BHARAT BIOTECH

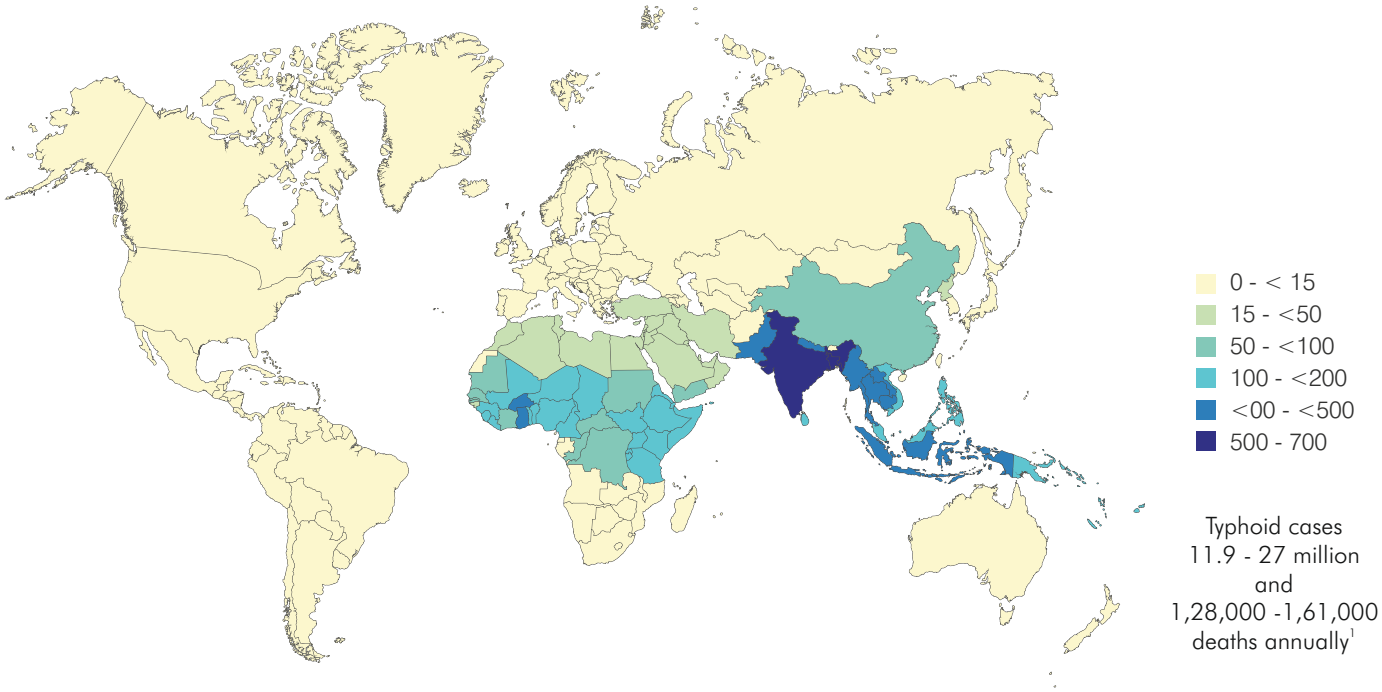
WORLD'S FIRST TYPHOID CONJUGATE VACCINE

WITH **OUTSTANDING** GLOBAL EFFICACY RESULTS

Typbar TCV®

Typhoid Vi Capsular Polysaccharide-Tetanus Toxoid Conjugate Vaccine

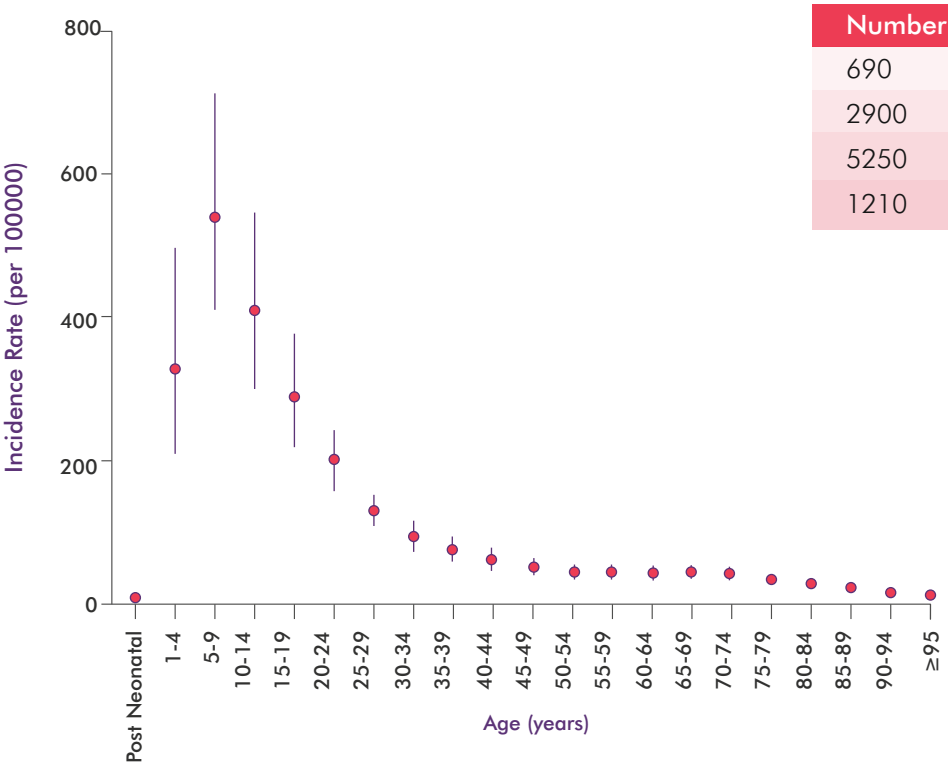
1. GLOBAL PREVALENCE OF TYPHOID[1]



Typhoid cases
11.9 - 27 million
and
1,28,000 -1,61,000
deaths annually[1]

Typhoid has higher incidence in children compared to other age groups

Global age-specific incidence rates[1]



Typhoid Prevalence in India[2,3]

Number cases/100,000	Age group
690	0-1 year
2900	2 – 4 years
5250	5 – 15 years
1210	≥16 years

- Incidence rates were quite higher among children between 1-14 years.
- South Asia reported the highest age-standardized incidence rate (549 cases per 100,000 person-years) and the largest number of cases (10.3 million), accounting for 71.8% of global cases in 2017.
- About 20.5% of DALYs (Disability-Adjusted Life Year) occurred among children younger than 5 years of age, and 67.0% occurred among children younger than 15 years of age.

2. ALL CONJUGATE VACCINES ARE NOT SAME

A conjugate vaccine is a substance that is composed of a polysaccharide antigen fused (conjugated) to a carrier molecule. This enhances the efficacy of the vaccine.

a. Purity of components

- Polysaccharide: Vi-polysaccharide- Culturing & processing
- Carrier Protein: High purity Tetanus Toxoid enhances the conjugation.

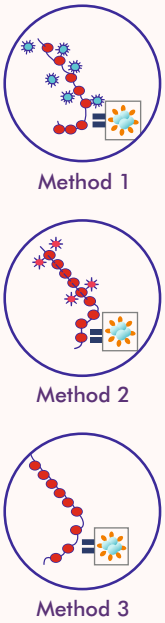
b. De-O-Acetylation[4]

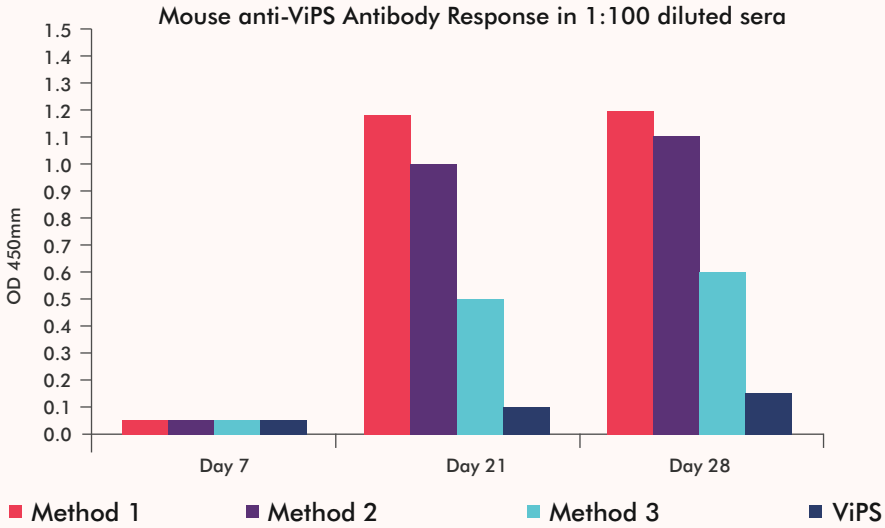
- Immunogenicity of Vi is closely related to its degree of O-acetylation. Partial de-O-acetylation on Vi enhance immunogenicity due to additional epitiopes created.
- Alkaline hydrolysis by sodium carbonate and bicarbonate buffer can do partial de-O-acetylation on ViPS.

c. Length of the Polysaccharide[5]

- Intermediate Oligo saccharides (11-16 repeated units) gives optimum immunogenicity, compared to shorter and longer polysaccharides.

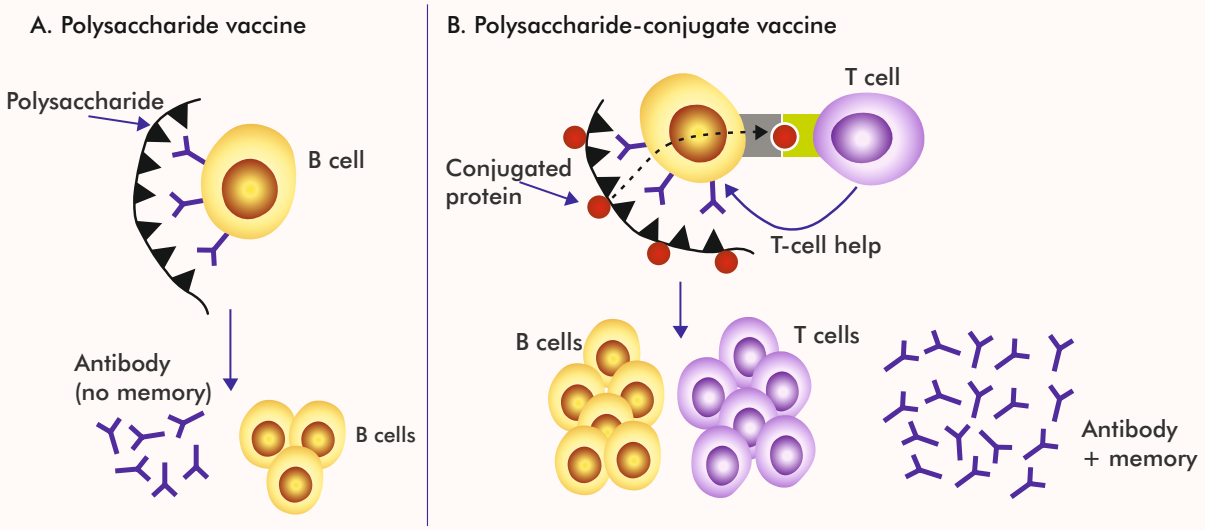
d. Conjugation method





- Conjugation methodology affects immunogenicity

HOW DOES A CONJUGATE VACCINE WORK?[6]



3. WHY USE A CONJUGATE VACCINE?[7]

	Polysaccharide vaccine	Conjugate Vaccine
Cells Stimulated	B cells	B & T cells
Antibody Titer	Low	High
Quality of Antibody (Avidity)	Low	High
Cell Mediated Immunity	Absent	Present
Duration of Response	Short-Lived	Long-lived
Immunological Memory	Poor	Strong
Booster Response	Poor	Strong
Effective Ages	> 2yr	≥ 6Months and above

4. TYPBAR TCV® - PRODUCT CHARACTERISTICS

	Specification	Typical end of shelf life (36 months) results
Description	A clear colorless liquid	Complies
Identification (Ouchterlony)	Clear precipitation arc should be observed	Clear precipitation arc was observed
pH	6.5-7.5	7.0
Extractable volume	NLT 0.5 mL	0.53 – 0.55 mL
O-Acetyl content (Hestrin)	0.064 - 0.106 µMoles / dose	0.096 µMoles /dose
Vi Content	NLT 25 µg of Vi Polysaccharide	29 µg Vi PS/dose
Free Vi-PS	NMT 20%	5.2 %
Pyrogens	Summed up responses of 3 rabbits should not exceed 1.15°C	0.6°C
Abnormal toxicity test	All animals should survive for 7 days and show no weight loss	Complies
Sterility	Should comply with sterility test	Sterile
Osmolality	250-350 mOsmol/kg	275 mOsmol/kg
Bacterial Endotoxin	NMT 3750 IU/dose	Less than 3750 IU/dose

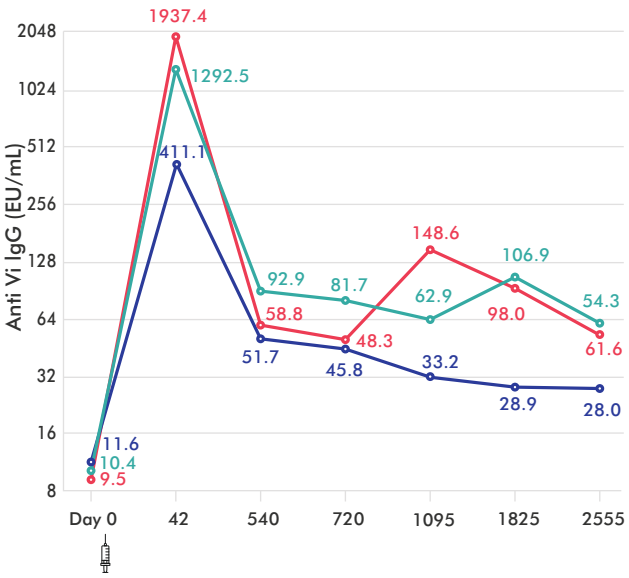
5. TYPBAR TCV® - CLINICAL DEVELOPMENT

Clinical Stage	Age Group	No. of Subjects	Location	Endpoint
Phase II	Teenagers: 13 to 17 years, Children: 6-12 & 2-5 years	100	India	Safety / Immunogenicity
Phase III	6 months to 45 years	981	India	Immunogenicity / Safety
Phase III 2 yrs booster	6 months to 45 years	944	India	Immunogenicity
Phase III till 3 years	6 months to 45 years	533	India	Immunogenicity
Phase III till 5 years	6 months to 45 years	533	India	Immunogenicity
Phase III till 7 years	6 months to 45 years	156	India	Immunogenicity
Phase IV (Comparator to Typhim-Vi)	2 to 15 years	340	India	Safety & Immunogenicity
Phase IV (Non-interference to MCV)	8 to 10 Months	500	India	Safety & Immunogenicity
Phase IV (Adults)	≥18 to ≤65 years	300	India	Immunogenicity & Safety
PMS-1	6 months & above	~5000	India	Safety
PMS-2	6 months & above	~4000	India	Safety

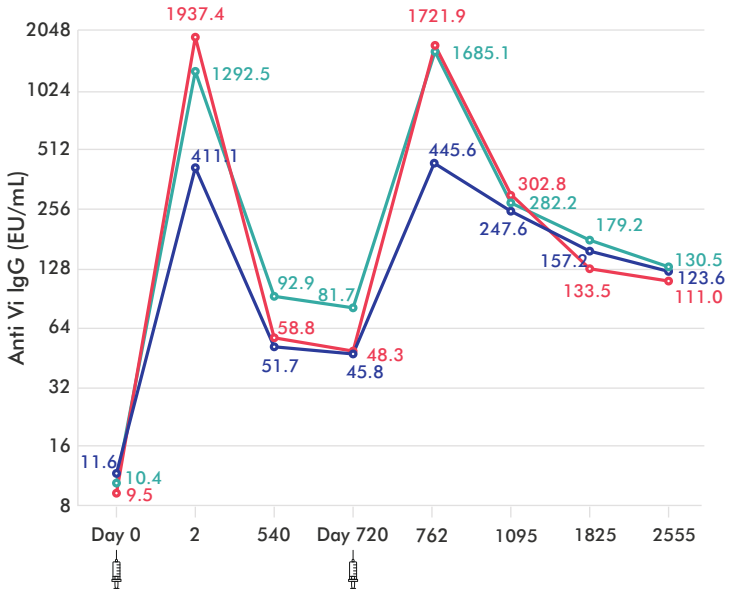
6. TYPBAR TCV® - LONG TERM IMMUNOGENICITY STUDY[8]

A. IMMUNOGENICITY

GMT ≤2yrs and >2-45yrs for Typbar TCV® & Typbar (Single Dose)



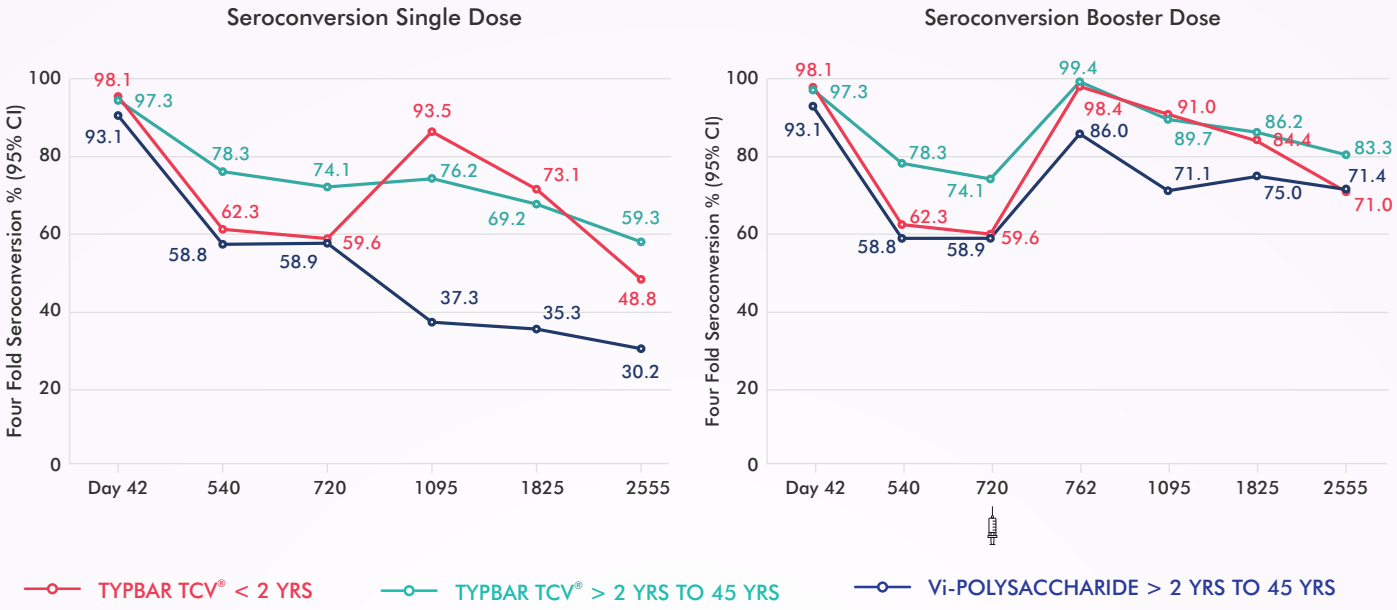
GMT ≤2yrs and >2-45yrs for Typbar TCV® & Typbar (Booster Dose)



TYPBAR TCV® < 2 YRS — TYPBAR TCV® > 2 YRS TO 45 YRS — Vi-POLYSACCHARIDE > 2 YRS TO 45 YRS

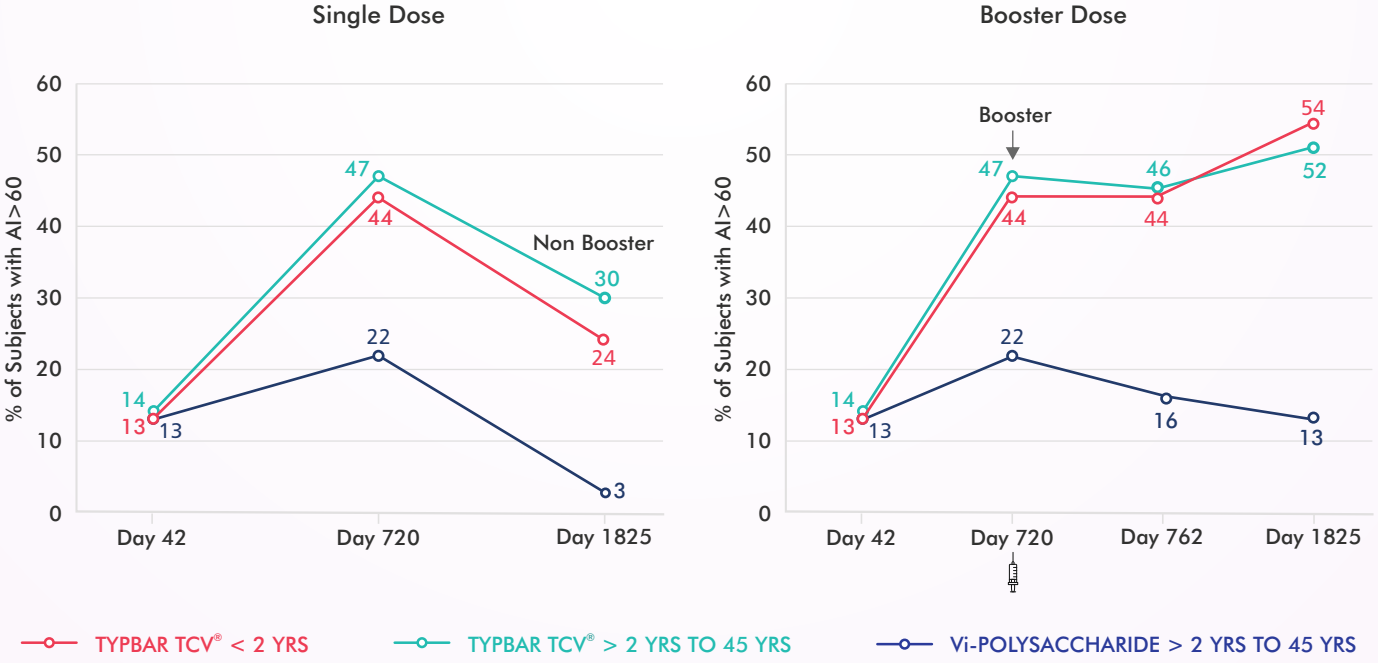
- GMT titers of anti-Vi antibodies are 2 fold higher in subjects who were administered with Typbar TCV® compared with Vi-PS vaccine.
- Boostered subjects continued to exhibit higher titers at 3 Years compared to non-boostered subjects, same trend continued up to 7 years.

B. SEROCONVERSION



- Typbar-TCV® reported ~ 70% four-fold seroconversion after 5 years of single dose in both cohorts (>6 months -2 Years, >2 years).
- Boostered subjects showed higher seroconversion rates (~85%), compared to non-boostered subjects.

C. AVIDITY INDEX OF TYPBAR TCV®

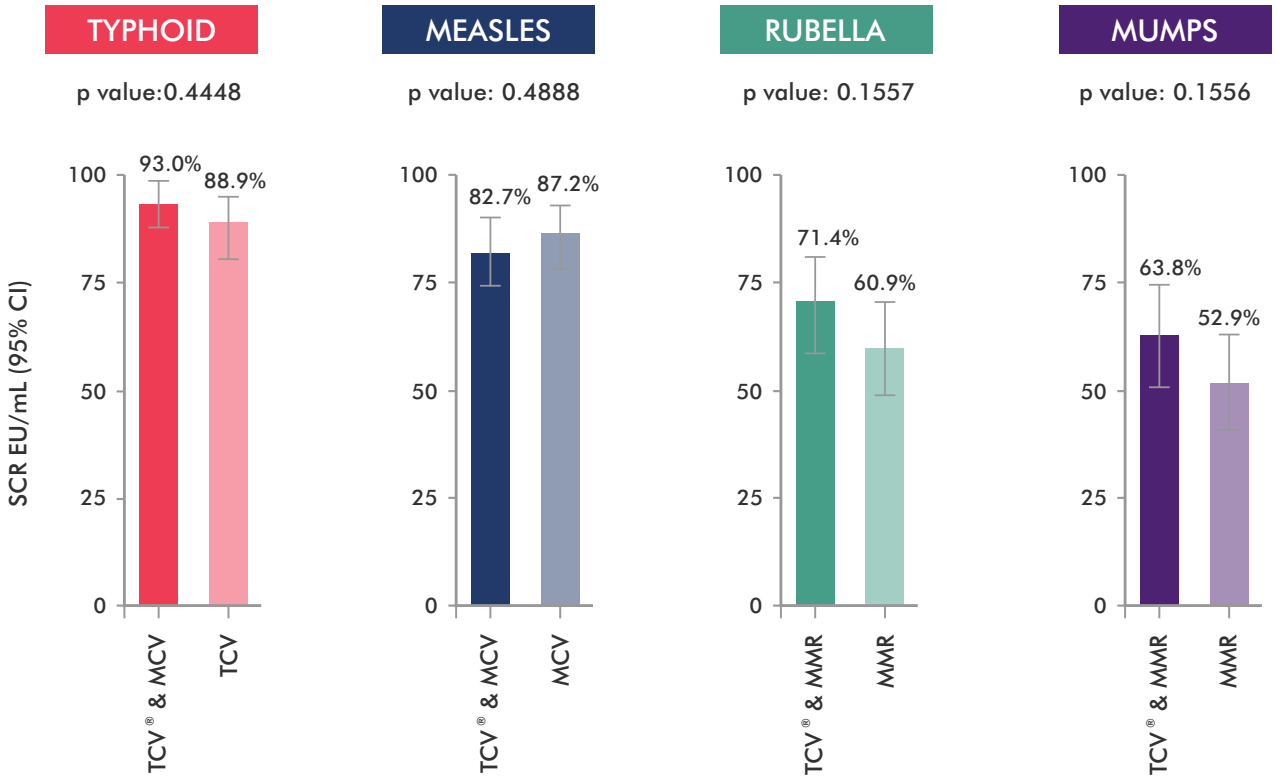


- Avidity index of Typbar TCV® antibodies is high and enhanced with a booster dose.

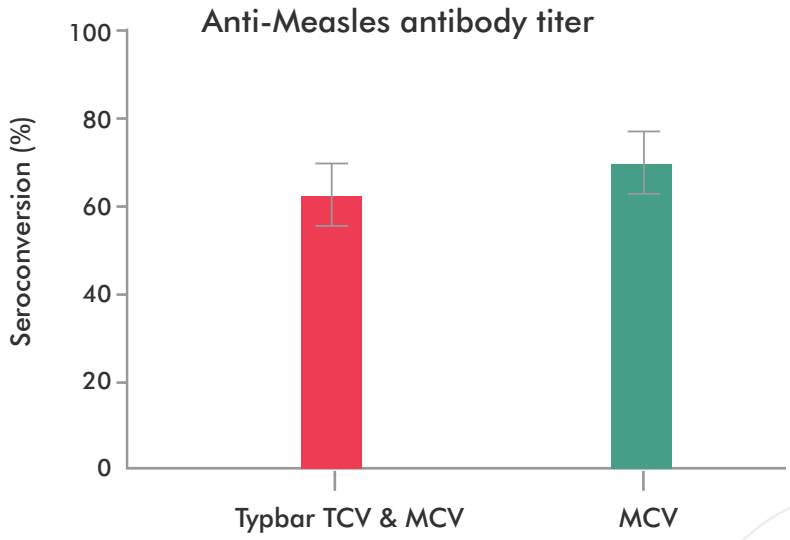
Typbar TCV® induces higher immunogenicity compared to polysaccharide vaccines

7. TYPBAR TCV® DOES NOT INTERFERE WITH MCV & MMR

A. Non-interference established in Indian Children[9]



B. Non-interference established in African(Malawi) Children[10]



- Non-interference of Typbar TCV® with MCV is established in both Asian and African children.
- Co-administration of Typbar TCV® with MMR/MCV vaccine did not interfere with the serological response.

WHO-SAGE (Strategic Advisory Group of Experts) Recommendation

2017, 92, 729–748 No 48

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

1ST DECEMBER 2017, 92th YEAR / 1ER DÉCEMBRE 2017, 92e ANNÉE
No 48, 2017, 92, 729–748
http://www.who.int/wer

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Meeting of the Strategic Advisory Group of Experts on immunization, October 2017 – conclusions and recommendations

Réunion du Groupe stratégique consultatif d'experts sur la vaccination, octobre 2017 – conclusions et recommandations

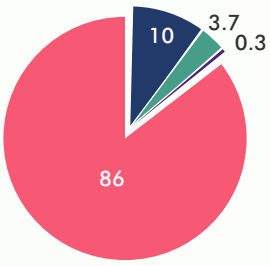
- SAGE recommended the introduction of TCV for infants and children over 6 months of age as a single dose in typhoidendemic countries.
- Introduction of TCV should first be prioritized to countries with the highest burden of disease or a high burden of antimicrobial resistant S.Typhi.
- Co-administration data with MCV (measles only and measles-mumps-rubella vaccines) showed no interference with the immune response or increased reactogenicity.

Licensed TCV (Typbar-TCV) demonstrates that it is likely to offer longer and higher protection than ViPS and Ty21a, and supports a recommendation for its public health use- SAGE, WHO[11]

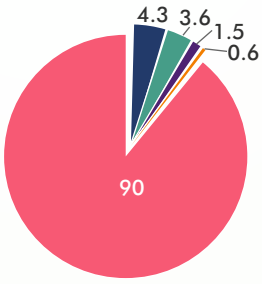
8. TYPBAR TCV® - SAFETY

I. Phase 3 Clinical Trial[12]:

>6 months to ≤ 2 years Group (N=327)

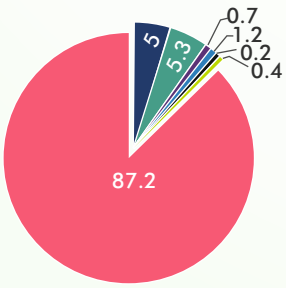


>2 years to ≤ 45 years Group (N=340)

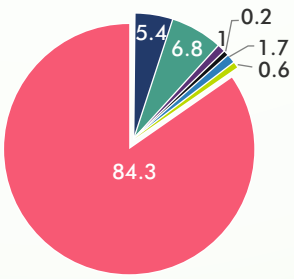


II. Phase 3: Efficacy Trial (Nepal)[13]

Typbar TCV® N=10005

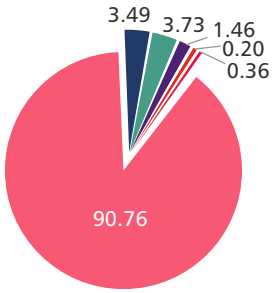


Control (Men A) N=10014

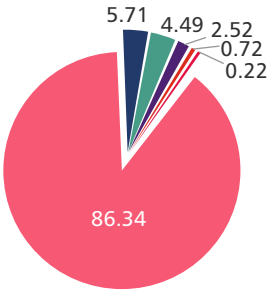


III. Post-Marketing Surveillance: Period-I (Feb 2016 to Oct 2016)[14]

>6 Months to ≤2 Years Group (N=2298)

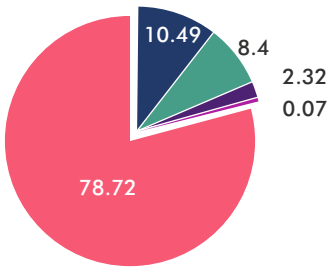


>2 Years to ≤ 45 Years Group (N=2693)

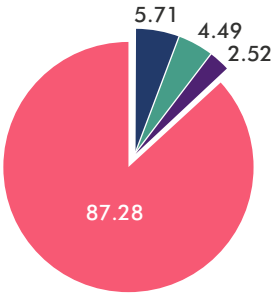


IV. Post-Marketing Surveillance: Period-II (Apr 2017 to Oct 2018)[15] Based on Brighton Criteria

>6 Months to ≤2 Years Group (N=1874)

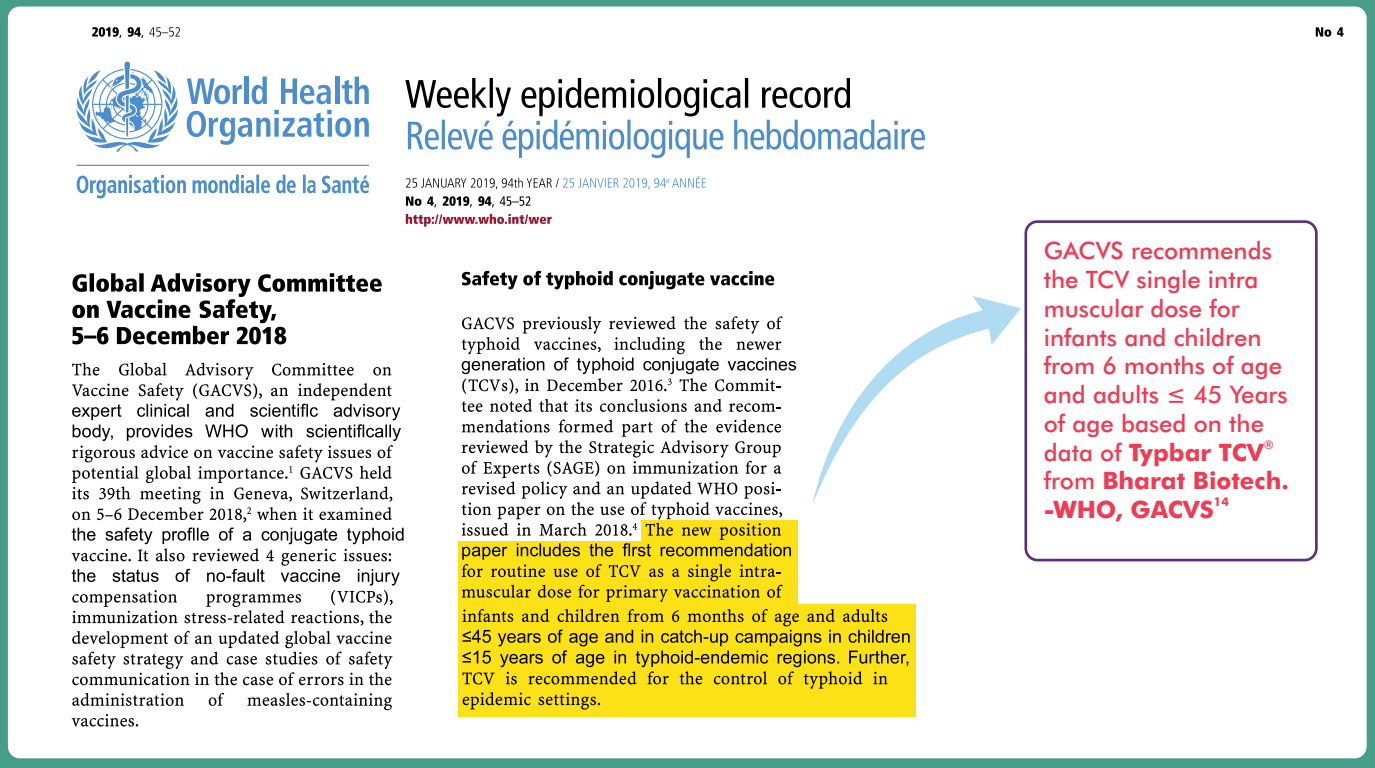


>2 Years to ≤45 Years Group (N=2024)



- Typbar TCV® is safe and well-tolerated vaccine.
- Most AEs following vaccination were found to be mild in nature.

WHO-GACVS (Global Advisory Committee on Vaccine Safety) recommendation



2019, 94, 45–52 No 4

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

25 JANUARY 2019, 94th YEAR / 25 JANVIER 2019, 94e ANNÉE
No 4, 2019, 94, 45–52
http://www.who.int/wer

Global Advisory Committee on Vaccine Safety, 5–6 December 2018

The Global Advisory Committee on Vaccine Safety (GACVS), an independent expert clinical and scientific advisory body, provides WHO with scientifically rigorous advice on vaccine safety issues of potential global importance.[1] GACVS held its 39th meeting in Geneva, Switzerland, on 5–6 December 2018,[2] when it examined the safety profile of a conjugate typhoid vaccine. It also reviewed 4 generic issues: the status of no-fault vaccine injury compensation programmes (VICPs), immunization stress-related reactions, the development of an updated global vaccine safety strategy and case studies of safety communication in the case of errors in the administration of measles-containing vaccines.

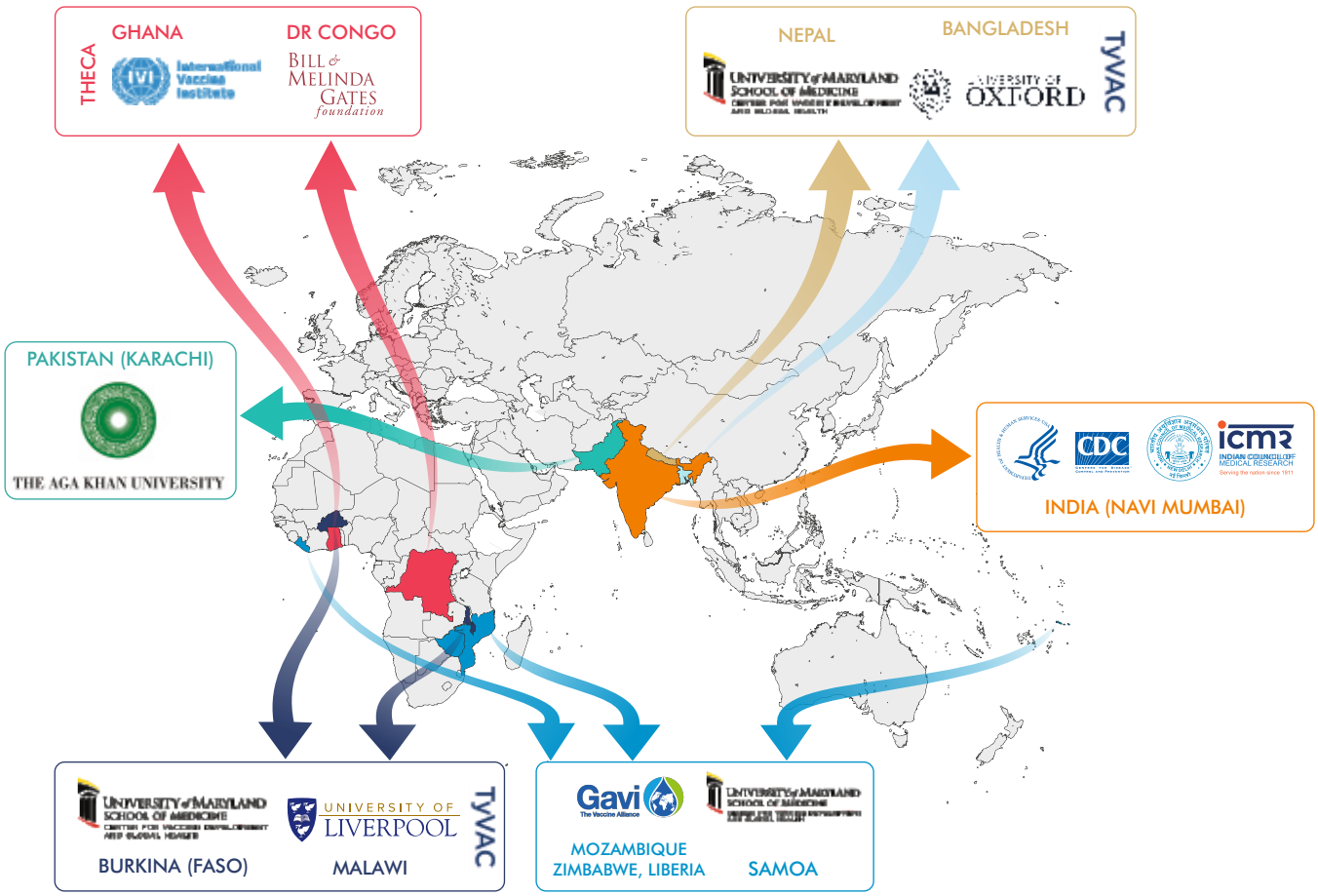
Safety of typhoid conjugate vaccine

GACVS previously reviewed the safety of typhoid vaccines, including the newer generation of typhoid conjugate vaccines (TCVs), in December 2016.[3] The Committee noted that its conclusions and recommendations formed part of the evidence reviewed by the Strategic Advisory Group of Experts (SAGE) on immunization for a revised policy and an updated WHO position paper on the use of typhoid vaccines, issued in March 2018.[4] The new position paper includes the first recommendation for routine use of TCV as a single intramuscular dose for primary vaccination of infants and children from 6 months of age and adults ≤45 years of age and in catch-up campaigns in children ≤15 years of age in typhoid-endemic regions. Further, TCV is recommended for the control of typhoid in epidemic settings.

GACVS recommends the TCV single intra muscular dose for infants and children from 6 months of age and adults ≤ 45 Years of age based on the data of **Typbar TCV®** from **Bharat Biotech. -WHO, GACVS**[14]

9. TYPBAR TCV® EFFICACY STUDIES ACROSS THE WORLD

Clinical Stage	Age Group	No. of Subjects	Location	Endpoint	Status	Status
Oxford Human Challenge Study	18 - 60 years	112	UK	Protective efficacy in clinical end points & lab features after challenge with live S.enterica	Completed	87.1%
Vaccine Efficacy Study	9 months - 16 years	20019	Nepal	Safety & Efficacy	Completed	1st year - 81.6% 2nd year - 79.0%
Oxford Sero Efficacy Modelling Study	6 months - 45 Years	981	India	Sero Efficacy	Completed	85%
Vaccine Efficacy Study	9 months to 12 years	28130	Malawi	Safety, Efficacy & Non-interference with MCV	Completed	80.7%
TCV introduction programme in Navi Mumbai	9 months to 14 years	~120000	India	Safety & Efficacy	Completed	-
TCV mass vaccination programme	6 months to 10 Months	23407	Pakistan	Safety & Efficacy	Completed	95%
Vaccine Effectiveness Studies	9 months - 16 years	61756	Bangladesh	Safety & Efficacy	Completed	85%
Cluster-randomized Phase 3 trial of Typbar TCV	9 months to <16 Years	~28000	Ghana	Herd immunity, overall and total effects of vaccination	Ongoing	-
A mass vaccination campaign with nested case-control effectiveness study	9 months to <16 Years	~185000	Democratic Republic of Congo	Vaccine effectiveness, cost-effectiveness, safety and feasibility	Ongoing	-
Case control study	6 months - 16 years	504 (Suspected cases)	Zimbabwe	Vaccine effectiveness	Completed	75%



A. Human Challenge Model[16]

A phase II b, comparative, randomised controlled trial of vaccines against Salmonella typhi using a human challenge model of typhoid infection

UNIVERSITY OF OXFORD

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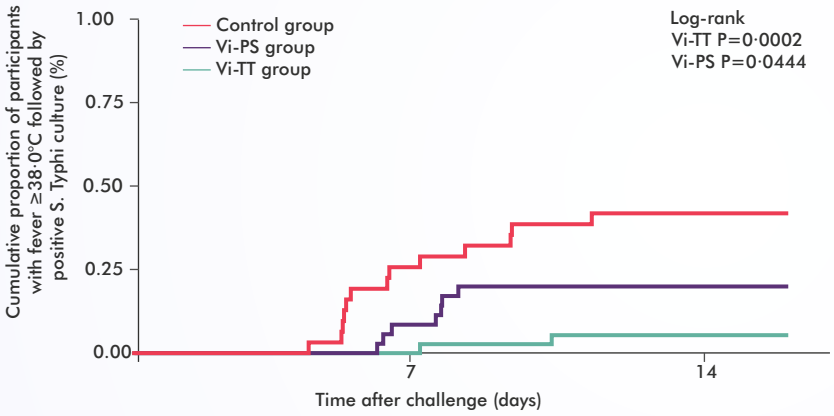
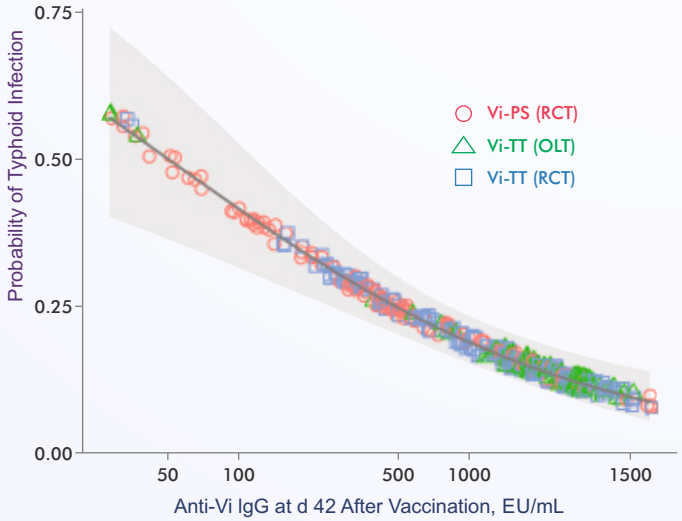
Lead Innovation



Relative Protective Effect for TCV as compared to control
87.1% (95% CI: 47.2 to 96.9%)
Relative Protective Effect for ViPS as compared to control
52.3% (95% CI: 4.2 to 78.2%)

Typbar TCV®
vaccine efficacy is 87.1%.

B. Typbar TCV® - Sero Efficacy[17]



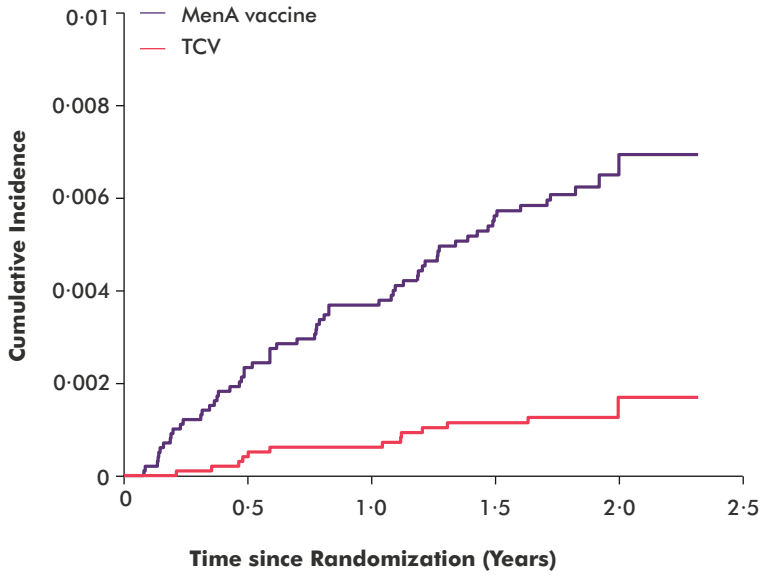
- The infected persons proportion in each group (seroincidence) from Phase 3 clinical study was compared using relative risk (RR) and vaccine seroefficacy (VSE), computed as follows

  $VSE = 1-[RR_{C/P} X (1-VE_{P/0})]$;

- Estimated the seroefficacy of Typbar TCV® vaccine is 85%.
- Typbar TCV® substantially reduces the number of serologically defined clinical or subclinical infections in infants, children, and adults.

EXCELLENT EFFICACY TRIALS

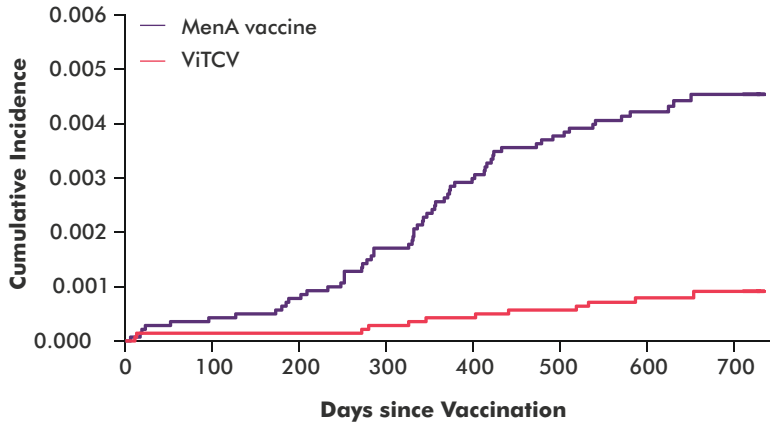
A. Efficacy of Typbar TCV® in Nepal[18]



Number at risk

MenA	10013	9707	9485	9120	2274	..
TCV	10005	9738	9534	9142	2285	..

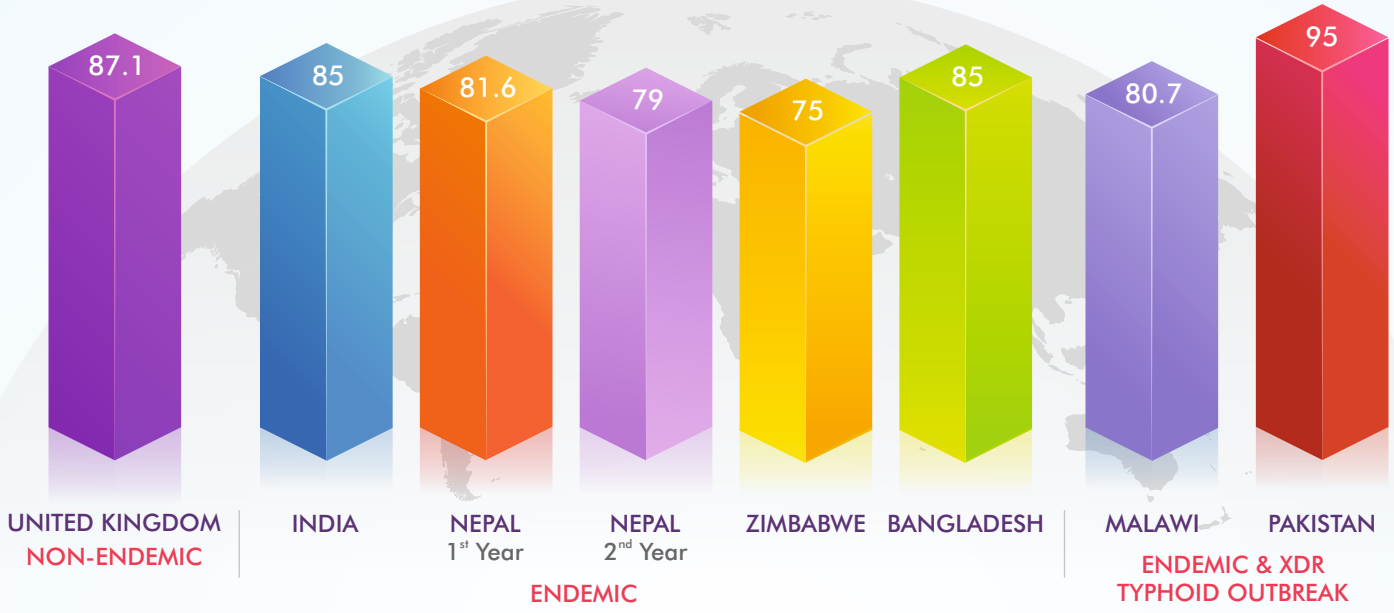
B. Efficacy of Typbar TCV® in Malawi[19]



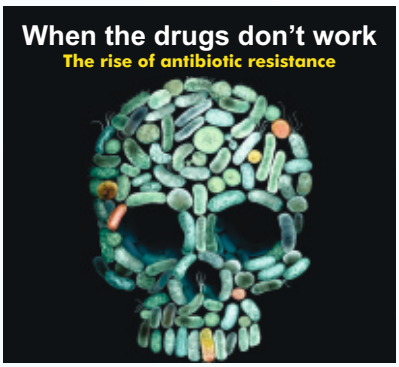
Number at risk

MenA	14,061	14,048	14,036	14,021	14,002	13,989	11,517	4769
Vi-TCV	14,069	14,061	14,057	14,052	14,050	14,047	11,606	4830

C. Efficacy of Typbar TCV® across the World[16, 17, 13, 18, 24, 19, 23, 25]

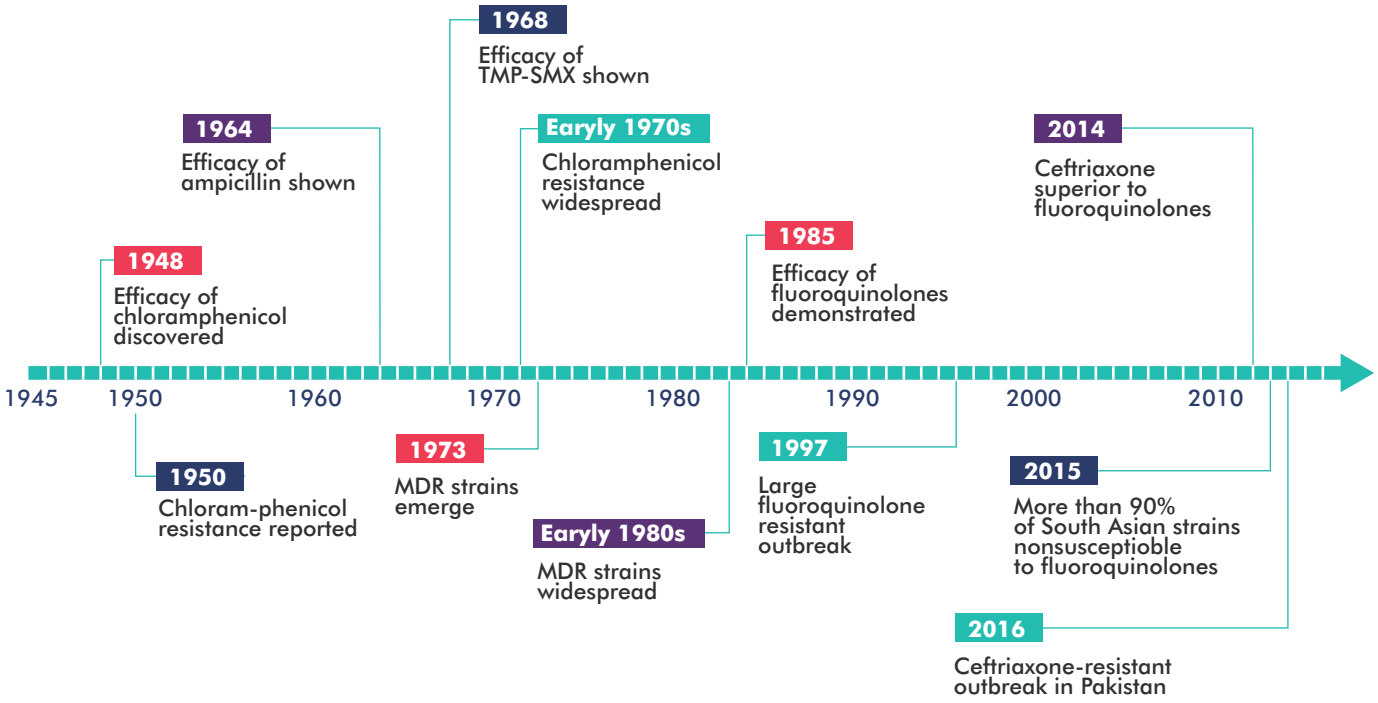


10. EMERGENCE OF ANTIMICROBIAL RESISTANCE (AMR)[21]

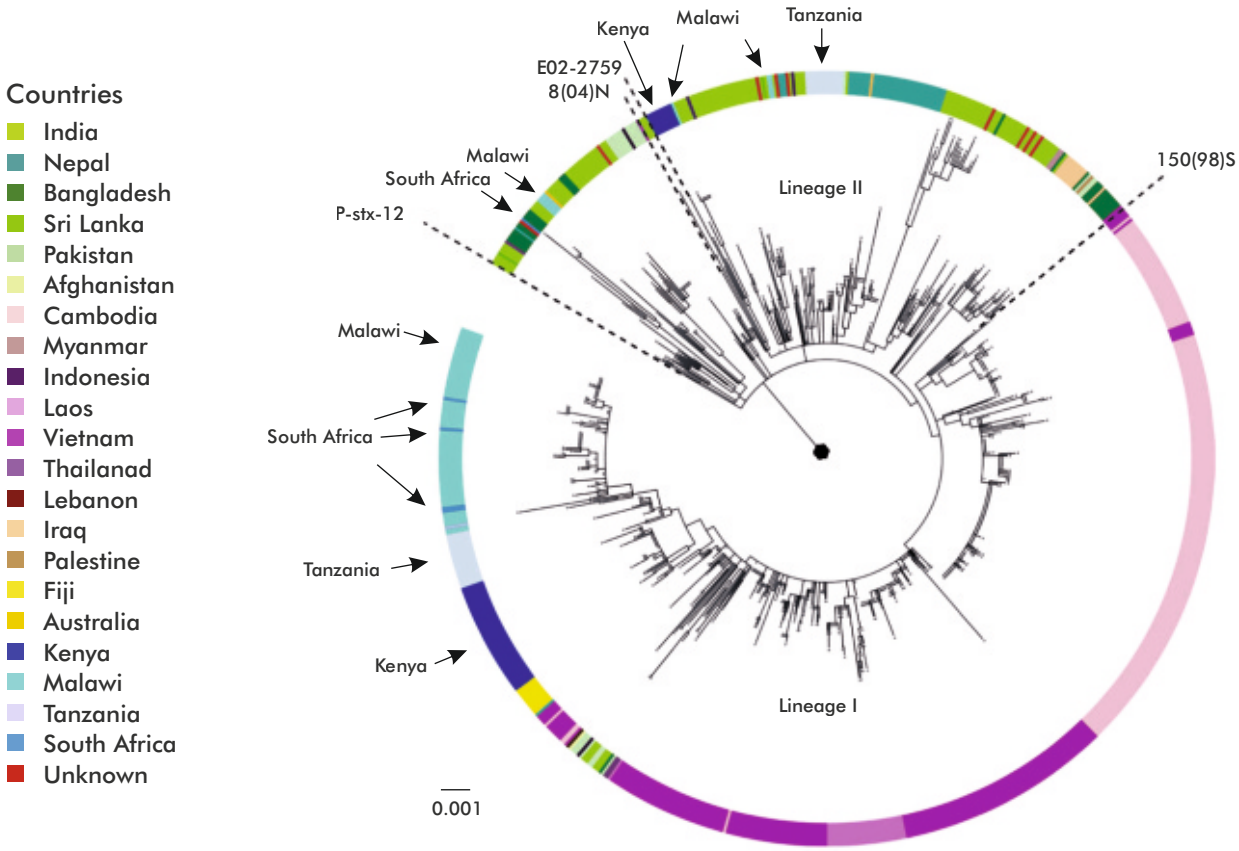


- The World Health Organization has described antibiotic resistance as a "global health emergency".
- The typhoid superbug, which is resistant to five types of antibiotics, has infected many people since 2016 in Pakistan.
- About 60% of the Typhoid cases were drug resistant.

Emergence of Antimicrobial Resistance in Salmonella Typhi[20]



MULTIDRUG-RESISTANT H58 CLADE OF SALMONELLA TYPHI[22]

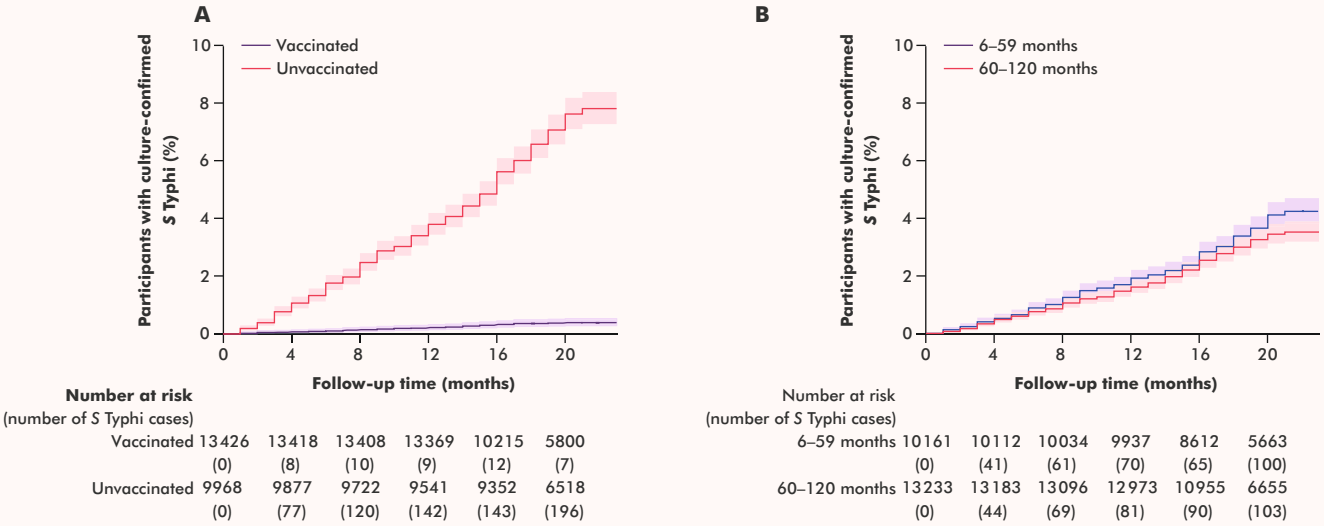


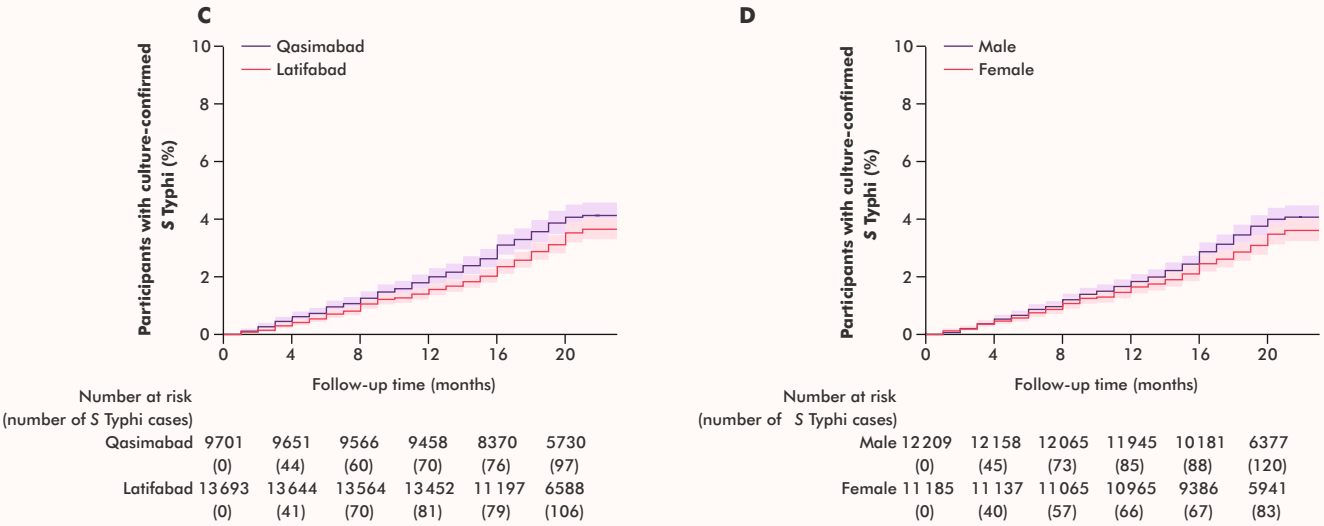
- The coloured ring indicates the countries of isolation; countries discussed in the text are labeled around the tree. Branch lengths are indicative of the estimated substitution rate per variable site.

MULTI DRUG RESISTANCE - TYPBAR TCV® EFFICACY[23]

THE AGA KHAN UNIVERSITY

- The Aga Khan University, Hyderabad, Pakistan has initiated a Typbar-TCV immunisation campaign to control the XDR (Extensively drug-resistant) Typhoid outbreak in Sindh province of Pakistan.
- Approximately 200,000 children aged 6 months to 10 years were vaccinated from Feb 21, 2018, to Dec 31, 2018.
- Active surveillance for suspected and blood-culture-confirmed S Typhi was established in hospitals, clinics, and laboratories to assess the cases of suspected typhoid fever, culture-confirmed S Typhi, and antimicrobial resistance.
- A total of 23,407 children from the census registry and surveillance system were included in the vaccine effectiveness analysis.
- Vaccine effectiveness against suspected S Typhi (regardless of culture confirmation), 95% (93–96) against culture-confirmed S Typhi, and 97% (95–98) against XDR S Typhi.





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THE Typbar TCV® ADVANTAGE

A single dose of Typbar TCV® (25µg/05mL) elicits robust immune response of 97.7%, with four-fold seroconversion across all age groups beyond 6 months of age.

Offers high avidity (especially IgG having high bactericidal activity) that persists up to 7 years across all age groups, according to the available data.

Co-administration of Typbar TCV® with MCV/MMR vaccine exhibits no serological interference with excellent safety and compatibility, proven in Indian and Malawian children.

Typbar TCV® vaccine efficacy has been established across the globe, UK-87.1%, Nepal-81.6%, Bangladesh-85%, Malawi-80.7%, India-85% (Sero efficacy) Zimbabwe-75% and Pakistan-95%.

Offers a flexible dose of vaccination along with good safety and immunogenicity, in line with WHO Technical Report Series.

In partnership with:

BILL & MELINDA GATES foundation | Gavi The Vaccine Alliance | Stanford University

TyVAC Typhoid Vaccine Acceleration Consortium
CENTER FOR VACCINE DEVELOPMENT • OXFORD VACCINE GROUP • PATH

UNIVERSITY OF MARYLAND

UNIVERSITY OF OXFORD | CDC CENTERS FOR DISEASE CONTROL AND PREVENTION | NICED | NMMC

PUBLICATIONS

Clinical Infectious Diseases

MAJOR ARTICLE

Safety and Immunogenicity of a Vi PolysaccharideTetanus Toxoid Conjugate Vaccine (Typbar-TCV) in Healthy Infants, Children, and Adults in Typhoid Endemic Areas: A Multicenter, 2-Cohort, Open-Label, Double-Blind, Randomized Controlled Phase 3 Study

Vaccine 39 (2021) 66826690

Contents lists available at ScienceDirect

Vaccine

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

Persisting antibody responses to Vi polysaccharidetetanus toxoid conjugate (Typbar TCV) vaccine up to 7 years following primary vaccination of children < 2 years of age with, or without, a booster vaccination

Krishna Mohan Vadrevu [a], Dugyala Raju [a], Sandhya Rani [a], Siddharth Reddy [a], Vamshi Sarangi [a], Raches Ella [a,*], Bhuvaneswara Javvaji [b], Niranjana S. Mahantshetty [c], Sudhakar Battu [d], Myron M. Levine [e]

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Human Vaccines & Immunotherapeutics

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/khvi20

A multi-centre, post-marketing surveillance study of Vi polysaccharide–tetanus toxoid conjugate vaccine (Typbar TCV®) in India

Raghu Reddy, Bhargav Reddy, Vamshi Sarangi, Siddharth Reddy, Raches Ella & Krishna Mohan Vadrevu

Articles

THE LANCET

Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of Salmonella Typhi: a randomised controlled, phase 2b trial

Celina Jin, Malick M Gibani, Maria Moore, Helene B Juel, Elizabeth Jones, James Meiring, Victoria Harris, Jonathan Gardner, Anna Nebykova, Simon A Kerridge, Jennifer Hill, Helena Thomaides-Brears, Christoph J Blohmke, Ly-Mee Yu, Brian Angus, Andrew J Pollard

Lancet 2017; 390: 247280

Published Online September 28, 2017 http://dx.doi.org/10.1016/ S0140-6736(17)32149-9

Summary

Background Salmonella enterica serovar Typhi (S Typhi) is responsible for an estimated 20 million infections and 200 000 deaths each year in resource poor regions of the world. Capsular Vi-polysaccharide-protein conjugate vaccines (Vi-conjugate vaccines) are immunogenic and can be used from infancy but there are no efficacy data for the leading candidate vaccine being considered for widespread use. To address this knowledge gap, we assessed the efficacy of a Vi-tetanus toxoid conjugate vaccine using an established human infection model of S Typhi.

The NEW ENGLAND JOURNAL of MEDICINE

Original Article

Safety and Efficacy of a Typhoid Conjugate Vaccine in Malawian Children

Priyanka D. Patel, M.B., B.S., Pratiksha Patel, M.B., B.S., Yuanyuan Liang, Ph.D., James E. Meiring, Ph.D., Theresa Misiri, M.P.H., Felistas Mwakiseghile, M.Sc.,

THE LANCET

Articles

Protection by vaccination of children against typhoid fever with a Vi-tetanus toxoid conjugate vaccine in urban Bangladesh: a cluster-randomised trial

Firdausi Qadri*, Farhana Khanam*, Xinxue Liu*, Katherine Theiss-Nyland, Prasanta Kumar Biswas, Amirul Islam Bhuiyan, Faisal Ahmmed, Rachel Colin-Jones, Nicola Smith, Susan Tonks, Merryn Voysey, Yama F Mujadidi, Olga Mazur, Nazmul Hasan Rajib, Md Ismail Hossen, Shams Uddin Ahmed, Arifuzzaman Khan, Nazia Rahman, Golap Babu, Melanie Greenland, Sarah Kelly, Mahzabeen Ireen, Kamrul Islam, Peter OReilly, Karin Sofia Scherrer, Virginia E Pitzer, Kathleen M Neuzil, K Zaman, Andrew J Pollard, John D Clemens

Lancet 2021; 398: 67584

Published Online August 9, 2021 https://doi.org/10.1016/ S0140-6736(21)01124-7

Summary

Background Typhoid fever remains a major cause of morbidity and mortality in low-income and middle-income countries. Vi-tetanus toxoid conjugate vaccine (Vi-TT) is recommended by WHO for implementation in high-burden countries, but there is little evidence about its ability to protect against clinical typhoid in such settings.

Methods We did a participant-masked and observer-masked cluster-randomised trial preceded by a safety pilot phase

THE LANCET

Articles

Efficacy of typhoid conjugate vaccine in Nepal: final results of a phase 3, randomised, controlled trial

Mila Shakya*, Merryn Voysey*, Katherine Theiss-Nyland*, Rachel Colin-Jones*, Dikshya Pant*, Anup Adhikari, Susan Tonks, Yama F Mujadidi, Peter OReilly, Olga Mazur, Sarah Kelly, Xinxue Liu, Archana Maharjan, Ashata Dahal, Naheeda Haque, Anisha Pradhan, Suchita Shrestha, Manij Joshi, Nicola Smith, Jennifer Hill, Jenny Clarke, Lisa Stockdale, Elizabeth Jones, Timothy Lubinda, Binod Bajracharya, Sabina Dongol, Abhilasha Karkey, Stephen Baker, Gordan Dougan, Virginia E Pitzer, Kathleen M Neuzil, Shrijana Shrestha*, Buddha Basnyat*, Andrew J Pollard*, for the TyVAC Nepal Team

Lancet Glob Health 2021; 9: e156168

See Comment page e1483

*Contributed equally

Members are listed at the end of the Article

Summary

Background Typhoid fever is a major public health problem in low-resource settings. Vaccination can help curb the disease and might reduce transmission. We have previously reported an interim analysis of the efficacy of typhoid conjugate vaccine (TCV) in Nepali children. Here we report the final results after 2 years of follow-up.

Methods We did a participant-masked and observer-masked individually randomised trial in Lalitpur, Nepal, in which 20 019 children aged 9 months to younger than 16 years were randomly assigned in a 1:1 ratio to receive a single dose

THE LANCET

Articles

Effectiveness of typhoid conjugate vaccine against culture-confirmed Salmonella enterica serotype Typhi in an extensively drug-resistant outbreak setting of Hyderabad, Pakistan: a cohort study

Mohammad Tahir Yousafzai, Sultan Karim, Sonia Qureshi, Momin Kazi, Hina Memon, Amber Junejo, Zohra Khawaja, Najeeb Ur Rehman, Muhammad Sajid Ansari, Rafey Ali, Ikram Uddin Ujjan, Heera Mani Lohana, Naveed M Memon, Mudassar Hussain, Roohi Nigar, Naor Bar-Zeev, Farah Naz Qamar

Lancet Glob Health 2021; 9: e115462

See Comment page e1047

Summary

Background Salmonella enterica serotype Typhi (S Typhi) is a major public health problem in low-income and middle-income countries. We aimed to investigate the effectiveness and impact of the typhoid conjugate vaccine Typbar-TCV against S Typhi among children in an outbreak setting of extensively drug-resistant (XDR) S Typhi in Pakistan.

Vaccine 40 (2022) 41994210

Contents lists available at ScienceDirect

Vaccine

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

Effectiveness of typhoid conjugate vaccine in Zimbabwe used in response to an outbreak among children and young adults: A matched case control study

Maria S. Lightowler [a,*], Portia Manangazira [b], Fabienne Nackers [a], Michel Van Herp [c], Isaac Phiri [b], Kuziwa Kuwenyi [c], Isabella Panunzi [c], Daniela Garone [c], Farayi Marume [c], Andrew Tarupiwa [d], Eva Ferreras [a], Clemence Duri [e], Francisco J. Luquero [a]

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THE LANCET

Articles

Safety and immunogenicity of a typhoid conjugate vaccine among children aged 9 months to 12 years in Malawi: a nested substudy of a double-blind, randomised controlled trial

Njinache Nampota-Nkomba, Osward M Nyirenda, Lameck Khonde, Victoria Mapemba, Maurice Mbewe, John M Ndaferankhande, Harrison Msuku, Clemens Masesa*, Theresa Misiri, Felistas Mwakiseghile, Priyanka D Patel, Pratiksha Patel, Ifyaet Johnson-Maya, Marcela F Pasetti, Robert S Heyderman, J Kathleen Tracy, Shrimati Datta, Yuanyuan Liang, Kathleen M Neuzil, Melita A Gordan, Matthew B Laurens, on behalf of the Typhoid Vaccine Acceleration Consortium team

Lancet Glob Health 2022; 10: 132635

Summary

Background Typhoid fever is a substantial public health problem in Africa, yet there are few clinical trials of typhoid conjugate vaccine (TCV). We assessed immunogenicity and safety of Typbar TCV in Malawi.

FROM THE PRESS

nature

In its Yearbook, Nature journal declared Typbar TCV® as one of the treatments that made headlines in 2018.

The World Health Organization approved a vaccine against typhoid fever called Typbar TCV®, short for typhoid conjugate vaccine. It is the only vaccine deemed safe enough for use in infants starting at six months of age. The vaccine is produced by Hyderabad, India–based Bharat Biotech and is the first conjugate vaccine—a vaccine in which a weak antigen is attached to a strong antigen to elicit antibody responses—against the bacterial disease that affects up to 20 million people annually.

The approval came after the vaccine was tested in a trial in which volunteers ingested a dose of Salmonella typhi, the bacterium that causes typhoid. The trial found that 87% of those sorted into the vaccine group were protected against the disease (Lancet 390, 2472–2480, 2017).

The Telegraph

In March, WHO prequalified a new typhoid vaccine, Typbar TCV®, which can be used in children as young as six months old, and is more effective than other vaccine.

BBC NEWS

TYPHOID VACCINE 'WORKS FANTASTICALLY WELL'

On December 2019, BBC mentioned Typbar TCV® vaccine, a game-changer and would reduce the "terrible toll wrought by typhoid".

A volunteer drinks a solution containing typhoid bacteria during the vaccine trial at Oxford University. ***Pic: Andrew Testa for New York Times***

The New York Times

THEY SWALLOWED TYPHOID BACTERIA - ON PURPOSE

More than 100 residents of Oxford, England, took part in a trial of a new typhoid vaccine.

Typbar TCV® is the only effective vaccine that is also safe for infants, and is already used widely in India.

REUTERS

New typhoid fever vaccine protects young children

(Reuters Health) - The first field trial of a new typhoid vaccine that can be used in young children provides protection for 81.6% of recipients, opening the door to better control of a disease that affects 11 million people each year and kills roughly 117,000.

THE HINDU

Bharat Biotech's typhoid vaccine offers 82% protection

Phase-III clinical trial carried out in Nepal in over 10,000 children.

A typhoid vaccine (Typbar TCV) developed by the Hyderabad-based Bharat Biotech has shown 81.6% efficacy in preventing typhoid fever at 12 months in a Phase-III clinical trial. The trial was carried out in Nepal in over 10,000 children who received the vaccine.

A single does of the vaccine was found to be effective in preventing typhoid in children aged nine months to 16 years. The vaccine confers protection two-three weeks after vaccination. The duration of protection is currently not known. The results of the trial were published in *The New England Journal of Medicine* (NEJM).

Typbar TCV®

Typhoid Vi Capsular Polysaccharide-Tetanus Toxoid Conjugate Vaccine

PATENTS

Germany - 14841291.9 | Ireland - 14841291.9 | United Kingdom - 14841291.9
Belgium - 14841291.9 | Switzerland - 14841291.9 | France - 14841291.9 | Netherland - 14841291.9
Sweden - 14841291.9 | Denmark - 14841291.9 | Russia - 2016110576 | Korea - 10-2016-7007378
Ukraine - 2016 02951 | Vietnam - 1-2016-01038 | Mexico - mx/a/2016/002386 | Malaysia - PI 2016000339
USA - 14/913816 | USA-Continuation 1 - 16/051933

ABRIDGED PRESCRIBING INFORMATION

Therapeutic indications: Typbar TCV® is indicated for active immunization against salmonella typhi infection in ≥6 months to ≤45years age group. **Dosage and method of administration:** Inject 0.5 mL intramuscularly. Typbar TCV® should be given intramuscularly in the deltoid or the vastus lateralis of subjects. Typbar TCV® should not be injected into the gluteal area or areas where there may be a nerve trunk. Prevention becomes effective in 2-3 weeks after immunization. **PFS Handling procedure:** Prior to administration, ensure that the plunger rod is firmly attached to the rubber stopper by turning the plunger rod clockwise until slight resistance is felt. Do not over tighten. Remove rubber tip-cap from the syringe and fix the needle on syringe by turning in clock wise direction into luer lock until it is securely fixed to the syringe, remove the needle cap before injecting. Do not rotate luer lock. Finger grip with back stopper will prevent Plunger rod coming out from the syringe Barrel. "Do not remove the back-stopper from the syringe." Dosage & schedule: The immunizing dose for adults, children and infants of age ≥6 months to ≤ 45years is single dose of 0.5 mL; a booster dose may be given after 3years. **Contraindications: 1)** Hypersensitivity to any constituent of the vaccine. **2)** Pregnant & lactating women. **3)** In the event of fever or severe infection. **Special warning/ Precautions: 1)** Do not administer intravenously, intradermally, or subcutaneously. **2)** Typbar TCV® protects against typhoid fever caused by Salmonella typhi Ty2. Protection is not conferred against Salmonella Paratyphi and other non-typhoidal Salmonellae. **3)** Epinephrine injection (1:1000) must be immediately available in case of an acute anaphylactic reaction or any allergic reaction occurs due to any component of the vaccine. The vaccinee should remain under medical supervision for not less than 30 minutes after vaccination. Like all other vaccines, supervision and appropriate medical treatment should always be available to treat any anaphylactic reactions following immunization. **Interaction with other medicinal products/ other forms of interaction:** For concomitant or co-administration use different injection sites and separate syringes. Typbar TCV® should not be mixed with any other vaccine or medicinal product, because the interactions with other vaccines or medical products have not been established. **Pregnancy and lactation:** Safety and effectiveness have not been established in pregnant women and in nursing mothers. **Adverse reactions:** Clinical trial experience The safety of Typbar TCV® vaccine was established in phase II and III clinical trials. In the phase II study conducted in India with 100 children aged 2-17years, no significant adverse events were demonstrated to be associated with the vaccine. Commonly reported adverse events included pain at injection site, swelling, fever and headache. In the larger phase III study, a total of 981 healthy subjects were enrolled into the study at 8 clinical sites. The most common general and local adverse events were fever (5-10%) and pain at injection site (2-3%) post vaccination. All these events were resolved within 48 hours with symptomatic treatment. Uncommon adverse events observed were itching, swelling, malaise and myalgia. The adverse events reported were similar in nature as reported with other commercial Vi vaccines. No vaccine-related serious adverse events (SAEs) were reported in the clinical trial. **Overdose:** No case of overdose has been reported. **Pharmacological properties – Pharmacodynamic properties:** All conjugate vaccine studies have shown that the efficacy and immunogenicity of Typbar TCV® are higher than the plain Vi polysaccharide vaccine. **Pharmacokinetic properties:** Evaluation of pharmacokinetic properties is not required for vaccines. Pharmaceutical particulars – Incompatibilities: This medicinal product must not be mixed with other medicinal products. **Special precautions for storage:** The vaccine should be stored at +2°C to 8°C. Do not freeze. Discard if frozen. Shake well before use. Protect from light. Keep out of reach of children. Do not use the vaccine after the expiration date shown on the label. Opened vial should be used within 6 hours when stored at +2°C to +8°C. For multi dose vials use different syringe each time to vaccinate. **Presentation:** Typbar TCV® is presented in USP type 1 glass vial and Pre Filled Syringes - Single dose Vial : 0.5 mL, Single dose PFS : 0.5 mL & Multi dose Vial : 2.5 mL.

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