J Nepal Health Res Counc 2025 Jan-March; 23 (66): 82-88

Immunogenicity and Safety Profile of Typhoid Conjugate Vaccine (Vi-DT) Among Nepali Children

Santosh Adhikari,[1] Ganesh Kumar Rai,[1,2] Ram Hari Chapagain,[1,2] Bishnu Rath Giri,[1] Prakash Joshi,[1,2] Nisha Jyoti Shrestha,[1,2] Bina Prajapati Manandhar,[1,2] Suresh Man Tamang,[1] Jessica Maharjan,[1] Bibesh Thapaliya,[1] Birendra Prasad Gupta,[3] Deok Ryun Kim,[3] Sridhar Vemula,[3] Sushant Sahastrabuddhe,[3] Tarun Saluja[3]

[1]Kanti Childrens Hospital, [2]National Academy of Medical Sciences, [3]International Vaccine Institute.

ABSTRACT

Background: Typhoid fever remains a major concern in tropical countries. The availability of an effective vaccine could be an important inclusion to currently available interventions. We reported on our evaluation of the immunogenicity and safety of the typhoid conjugate vaccine (Vi-DT) among Nepali children.

Methods: The study was an observer blinded, active controlled, randomized phase III clinical trial in children above 6 months and less than 18 years old. Three different lots of Vi-DT(Vi- Diptheria Toxoid); test vaccine and Vi-TT (Vi-Tetanus Toxoid); comparator vaccines were administered to eligible children. Seroconversion was assessed with blood samples collected at baseline and 4 weeks after the vaccination. A rise of at least 4-fold vi-antibody titer from the baseline was used to indicate positive seroconversion. Data on solicited and unsolicited adverse events were collected.

Results: Four hundred and eighty-eight children participated in the study. Seroconversion rate was 98.61% and 98.36% among participants who received Vi-DT and Vi-TT vaccines respectively. One immediate adverse event was observed only for Vi-DT group. One hundred forty-two and 66 solicited AEs within 7 days were observed with test and comparator vaccine respectively. Unsolicited AEs within 28 days were 125 for test vaccine compared and 77 for the comparator vaccine. Two SAEs were reported which were Not- related to study vaccine.

Conclusions: The overall seroconversion in Vi DT vaccine was non inferior to the comparator vaccine and the safety profile of the vaccine was good without any life-threatening events.

Keywords: Immunogenicity; Nepal; safety profile; typhoid conjugate vaccine; Vi-DT.

INTRODUCTION

Typhoid fever causes considerable morbidity and mortality among children in Asian countries with improper sanitation and poor hygiene.[1] It is a treatable disease but the increase of resistance to antibiotics is becoming a major challenge.[2] The availability of an effective and long acting vaccine against typhoid will be an important addition to currently-deployed preventive interventions along with available few vaccines although there has been the practice of prescribing oral typhoid vaccine to travelers to endemic countries, pregnant women, severely immunocompromised people, HIV positive travelers, persons with diabetes, chronic liver disease and splenectomy. [3]

Currently, there are three typhoid conjugate vaccines commercially available in India which are injectable unconjugated inactivated typhoid vaccine, live oral typhoid vaccine, typhoid conjugated polysaccharide vaccine and the conjugate vaccine has longer immune response than the oral vaccine. The oral vaccine has to be administered in every two years while the injectable polysaccharide conjugated vaccine has been supposed to provide the lifelong immunity. The SK bioscience-based vaccine manufactured purified Vi polysaccharide of S. Typhi is conjugated with diphtheria Toxoid (Vi-DT). Phase I and II trials in the Philippines were highly successful.[4] Nepal, a low income country with limited clean water supply and poor sanitation is endemic to enteric fever.[5] There has been about 9% of total positive cultures with burden of salmonella from a tertiary child

Correspondence: **Dr Santosh Adhikari, Kanti Children's Hospital, Maharajgunj, Kathmandu, Nepal. Email: drsantoshadhikari2009@gmail.com, Phone: +9779869398751.**

referral hospital.[6] The high incidence and the poor sanitation is major problem to control typhoid so for control of this condition, a vaccine with long action and cost effectives is a big challenge.

The observer blinded active controlled study is designed to explore immunogenicity and safety profile of typhoid conjugate vaccine (Vi-DT) in Nepal manufactured by SK Biosciences of South Korea which is administered via intramuscular injection. The Vi-DT vaccine has been evaluated in previous trials. [7]

METHODS

The study is observer blinded, active controlled, randomized phase III study of clinical trial which was conducted in four different sites in Nepal where the participants were from 6 months to 45 years old. Our site was focusing on only the children where the participants were from 0 to less than 18-year-old which three different age strata. The ethical clearance was obtained from Institutional Review Boards of the Nepal Health Research Council (NHRC), Department of Drug Administration (DDA) and the International Vaccine Institute. Our site had enrolled only children below 18 years of age who have fulfilled the inclusion and exclusion criteria and this study focused on the children only.

In this study the parents and the participants were briefed about the study ongoing for the typhoid vaccination. Signed informed consent (additionally assent if aged 7-17 years old) was obtained from all participants after the rationale and procedures of the trial had been explained and eligibility confirmed. The screening of the participants had been done. The inclusion and exclusion criteria were predefined which must satisfy the voluntary participants of Nepal. The inclusion criteria include the healthy children of age 6 months to less than 18 years, no any past history of vaccine for typhoid, no past history of salmonella typhoid infection as per the medical history given by parents, no any history of vaccine allergy and under any Immunotherapeutics. Those who fulfill the criteria were enrolled in the study and randomized. The base line immunogenicity was marked by taking the first blood sample before administering the vaccine.

Those who had fulfilled the inclusion and exclusion criteria were randomly assigned to the prepared block of (1:1:1) by block randomization as of active controlled part, stratified by age (6 months to <2 years, 2 years to <18 years, into one of four groups (A–D). The master randomization sheet was provided from the sponsor. Those who were randomized were matched in the master randomized chart by the un-blinded investigational product administrator. Participants in groups A–C received a single dose (25 µg; 0·5 mL) of Vi-DT test vaccine via intramuscular injection from one of three good manufacturing practice lots (group A received lot 1, group B received lot 2, and group C received lot 3), and those in group D received a single dose (25 µg; 0·5 mL) of the Vi-TT vaccine via intramuscular injection. The participants were observed for 30 minutes after vaccination to observe any adverse events occurred.

The Diary cards were given to the parents after 30 minutes of observation. They were clearly instructed to fill it and were told that there will be reminder call to fill it up. They were also told that there will be follow up for any events occurred via phone call on each day till first 7 days of vaccination. They were advised to bring back the diary card to site on follow up visit which were reviewed and the data filled encrypted to electronic system.

The follow up was done on 28 days of vaccination with a window period of 3 days before or after 28 days. On this visit physical examination of the participants done as well as second blood sampling was collected. Again they were given a diary card where any events occurred were advised to fill up and bring back on the final visit after 24 weeks from the vaccination. There was modification of the final visit due to COVID-19 pandemic and the travel restriction from government of Nepal. This made a mixture of physical and phone call follow up visit. The final visit included the third blood sampling which was planned to see the immunogenicity in 6 months of vaccination.

The adverse events which occurred within 30 minutes of vaccine administration were named as immediate; those occurred within 7 days were solicited adverse events and unsolicited adverse events were reported within 28 days after the vaccination. There were solicited adverse events identified and the grading was done according to the clinical presentations and the duration. The unsolicited adverse events and serious adverse events were also predefined. The Adverse events were graded as per severity depending on the protocol. [(8)] They were graded as mild if the events didn't hamper the daily activities while moderate if they had some effect in daily routine activities and needed medication to relieve the events. Serious adverse events were life threatening conditions, death or needed hospital admission.

The rise of at least 4-fold vi-antibody titer from the baseline is assumed to be positive seroconversion. The laboratory analysis was done in IVI, Korea. The adverse

events among the two different groups of children were studied to find out the safety profile. Descriptive and analytical statistics were performed with SAS 9.4. The study is registered in clinical trials.gov with the trial registry number NCT03933098. [8]

RESULTS

A total of 497 participants were potential screened from 08 Dec 2019 to 01 Mar 2020. Four hundred eighty-eight participants were enrolled and randomly assigned to groups A, B, C, or D (122 participants in each group), with a total of 366 participants in Vi-DT test group and 122 subjects in Vi-TT comparator group as shown in the CONSORT flow diagram in Figure 1.

The total set of 488 children enrolled in study. Cohort of 366 were randomized to test vaccine and 122 to the comparator vaccine. The final analysis set included the 359 and 122 for test and comparator vaccine. One participant refused blood sample collection and 12 were lost to follow up due to migration of the people during COVID-19 Pandemic The follow up of the participants was revised due to COVID-19 pandemic which was during the trial. The revision was to conduct the phone call for the follow up where the general information was gathered that were need in the clinical case report form. The full set of data is shown in the CONSORT flow diagram in Figure 1.

CONSORT of the participants involved in our site

The mean age was 3.12 years with SD of 3.50 years for Vi-DT vaccine while 2.98 years with SD of 3.24 years. The mean height was 89.10 cm for Vi-DT vaccine while 88.64 cm for Vi-TT and mean weight was 14.51 kg for Vi-DT while 14.32 kg for the Vi-TT vaccine group on day of vaccine administration which is shown in the table 1. The height, weight and vitals with physical examination was done in every visit to the site.

Table 1. Demographic distribution of Participants in Vi-DT and Vi-TT vaccine groups.

Variables	Vi-DT vaccine group (N=366)	Vi-TT vaccine group (N=122)	P value*
Male (%)	202 (55.19%)	58 (47.54%)	0.1424
Mean (SD) age at enrollment (years)	3.12 (3.50)	2.98 (3.24)	0.7066
Mean (SD) Height (cm)	89.10	88.64	0.9574
Mean (SD) Weight (kg)	14.51	14.32	0.9417
6 months to <2 years	Vi-DT vaccine group (N=252)	Vi-TT vaccine group (N=84)	
Male (%)	135 (53.57%)	40 (47.62%)	0.3443
2 years to <18 years	Vi-DT vaccine group (N=114)	Vi-TT vaccine group (N=38)	
Male (%)	67 (58.77%)	18 (47.37%)	0.2201

[Note] SD: Standard deviation.

* P-value has been derived from Chi-square test for gender and from t-test for continuous variable (age, height, and weight).

Comparison of Vi-TT, Vi-DT in two different age groups:

The pediatric age group was divided into two groups as per the protocol. The increase of the anti-Vi antibody titers compared to baseline with at least 4-fold is the desired immunogenicity of the vaccine. Those who have less antibody titer are assumed to be vaccine failure. The immunogenicity of the Vi-TT and Vi-DT vaccine was compared, and the results are shown in table no. 2

Table 2. Seroconversion of Vi-DT Vs Vi-TT at 4 and 24 weeks in two different age group.

	Age group (seroconversion rate)		
	6 mth-<2	2 years -<18	P value*
Immunogenicity Vi-DT at 4 weeks	97.96%	100.00%	0.1830
Immunogenicity Vi-TT at 4 weeks	97.62%	100.00%	1.0000
Immunogenicity Vi-DT at 24 weeks	97.85%	98.10%	1.0000
Immunogenicity Vi-TT at 24 weeks	100.00%	97.06%	0.3400

* P-value has been derived from Chi-square test for immunogenicity comparison at 4 weeks and from Fisher's exact test for immunogenicity comparison at 24 weeks.

Comparison of adverse effect of vaccines among two different pediatric age group:

The adverse events that were found in two groups were enlisted and the comparison was done among the two pediatric age groups. There was 1 immediate reaction after vaccination in Vi-DT vaccine whereas no immediate adverse even with vi-TT vaccine. This was mild in severity and considered to be definitely related to the vaccine.

There were a total of 142 (114 mild, 24 moderate, 4 severe) solicited adverse events noticed among 66/366, 18.03% participants with VI-DT vaccine while 66 (53 mild, 13 moderate, 0 severe) solicited adverse events among 34/122, 24.87% participants with Vi-TT vaccine. The adverse events are enlisted in table 3.

The solicited and unsolicited adverse events are listed in the annex tables. The most common solicited local adverse events were pain/tenderness, erythema, swelling, pruritus, pain/tenderness while solicited systemic events were diarrhea, fever, vomiting, lethargy, irritability, nausea, drowsiness for both vaccines. There is no statistical significance in adverse events between study and comparator vaccine.

Serious Adverse events:

There were two serious adverse events (SAE). An 18-month female child experienced vomiting, diarrhea and fever four days of administration of test vaccine. This child was managed in hospital and discharged after 24 hours once the child was stable. A 15-month male child experienced lower lobe pneumonia after 28 days of administration of test vaccine who was also managed with admission of 4 days in hospital. Both serious adverse events were not related to the vaccine.

Table 3. Adverse events profile of participants after vaccination with Vi-DT vs Vi-TT vaccine.

	Vi-DT Group			Vi-TT Group			P value
	Overall	Local AE	Systemic AE	overall	Local AE	Systemic AE	
Immediate Reaction within 30 minutes of Post vaccination							
All ages	1/366 (0.27%)	1/366 (0.27%)	0/366 (0.00%)	0/122 (0.00%)	0/122 (0.00%)	0/122 (0.00%)	1.000
6 months < 2 years	1/252 (0.4%)	1/252 (0.4%)	0/252 (0.00%)	0/84 (0.00%)	0/84 (0.00%)	0/84 (0.00%)	1.000
2 years - <18 years	0/114 (0.0%)	0/144 (0.0%)	0/144 (0.00%)	0/38 (0.00%)	0/38 (0.00%)	0/38 (0.00%)	-
Solicited adverse events within 7 days after vaccination (related to vaccine)							
All ages	66/366 (18.03%)	27/366 (7.38%)	52/366 (14.21%)	34/122 (27.87%)	20/122 (16.39%)	23/122 (18.85%)	0.0198 [1] 0.0035 [2] 0.2180 [3]
6 months < 2 years	51/252 (20.24%)	16/252 (6.35%)	42/252 (16.67%)	26/84 (30.95%)	14/84 (16.67%)	20/84 (23.81%)	0.0430 [1] 0.0041 [2] 0.1439 [3]
2 years - <18 years	15/114 (13.16%)	11/114 (9.65%)	10/114 (8.77%)	8/38 (21.05%)	6 (15.79%)	3/38 (7.89%)	0.2396 [1] 0.3718 [2] 1.0000 [3]
Unsolicited adverse events within 4 weeks after vaccination							
All ages	78/366 (21.31%)			38/122 (31.15%)			0.0271
6 months < 2 years	65/252 (25.79%)			30/84 (35.71%)			0.0804
2 years - <18 years	13/114 (11.40%)			8/38 (21.05%)			0.1355
Serious adverse events(SAE) during entire study period							
All ages	2/366 (0.55%)			0/122 (0.00%)			1.000
6 months < 2 years	2/366 (0.55%)			0/122 (0.00%)			1.000
2 years - <18 years	0/366 (0.00%)			0/122 (0.00%)			1.000
Gastrointestinal system (Acute Gastroenteritis)	1/366 (0.27%)			0/122 (0.00%)			1.000
Respiratory System (lower lobe pneumonia)	1/366 (0.27%)			0/122 (0.00%)			1.000

Comparison of solicited AE between Vi-DT group and Vi-TT group for overall cases [1]; For local AE [2] and for systemic AE [3]

DISCUSSION

Our study shows that the Vi-DT vaccine is immunogenic and non-inferior to the locally licensed, WHO-prequalified Vi-TT vaccine when given as a single dose, at 4 weeks after vaccination in all age group children. Equivalence among three good manufacturing practices of the Vi-DT vaccine was also shown.[7]

Two serious adverse events were reported during 4 weeks after vaccination. One was pneumonia and the other was gastroenteritis. None of which were considered related to the Vi-DT or Vi-TT vaccines.

In our study, we observed that there were 142 (114 mild, 24 moderate, 4 severe) solicited AE with VI-DT vaccine while 66 (53 mild, 13 moderate, 0 severe) solicited AE with Vi-TT vaccine. The study done by Qamar et al. has shown that there was significantly higher AEFI among very young children (age group 6 to 12 months) as compared to 2 to 3 years old children on administrating of Typbar TCV vaccine which is the comparator vaccine in our study.[9]

The test vaccine Vi DT has shown the non-inferiority to the comparator vaccine Typbar TCV. The Typbar-TCV is effective in protecting children against S Typhi infection in an outbreak setting, and was able, with moderate deployment, to curtail a major XDR S Typhi outbreak in a densely populated setting. The vaccine shows efficacy against S Typhi irrespective of antimicrobial resistance.[10]

The resistant enteric infections are a global problem where the global dissemination may be changed which is shown by the study done by Wong VK et al.[11] The emergence of antimicrobial-resistant S Typhi infections contributed to the recommendations by WHO for the introduction of typhoid conjugate vaccines in populations at high risk of infection. The World Health Organization (WHO) identified salmonellae as high-priority pathogens for development of new antibiotics and salmonella remains in the list of WHO priority.[12]

The immediate adverse reactions did not differ in frequency between Vi-DT and Vi-TT vaccine groups. Most unsolicited adverse events were classified as mild to moderate in severity and were judged as unrelated to vaccine administration. There was no difference in the frequency of unsolicited adverse events reported between each lot of Vi-DT vaccine and Vi-TT vaccine group D. Two serious adverse events were reported between 4 weeks and 24 weeks in Vi-TT vaccine groups A–C, both of which were considered unrelated to the study vaccine. Overall, the Vi-DT vaccine was well tolerated, and its safety profile is satisfactory and similar to the safety profile of the Vi-TT vaccine.[7]

We found no difference in the anti-Vi IgG seroconversion rate at 24 weeks between Vi-DT vaccine groups A–C and Vi-TT group D. There was a significant difference in the anti-Vi IgG GMT in all participants at 24 weeks, which was due to a significant difference in participants aged 6 months to younger than 2 years; no differences in participants aged 2 years to younger than 18 years, or those aged 18 years to 45 years were observed. These findings need to be investigated further to fully understand the reason for these age-specific differences.

Several studies have reported the safety and immunogenicity of the Vi-TT vaccine and other typhoid conjugate vaccines in individuals older than 2 years.[13,14] However, data on the safety and immunogenicity of the Vi-TT vaccine in younger children are scarce, except from studies done in Indonesia and India. A recent single-blind study in India, involving a small sample of individuals aged 6 months to 45 years and a short-term follow-up period, compared a locally produced typhoid conjugate vaccine (manufactured by Cadila Healthcare, Ahmedabad, India) with the Typbar TCV Vi-TT vaccine, and showed similar immunogenicity and safety of the two vaccines.[15] The long-term extension of this study is ongoing, and will evaluate the persistence of antibodies at around 3 years after primary vaccination. The Vi-DT vaccine safety and reactogenicity data are consistent with those reported in other phase 3 studies of the Vi-TT vaccine, and they confirm the safety profile of the phase 2 study of the Vi-DT vaccine in children younger than 2 years.[16-18]

Overall, our study shows that the Vi-DT test vaccine is safe, immunogenic, and non-inferior to the licensed Vi-TT vaccine when given as a single dose in all age groups, including in children aged 6 months to younger than 2 years. The Vi-DT vaccine was non-inferior to the Vi-TT vaccine in all participants and in each age stratum in terms of the anti-Vi IgG seroconversion rate, and the Vi-DT vaccine lot-to-lot consistency, measured by anti-Vi IgG GMTs, was shown at 4 weeks following vaccination. Non-inferiority of the Vi-DT vaccine compared with the Vi-TT vaccine measured by anti-Vi IgG GMTs, the lot-to-lot consistency measured by anti-Vi IgG seroconversion rates, and non-interference of the measles-rubella

vaccine with the Vi-DT vaccine at 4-week post-vaccination were also shown.

One of the limitations of our study was that a sufficient number of participants eligible for the concomitant measles-rubella vaccine could not be enrolled in the study due to a government-initiated measles-rubella vaccine catch-up campaign that occurred during the course of the study. Therefore, to achieve the objective of showing immune non-interference of the Vi-DT vaccine with a measles-containing vaccine, a separate, add-on study with sample size of 360 infants aged 9-15 months was planned as an amendment to the current study protocol. These results will be published in a separate publication.

Another limitation of our study was caused by the ongoing COVID-19 pandemic. The associated travel restrictions resulted in an increased number of follow-up visits that occurred out of the predefined visit window, and hence, many protocol deviations. However, these protocol deviations had minor effects on the per-protocol analysis. By conducting the study in Nepal, which is a typhoid-endemic country, there was a possibility of enrolling individuals with subclinical infection or asymptomatic carriers. However, we consider that any potential sources of error were equally distributed among the four randomized groups, and that statistical comparisons were therefore unaffected.

CONCLUSIONS

In conclusion, the findings of our study show that a single dose of Vi-DT vaccine elicits seroconversion rates similar to that of the WHO-prequalified Vi-TT typhoid conjugate vaccine. The results also indicate lot-to-lot equivalence of the Vi-DT vaccine, supporting the robustness of the manufacturing process. The overall results show that the Vi-DT vaccine is safe and immunogenic in children, and they support initiation of the licensure process leading to WHO prequalification.

ACKNOWLEDGMENTS

We would like to acknowledge the Bill & Melinda Gates Foundation for funding this study (OPP1115556). We would also like to thank the International Vaccine Institute (IVI), Korea for sponsorship (IVI T003), Croissance Clinical Research (CRO) and Zifo technologies, India for study management. We are grateful for the site and the research team of IVI T003 to help in every step for successful completion of clinical trials. The participants of this trial are especial important who are the backbone of the study.

CONFLICT OF INTEREST

We disclose no potential conflict of interest with author(s).

REFERENCES

1. GBD 2017 Typhoid and Paratyphoid Collaborators. The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Infect Dis. 2019 Apr;19(4):369-381.

2. Barac R, Als D, Radhakrishnan A, Gaffey MF, Bhutta ZA, Barwick M. Implementation of Interventions for the Control of Typhoid Fever in Low- and Middle-Income Countries. Am J Trop Med Hyg. 2018 Sep;99(3_Suppl):79-88.doi: https://doi.org/10.4269/ajtmh.18-0110

3. Freedman DO, Chen LH. Vaccines for International Travel. Mayo Clin Proc. 2019 Nov;94(11):2314-2339.doi: https://doi.org/10.1016/j.mayocp.2019.02.025

4. Capeding MR, Alberto E, Sil A, Saluja T, Teshome S, Kim DR et. al Immunogenicity, safety and reactogenicity of a Phase II trial of Vi-DT typhoid conjugate vaccine in healthy Filipino infants and toddlers: A preliminary report. Vaccine. 2020 Jun 9;38(28):4476-483.doi: https://doi.org/10.1016/j.vaccine.2019.09.074

5. World Bank. World development indicators. 2019. Accessed 15 March 2023 Available at: https://datacatalog.worldbank.org/dataset/world-development-indicators.

6. Pokhrel N, Chapagain R, Thakur CK, Basnet A, Amatya I, Singh R, et al. Salmonella infection among the pediatric population at a tertiary care children's hospital in central Nepal: a retrospective study. Frontiers in Microbiology. 2023 Sep 29;14:1218864.doi: https://doi.org/10.3389/fmicb.2023.1218864

7. Kumar Rai G, Saluja T, Chaudhary S, Tamrakar D, Kanodia P, Giri BR et. al Safety and immunogenicity of the Vi-DT typhoid conjugate vaccine in healthy volunteers in Nepal: an observer-blind, active-controlled, randomised, non-inferiority, phase 3

trial. Lancet Infect Dis. 2022 Apr;22(4):529-540.doi: https://doi.org/10.1016/S1473-3099(21)00455-2

8. National Library of Medicine, Immune non inferiority and safety of a Vi-DT Typhoid Conjugate Vaccine. Accessed at 15 Mar 2023, Available at:https://clinicaltrials.gov/ct2/show/NCT03933098

9. Qamar FN, Yousafzai MT, Khaliq A, Karim S, Memon H, Junejo A et. al Adverse events following immunization with typhoid conjugate vaccine in an outbreak setting in Hyderabad, Pakistan. Vaccine. 2020 Apr 23;38(19):3518-3523.doi: https://doi.org/10.1016/j.vaccine.2020.03.028

10. Yousafzai MT, Karim S, Qureshi S, Kazi M, Memon H, Junejo A et. al 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. Lancet Glob Health. 2021 Aug;9(8):e1154-e1162.doi: https://doi.org/10.1016/S2214-109X(21)00255-2

11. Wong VK, Baker S, Pickard DJ, Parkhill J, Page AJ, Feasey NA, et al. Phylogeographical analysis of the dominant multidrug-resistant H58 clade of Salmonella Typhi identifies inter- and intracontinental transmission events. Nature genetics. 2015 Jun;47(6):632-9.[Article]

12. WHO, WHO publishes the list of bacteria for which new antibiotics are urgently needed. 27 Feb 2017, Accessed on 15 Mar 2023, Available at: https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed.

13. Levine MM, Ferreccio C, Abrego P, Martin OS, Ortiz E, Cryz S. Duration of efficacy of Ty21a, attenuated Salmonella typhi live oral vaccine. Vaccine. 1999 Oct 1;17 Suppl 2:S22-7.doi: https://doi.org/10.1016/S0264-410X(99)00231-5

14. Lin FY, Ho VA, Khiem HB, Trach DD, Bay PV, Thanh TC, et al. The efficacy of a Salmonella typhi Vi conjugate vaccine in two-to-five-year-old children. N Engl J Med. 2001 Apr 26;344(17):1263-9.doi: https://doi.org/10.1056/NEJM200104263441701

15. Kundu R, Kandulna AK, Nayak U, Jangid SK, Babu TR, Vukkala R, et al. Immunogenicity and Safety of Typhoid Conjugate Vaccine in Healthy Indian Subjects: A Randomized, Active-controlled, Comparative Clinical Trial. Indian Pediatr. 2020 Jul 15;57(7):625-630.doi: https://doi.org/10.1007/s13312-020-1890-y

16. Shakya M, Colin-Jones R, Theiss-Nyland K, Voysey M, Pant D, Smith N, et. al TyVAC Nepal Study Team. Phase 3 Efficacy Analysis of a Typhoid Conjugate Vaccine Trial in Nepal. N Engl J Med. 2019 Dec 5;381(23):2209-2218.doi: https://doi.org/10.1056/NEJMoa1905047

17. Mohan VK, Varanasi V, Singh A, Pasetti MF, Levine MM, Venkatesan R, et al. 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 study. Clinical Infectious Diseases. 2015 Aug 1;61(3):393-402.doi: https://doi.org/10.1093/cid/civ295

18. Capeding MR, Sil A, Tadesse BT, Saluja T, Teshome S, Alberto E, et al. Safety and immunogenicity of Vi-DT conjugate vaccine among 6-23-month-old children: Phase II, randomized, dose-scheduling, observer-blind Study. EClinicalMedicine. 2020 Sep 9;27:100540.doi: https://doi.org/10.1016/j.eclinm.2020.100540