SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

For use of Registered Medical Practitioner or a Hospital.

Typhoid Vi Conjugate Vaccine

Typbar TCV®

1. NAME AND DESCRIPTION OF THE MEDICINAL PRODUCT

Typbar TCV® is a clear to slightly turbid liquid containing purified Vi capsular polysaccharide of *Salmonella Typhi* Ty2 conjugated to a non-toxic carrier protein, Tetanus Toxoid. Vi Capsular Polysaccharide of *Salmonella* Typhi alone elicits B cell response, but the conjugation of bacterial polysaccharide to a protein carrier provides foreign peptide antigens that are presented to the immune system eliciting antigen specific CD4+ T_h cells in what is referred to as T cell dependent antibody responses. A hallmark of T cell dependent responses, which are also elicited by toxoid is to induce both higher-affinity antibodies and long-term immune memory. Prevention becomes effective in 2-3 weeks after immunization. **Typbar TCV®** protects against typhoid fever caused by *Salmonella* Typhi. Protection is not conferred against *Salmonella* paratyphi and other non-typhoidal *Salmonellae* causing typhoid infection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

a) Composition for Single dose presentation in vial

Each dose of 0.5 mL contains:

Purified Vi-Capsular Polysaccharide of *Salmonella* Typhi Ty2 conjugated to Tetanus Toxoid	25 µg
Sodium chloride BP	4.5 mg
Water for Injections BP	q.s. to 0.5 mL

b) Composition for multi-dose presentation in vial

Each dose of 0.5 mL contains:

Purified Vi-Capsular Polysaccharide of *Salmonella* Typhi Ty2 conjugated to Tetanus Toxoid	25 µg
Sodium chloride BP	4.5 mg

2-Phenoxyethanol BP	5.0 mg
Water for Injections BP	q.s. to 0.5 mL

3. PHARMACEUTICAL FORM

Sterile Solution for Injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Typbar TCV® is indicated in infants, children and adults (≥6 months to ≤65years age group) for active immunization against *Salmonella* Typhi infection.

4.2 Posology, Schedule and Method of Administration

Inject 0.5 mL intramuscularly.

Single dose: 1 dose (0.5mL) in ≥6 months to ≤65 years age group

Typbar TCV® should be given intramuscularly in the vastuslateralis (anterolateral aspect of thigh) in infants <12 months of age or in the deltoid (upper arm) muscle in children ≥12 months of age. **Typbar TCV®** should not be injected into the gluteal area or areas where there may be a nerve trunk.

4.3 Contraindications:-

Hypersensitivity to any constituent of the vaccine.

4.4 Special Warning / Precautions

- Do not administer intravenously, intradermally, or subcutaneously.
- Like all other vaccines, supervision and appropriate medical treatment should always be available to treat any anaphylactic reactions following immunization.
- During fever or severe infection. 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.

4.5 Interaction with other medicinal products/ other forms of interaction

All commonly used vaccines (except pneumococcal vaccines) can safely and effectively administered simultaneously (on the same day) at separate sites without impairing antibody responses or increasing rates of adverse reactions

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.

4.6 Pregnancy and Lactation

Safety has not been established in pregnant women and in nursing mothers.

4.7 Effect on ability to drive and use machines

No studies on the effect of **Typbar TCV®** on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Clinical Trial Experience

The safety and immunogenicity of **Typbar TCV®** vaccine was established in phase 2 and 3 clinical trials.

In a phase 2 clinical trial conducted in India among 100 children aged 2-17 years, no significant adverse events were demonstrated to be associated with the vaccine. Commonly reported adverse events included pain and swelling at injection site, fever and headache.

In the larger phase 3 clinical trial[1], a total of 981 healthy subjects were enrolled into the study at 8 clinical sites into 2 study cohorts. A single arm, open label cohort enrolled 327 subjects between the age of ≥6 months to 2 years to receive a single dose of **Typbar TCV®**. A second randomized controlled arm recruited 654 subjects between the age >2 years to 45 years, allocated equally to receive a single dose of either **Typbar TCV®** or a comparator Vi Polysaccharide vaccine.

The most common general and local adverse events were fever (4-10%) and pain (3-4%) and swelling (1-2%) at injection site, post vaccination. All these events were resolved within 48 hours with symptomatic treatment. Uncommon adverse events observed were tenderness, and erythema at injection site, arthralgia, malaise and myalgia. No differences were observed in the adverse events reported between Typhoid Polysaccharide vaccine (Typbar) and **Typbar TCV®**. 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.

Post-Marketing Experience

Post Marketing Surveillance – Active and Passive ssurveillance was conducted in approximately 10000 vaccine recipients of **Typbar TCV®**.

Active surveillance was performed by physicians provided with PMS forms to report any observed adverse events. Passive surveillance was performed by voluntary reporting of adverse events by pediatricians/physicians across India. The adverse reactions observed in the PMS study were ranked under headings of frequency of occurrence using the following convention:

Very common: ≥10%
Common: ≥ 1% and < 10%
Uncommon: ≥ 0.1% and < 1%
Rare: ≥ 0.01% and < 0.1%
Very rare: < 0.01%

Fever, pain and swelling at injection site, pruritus/itching were common, whereas cough and cold are uncommon. Persistent crying, rash, Generalized Tonic Clonic Seizures (GTCS), chills and rigors were rare. The above events were reported from the post marketing surveillance study and it is not always possible to establish a causal relationship of these events to the product.

4.9 Overdose

No case of overdose has been reported.

4. 10 Immune response

4. 10.1 Phase 3 clinical study[1]

The phase 3 clinical trial that enrolled 981 healthy subjects into the trial across two age cohorts had 654 subjects aged >2 to <45 years (RCT) received a singledose of **Typbar TCV®** or Vi Polysaccharide vaccine and other 327 subjects aged >6 months to <2 years (OLT) received a single dose of **Typbar TCV®** vaccine only.

After a single dose of the vaccine, seroconversion (≥4-fold increase of anti-ViIgG antibodies) at 6 weeks post-vaccination in subjects aged 6 months to <2years, >2 to <5 years, >5 to <15 years and >15 to <45 years was 98.1%, 99%,99.3% and 91.9%, respectively.

Subjects were followed up for long term immunogenicity for a period of 3 and 5 years post-vaccination. Seroconversion rates (% with ≥4-fold increase in anti-Vi titer over baseline at day 0) of **Typbar TCV®** subjects at 3 and 5 years after vaccination in the RCT group (>2 to <45 years) remained to be high at 76.6% and 70.4% respectively. Similarly in the OLT (>6months to <2 years), ≥ 4-fold seroconversion rates of **Typbar TCV®** subjects at 3 and 5 years after vaccination are 78.1% and 76.6% respectively.

Sero Efficacy study[2]:

University of Oxford, U.K, estimated the sero efficacy of **Typbar TCV®** vaccine as 85% and showed that **Typbar TCV®** substantially reduces the number of serologically defined clinical or subclinical infections in infants, children, and adults compared to the Vi-PS vaccine.

4.10.2 Phase 4 Clinical Studies

TCV Measles non-interference study:

In a Phase 4 TCV Measles non-interference study, a total of 500 healthy infants of age group of 8 to 10 months were enrolled in this study.

Group 1: **Typbar TCV®** & Measles co-administration at 9 months.

Group 2: Measles at 9 months and **Typbar TCV®** at 10 months.

Group 3: **Typbar TCV®** at 8 months and Measles at 9 months.

Group 4: Only Measles at 9 months.

MMR vaccine was administered to all the 4 groups at 15 months of their age.

Antibody responses to **Typbar TCV®** and Measles in terms of GMT and 4-fold seroconversion on day 28 post vaccination were higher in Group 1 as compared to Group 2, 3 and 4. The above results indicate that concomitant administration of **Typbar TCV®** and Measles containing vaccine/MMR does not influence the antibody titers either ways and that the titers are more in the groups where concomitant administration of TCV and Measles was done. The safety profiles for each vaccination regimen were comparable and clinically acceptable. Based on the immunogenicity results, Concomitant administration of **Typbar TCV®** and Measles at 9 months of age revealed that the immune responses with respect to each antigen (i.e., Anti Vi IgG and Anti-measles IgG titers in terms of GMT and 4 fold seroconversion) was non-inferior to the responses seen when the vaccines are administered alone. The immunogenicity data support concomitant administration of Measles containing vaccine/MMR with **Typbar TCV®**.

Typbar TCV meningococcal type-A non-interference study: Group 1: Typbar TCV® & Measles co-administration at 9 months. In Burkina Faso, a double-blinded, randomized controlled trial was done to assess the safety and immunogenicity in children aged 15-23 months. In this study meningococcal type-A and measles-rubella vaccine is co-administered with typhoid conjugate. A total of 150

children were recruited and vaccinated and these 150 participants were divided into three groups.

Group 1: Typbar TCV , IPV and MR are co-administered.

Group 2: Typbar TCV , MR and MCV-A are co-administered.

Group 3: IPV, MR, and MCV-A are co-administered.

The results show that TCV can be safely co-administered at 15 months with MCV-V without interference. This novel study on the co-administration of TCV with MCV-A provides data to support large-scale uptakes in sub-Saharan Africa.

Typbar TCV® comparator study:

In the comparator phase 4 study (340 subjects), non-inferiority in the immune response of Typbar-TCV® as compared to Typhim Vi® has been examined. While safety profile of Typbar-TCV® is comparable to that of a WHO-prequalified typhoid vaccine – Typhim Vi®, its immune response, as measured by anti-Vi IgG titers– 28 days post vaccination, is non-inferior to Typhim Vi® vaccine.

Typbar TCV® safety & immunogenicity in older adults:

The phase 4 clinical trial that enrolled 300 healthy subjects into the trial across two age cohorts had 100 subjects aged >18 to <45 years (cohort 1) and other 200 subjects aged >45 years to <65 years (cohort 2) received a single dose of **Typbar TCV®** vaccine. After a single dose of the vaccine, Geometric mean titers of anti-Vi IgG antibody at pre- and post-vaccination in cohort 1subjects were 12 EU/mL, 1468.81 EU/mL and in cohort 2 subjects were 13.01 EU/mL, 1568.22 EU/mL respectively. The results indicating that the Typbar TCV® is safe and equally immunogenic in older adults.

4.10.3 A Phase 2b Human Challenge Study[3]

A Phase 2b Human Challenge study was conducted at Oxford University, UK using controlled human infection model of *Salmonella* Typhi. A total of 112

participants were randomly assigned (1:1:1) to receive a single parenteral dose of **Typbar TCV®**, Vi-PS-Typhim Vi, or control, meningococcal ACWY-CRM conjugate vaccine. About 1 month post-vaccination, participants were challenged orally with 1-5 × 10^4 colony forming units (CFUs) of *S Typhi* Quailes strain. The participants were followed up for a 2 week period post challenge for diagnosis of Typhoid fever. When an approximate field definition of typhoid fever was applied, such as fever ≥38.0°C followed by bacteraemia, the estimated vaccine efficacy of **Typbar TCV®** was 87.1% as compared to 52.3% in Typhim Vi® group. Four fold Seroconversion rate of **Typbar TCV®** was 100% compared to 88.6 % for Typhim Vi®.

4.10.4 Efficacy and Effectiveness Studies Across the Globe

Efficacy and effectiveness studies are conducting in several countries, such as Nepal, Bangladesh, Burkina Faso, Malawi, India and Pakistan.

Nepal[4]: A randomised controlled trial was conducted in Nepal to assess safety and efficacy of TCV in children from 9 months to 15 years of age, in which participants were randomised 1:1 to TCV or a capsular group A meningococcal vaccine. Approximately 20,000 children living in the Lalitpur district within Kathmandu valley, were enrolled in the study, and followed to measure both safety and efficacy data, which will include adverse events, hospitalisations, antibiotic use, and fever frequency. Typbar TCV® vaccine is found to be safe and well tolerated with 81.6% vaccine efficacy.

Pakistan[5]: Pakistan is facing the world's largest outbreak of extensively drug-resistant (XDR) Typhoid. Vaccination campaign for children aged 6 months to 10 years old with Typhoid Conjugate Vaccine (**Typbar-TCV®**) was conducted in high-risk areas of Hyderabad during 2018. About 207,000 children were vaccinated. Fever was followed by local reactogenicity 144/207,000 (1.89%). No serious AEFI was observed. Administration of a single dose of **Typbar-TCV®** among children aged 6 months to 10 years old during an outbreak setting of

Hyderabad Pakistan was safe. At the same time as the campaign, researchers set up a surveillance system in the same area over an 18-month period to screen a cohort of over 20,000 children, who received the vaccine, to detect cases of typhoid. They found that 9 out of 10 children in the cohort, or 89%, did not contract the disease.

India[6]: The Navi Mumbai Municipal Corporation (NMMC), India took a landmark decision to be the first in the world to introduce Typhoid Conjugate Vaccine (**Typbar TCV®**) into its immunization program, in two phases. This campaign marked the first public-sector introduction of TCV globally and aimed to vaccinate approximately 390,000 children aged 9 months to under 15 years. The events will reported through the routine AEFI surveillance and active phone follow-ups.

Malawi[7]: The TyVac conducted a phase 3 randomized, blinded, controlled clinical efficacy trial of typhoid Vi-capsular conjugate vaccine in Malawian children ages 9 months to 12 years. Participants were randomized in a 1:1 ratio to receive either typhoid Vi-capsular conjugate vaccine or meningococcal serogroup A conjugate vaccine. The subset of 200 children aged 9-11 months received typhoid Vi-capsular conjugate vaccine co-administered with measles-rubella vaccine at a different anatomic site. It was reported that **Typbar TCV®** vaccine is highly immunogenic (~500 fold increase form baseline titer) and non-interference with the Measles vaccine.

Burkina Faso[8]: A double-blinded, randomized controlled trial was done to assess the safety and immunogenicity in children aged 15-23 months. In this study meningococcal type-A and measles-rubella vaccine is co-administered at 15 months with MCV-A without interference. This novel study on the co-administration of TCV with MCV-A provides data to support large-scale uptake in sub-Saharan Africa.

Bangladesh[9]: A observer-blinded, cluster-randomized, controlled trial with 2 years follow-up to assess the protective impact of the Vi-TCV vaccine in children aged 9

months to <16 years. Approximately, 32500 participants were enrolled and in that >4800 participants had AEs assessed at 1 week following vaccination. Mild fever was the most common AE in both vaccine groups.

WHO SAGE Noted[10]:

SAGE re-emphasized the importance of programmatic use of typhoid vaccines for controlling endemic disease. Following review of results from different clinical trials of **Typbar TCV®** and other similar typhoid conjugate vaccines, SAGE recommended the introduction of Typhoid Conjugate Vaccine for infants and children over 6 months of age as a single dose in typhoid endemic countries. Routine programmatic administration of TCV is likely to be most feasible at existing vaccine visits at 9 months (Co-administration of measles and measles-mumps-rubella vaccines) of age or in the second year of life.

Introduction of Typhoid Conjugate Vaccine should first be prioritized for countries with the highest burden of disease or a high burden of antibiotic resistant *Salmonella* Typhi. Reviewing epidemiological and modelling data, SAGE recommended catch-up vaccination when feasible, with priority for catch up in the youngest age groups (up to 15 years of age), noting that the burden of disease and programmatic feasibility are greater in this age range than in adults. Weekly Epidemiological Record, No 48, 1st December 2017 and WHO Weekly Epidemiological Record on 25 January 2019 (Extract from report of GACVS meeting of 5-6 December 2018)[11]

Weekly Epidemiological Record, No 48, 1st December 2017

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties & Pharmacokinetics properties

Evaluation of Pharmacodynamic and pharmacokinetics properties is not required for vaccines.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

• Sodium chloride

•2-Phenoxyethanol (Multi dose presentation)

6.2 Incompatibilities

This vaccine must not be mixed with other medicinal products.

6.3 Shelf Life

The expiry date of the vaccine is indicated on the label and carton of the product.

6.4 Special Precautions for Storage

Store at +2°C to +8°C. Do not freeze. Discard if frozen. Shake well before use. Keep out of reach of children. Do not use the vaccine after the expiration date shown on the label. For multi dose vials use different syringe each time to vaccinate. After first opening, the vaccine can be used for up to 28 days provided

- It is stored between 2°C - 8°C
- It is NOT delivered in a Controlled Temperature Chain (CTC) programme. Should this be the case, the vaccine should be discarded after 6 hours or at the end of the session, whichever occurs first.

Refer Section 9 for Extended Controlled Temperature Conditions.

7. PRESENTATION

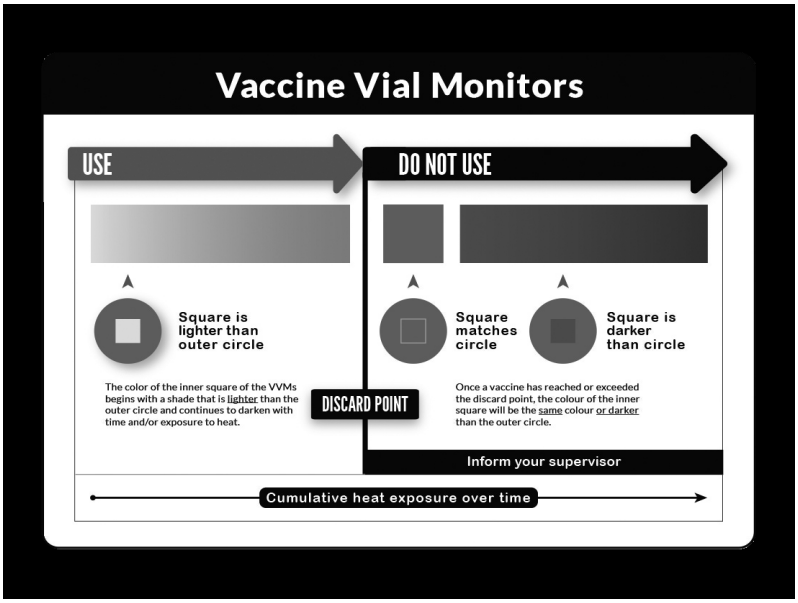
Typbar TCV® is presented in USP type 1 glass vial and Pre-filled syringe (PFS)

• Single dose Vial: 0.5 mL

• Multi dose Vial: 2.5 mL

8. The Vaccine Vial Monitor

Vaccine Vial Monitors (VVM30) dot is a part of the label on **Typbar TCV®** vials supplied through Bharat Biotech. VVM30 are supplied by TEMPTIME Corporation, USA. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.



The interpretation of the VVM30 is simple: Focus on the central square; its colour will change progressively. As long as the colour of this square is lighter than the colour of the ring, the vaccine can be used. As soon as the colour of the central square is the same colour as the ring or of a darker colour than the ring, the vial should be discarded.

9.0 Stability under Extended Controlled Temperature Conditions (WHO-ECTC guidelines)

This vaccine has been proven to remain stable for use beyond the traditional +2°C to +8°C cold chain under monitored conditions in keeping with the CTC, as

defined by the World Health Organization. If an immunization programme decides it is advantageous to apply a CTC strategy to delivery of this vaccine, it may do so according to one of the following two options: (a) removal from the traditional +2°C to +8°C cold chain for up to THREE consecutive days just prior to administration, when stored or transported at temperatures not exceeding 55°C ; or (b) removal from the traditional +2°C to +8°C cold chain for up to SEVEN consecutive days just prior to administration, when stored or transported at temperatures not exceeding 40°C.Once unopened vaccine vials are brought into either of these CTC scenarios, they must be used within the selected and tracked CTC time frame or appropriately discarded. All vials opened during an immunization session must be discarded after 6 hours or at the end of the session, whichever occurs first. The WHO recommends the use of an additional peak temperature threshold indicator to monitor that vaccines are not exposed to temperatures above the permitted threshold. Additional guidance on implementing a CTC delivery strategy is available from the World Health Organization.

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Manufactured by:

Bharat Biotech International Limited,
Sy. No. 230, 231 and 235, Genome Valley,
Turkapally, Shamirpet Mandal,
Medchal-Malkajgiri District - 500 078,
Telangana State, India.

For complaints and suggestions about the product, and any adverse event,

Please email: feedback@bharatbiotech.com

www.bharatbiotech.com

References:

1. Mohan VK, Varanasi V, Singh A, , Levine MM, Venkatesan R, Ella KM. "Safety and immunogenicity of a Vi polysaccharide-tetanus 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 stud y". *Clin Infect Dis.* 2015 Aug 1; 61 (3):393-402. doi: 10.1093/cid/civ295. Epub 2015 Apr 13.

2. Voysey M, Pollard AJ. Seroefficacy of Vi Polysaccharide- Tetanus Toxoid Typhoid Conjugate Vaccine (Typbar TCV)". Clin Infect Dis. 2018 Jun 18;67(1):18-24. doi: 10.1093/cid/cix1145.

3. Jin C, Gibani MM, Moore M, Juel HB, Jones E, Meiring J, Harris V, Gardner J, Nebykova A, Kerridge SA, Hill J, Thomaides-Brears H, Blohmke CJ, Yu LM, Angus B, Pollard AJ. **"**Efficacy and immunogenicity ofa Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of Salmonella Typhi: a randomisedcontrolled, phase 2b trial". Lancet. 2017 Dec 2;390(10111):2472-2480. doi: 10.1016/S0140-6736(17)32149-9. Epub 2017 Sep 28

4. Shakya M, Colin-Jones R, Theiss-Nyland K, Voysey M, Pant D, Smith N, Liu X, Tonks S, Mazur O, Farooq YG, Clarke J, Hill J, Adhikari A, Dongol S, Karkey A, Bajracharya B, Kelly S, Gurung M, Baker S, Neuzil KM, Shrestha S, Basnyat B, Pollard AJ; TyVAC Nepal Study Team."Phase 3 Efficacy Analysis of a T"yphoid Conjugate Vaccine Trial in Nepal". N Engl J Med. 2019 Dec 5;381(23):2209-2218. doi: 10.1056/NEJMoa1905047.

5. "Research finds new vaccine protecting children from typhoid". Available at: https://www.aku.edu/news/Pages/News_Details.aspx?nid=NEWS-002068,.

6. "Typhoid Conjugate Vaccine Introduction in Navi Mumbai, India". Available at: https://clinicaltrials.gov/ct2/show/NCT03554213.

7. 11th International Conference on Typhoid and other invasive Salmonelloses. March 26-28, 2019, Hanoi, Vietnam. Available at: https://www.coalitionagainsttyphoid.org/wp-content/uploads/2019/03/F_SABIN_Typhoid-Conference-booklet_web.pdf

8. Sirima SB, Ouedraogo A, Barry N, Siribie M, Tiono AB, Nébié I, Konaté AT, Berges GD, Diarra A, Ouedraogo M, Soulama I, Hema A, Datta S, Liang Y, Rotrosen ET, Tracy JK, Jamka LP, Neuzil KM, Laurens MB. Safety and immunogenicity of co-administration of meningococcal type A and measles-rubella vaccines with typhoid conjugate vaccine in children aged 15-23 months in Burkina Faso. Int J Infect Dis. 2021 Jan;102:517-523. doi: 10.1016/j.ijid.2020.10.103. Epub 2020 Nov 8. PMID: 33176205; PMCID: PMC7762715.

9. Theiss-Nyland K, Qadri F, Colin-Jones R, Zaman K, Khanam F, Liu X, Voysey M, Khan A, Hasan N, Ashher F, Farooq YG, Pollard AJ, Clemens JD. Assessing the Impact of a Vi-polysaccharide Conjugate Vaccine in Preventing Typhoid Infection Among Bangladeshi Children: A Protocol for a Phase IIIb Trial. Clin Infect Dis. 2019 Mar 7;68(Suppl 2): S74-S82. doi: 10.1093/cid/ciy1107. PMID: 30845333; PMCID: PMC6405281.

10. “SAGE on Typhoid Vaccine Policy Recommendations” available at:

https://www.who.int/immunization/sage/meetings/2017/october/1_Typhoid_SAGE_background_paper_Final_v3B.pdf?ua=1

11. “Safety of typhoid conjugate vaccine” available at: https://www.who.int/vaccine_safety/committee/topics/typhoid/Dec_2018/en/