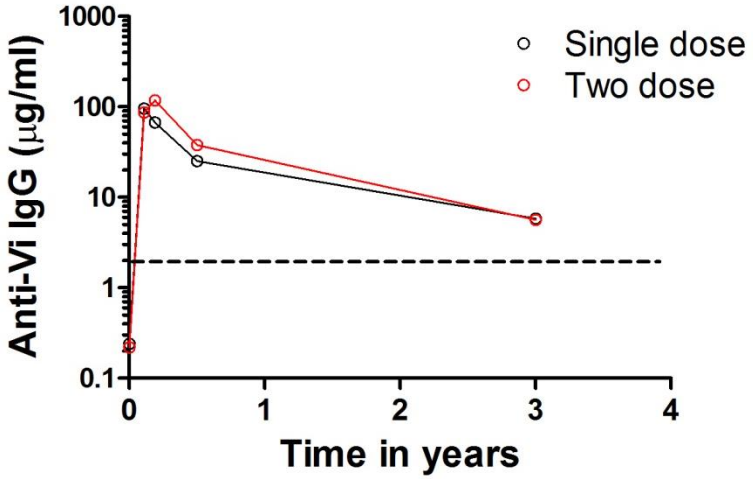
Dosage

- Vi dose dependent increase in immune response to Vi conjugate vaccines
- Highest response with 25µg Vi conjugate/dose in all 3 studies.
- Vi-rEPA efficacy study and Typbar-TCV phase III study - 25µg Vi conjugate/dose.

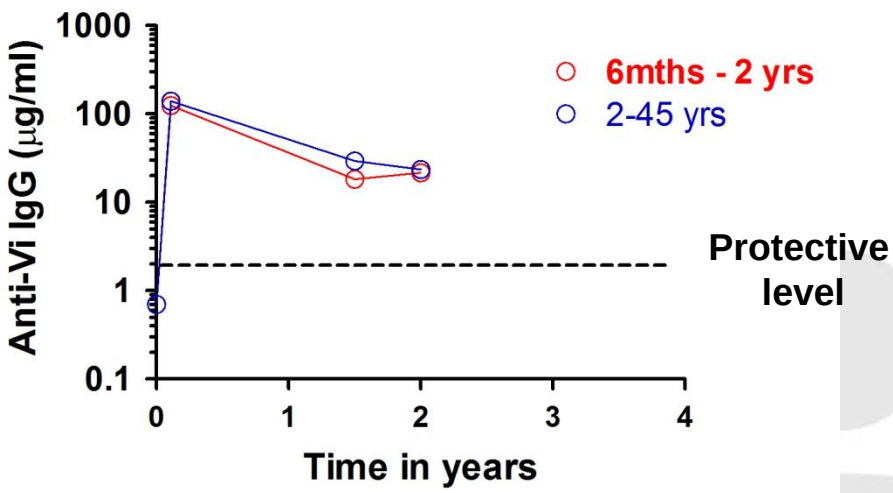
Canh DG, et al. Infect Immun. 2004.72(11):6586-6588.
Van Damme P, et al. PLoS One 2011. 6 (9): e25398.

Dose schedule

Vi-rEPA, 25µg Vi per dose



Typbar-TCV, 25µg Vi per dose

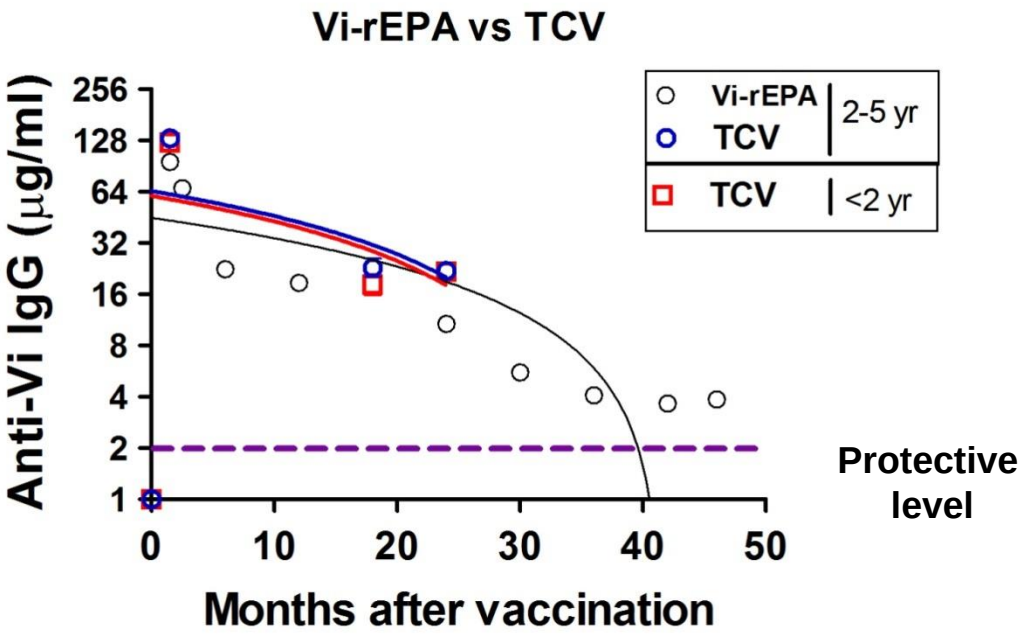


- Single dose schedule of 25µg Vi-rEPA, as immunogenic as two doses, over 30+ months of follow up.
- Single dose of 25µg Typbar-TCV; immunogenic over 2 years of follow up in ages 6 months – 45 years (3 year follow-up data under analysis).

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

Comparative immunogenicity

Eunice Kennedy Shriver National Institute of Child Health and Human Development



Anti-Vi antibodies persist over the protective titers for upwards of 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]

Efficacy – correlate of protection

- Based on a large efficacy study, VI-rEPA has been shown to be protective for 4 years and Ab titres protective over 8 years in 2-5 year age group and 10 years in adults[1]
- Based on data from the Vi-rEPA studies, an anti-Vi IgG titer 2.0 µg/ml is a suggested estimate of protective titer[2].
- In the absence of an internationally accepted Vi IgG standard serum, this is the best correlate for protective efficacy, currently available.

1. Szu S Expert Rev. Vaccines 2013.12(11):1273-1286.
2. Szu S, et al. Vaccine 2014. 32 (20): 2359-2363.

Compatibility with measles vaccine

- Typbar-TCV has been found to be compatible with measles vaccine

.

- Compatibility with MMR vaccines is also being studied.

Conclusions (1)

1. Target age group for TCV immunization in the UIP program
   - Primarily from 6 months age and above.
2. Number of vaccine doses in primary vaccination series
   - Single dose schedule.
3. Age dependency of primary vaccination series
   - May be necessary to give multiple doses in < 6 months of age.
4. Timing of booster dose
   - Spaced by at least 6 months from first vaccine dose.
   - If missed, booster dose can be given up to 3 years age.
   - School based booster program can also be considered.

Conclusions (2)

5. Immunological basis of protection, correlates of protection
   - Current guidance available based on NIH Efficacy studies.
   - Anti-Vi IgG, internationally accepted standard needed.
6. Persistence of protective levels of antibodies
   - Typbar-TCV is able to protect for 3 years (current data).
7. Compatibility with measles vaccine
   - Typbar-TCV found to be compatible with Measles containing vaccines.

Typbar-TCV: critical expectations met

- Safety and immunogenicity, as per WHO TRS for TCV.
- Evidence of protection up to 3 years.
- Dose schedule aligns with MCV immunizations.
- Compatibility with MCV.
- Flexible dose schedule with optional second dose in primary series.
- Evidence of booster responses: early (6 months) or late (2-5 years).
- 600,000 doses marketed thus far since launch of vaccine in August 2013, primarily in 6 months to 10 years age group. No SAEs reported.

Thank you

Team BHARAT Typbar-TCV

&

Dr Szu / Dr Imran Khan / Prof Levine / Prof Pollard

Bharat Biotech
Lead Innovation

UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE

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

NIBSC
Confidence in Biological Medicines

oxford vaccine group
UNIVERSITY OF OXFORD

प्रज्ञानं ब्रह्म
Manipal
INSPIRED BY LIFE

Thank You