ADVERSE EFFECTS OF TYPBAR-TYPHOID CONJUGATED VACCINE AMONG CHILDREN VACCINATED IN UNIVERSITY OF LAHORE TEACHING HOSPITAL

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Abstract

Background and Objectives: Rising incidence of XDR enteric fever in Pakistan requires extensive workup on safe availability of immunization. Aim of this study was to assess the frequency of adverse effects of Typbar TCV in children vaccinated in a tertiary care facility.

Methods: It was a descriptive study in which children aged 9 months to 15 years of age either gender coming for vaccination to paediatric opd from 1st Feb-2021 to 17th Feb-2021 were included. Post vaccination observation for 30 minutes was done for all children in hospital and were followed after 14 days on telephone for any local or systemic adverse effect after vaccination. Complications (systemic and local) were documented on proforma. All data were analyzed using SPSS 22.

Results: In our study, total 835 children were enrolled out of which 666 responded. Contact with 169 children was not possible because their lack of response and unavailability. Mean age was 4.9±4.06 years. Regarding local adverse effects, pain at site of injection was present in 30% children. Other local site reaction includes swelling in 17.7%, redness in 3% and limitation of movement in 2.4%. Systemic adverse effects included fever in 20.4%. Headache was present in 0.6% children, GI symptoms present in 0.9%.

Conclusion: With Typbar-TCV Typhoid Vi conjugate vaccine. fever, pain and local reactogenicity were the most common side effects. Safety profile of TCV can further be assessed with the help of large multi centre trials So Tybar –TCV Typhoid Vi conjugate vaccine can be encouraged to administered safely to all children as the incidence of XDR typhoid is rising.

Key Word: Conjugate vaccine, adverse effect, Enteric fever

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Among the available typhoid vaccines, TCV is preferred at all ages in view of its improved immunological properties, use in younger children and expected duration of protection. Other 2 vaccinations which include Ty21a (a live oral vaccine) and Vi capsular polysaccharide vaccine (ViPS) (an injectable subunit vaccine) has less immunity, cannot use in infant and less expected duration of protection. WHO in 2008 recommended TCV vaccine should be used against typhoid,[1] however, unfortunately, it was not widely implemented. Conjugated TCVs are now available which is consider a new generation vaccine. Studies regarding its safety and immunogenicity showed promising results in young children. In 2019–2020 GAVI approved funds so that TCVs are available for develo-ping countries.[2]

TCV give protection against S. Typhi which is the causative organism of typhoid in more than 90% cases.

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The characteristic clinical features in children of Typhoid are fever, vomiting, and loose stools. Southeast Asian and African regions are endemic areas.[3] It was estimated by global burden of disease that in 2017, nearly 11 million cases and almost 117 thousand deaths were due to Salmonella Typhi and the most affected area was South Asia with 72% of the global cases and 70% of the deaths.[4]

In Pakistan, it was estimated that about 90% of fluoroquinolones were inactive against Salmonella Typhi and 50% multidrug-resistant was reported against it.[5] An outbreak in 2016 was reported in Hyderabad, Pakistan of extensively drug-resistant Salmonella Typhi defined as resistant to ampicillin, chloramphenicol, trimethoprim sulfamethoxazole, fluoroquinolones, and 3rd generation cephalosporin.[6]

The aim of the study was to describe the adverse effects of Typbar-TCV as it is recently started in Punjab and little information is available regarding its side effects. This information will be helpful for the health practitioners in developing strategy to educate population regarding typhoid vaccination and its adverse effects.

METHODS

This descriptive study was conducted in department of Pediatrics, The University of Lahore teaching hospital after approval of hospital ethical committee and written informed consent of parents. Children aged 9 months to 15 years of either gender for vaccination from 1st Feb-2021 to 17 Feb-2021 were included in study. Children who were immunocompromised, on steroid therapy, taking antipyretic or NSAID due to any illness and children with diarrheal disease were excluded from the study. Post vaccination Observation for 30 minutes was done for all children in hospital and were followed after 14 days on telephone for any local or systemic adverse effect by doctors. All parents were counselled verbally that if they observe any adverse effect immediately report to the hospital. Complications including fever, swelling, pain, anaphylactic reaction, were documented on proforma attached. Non-probability sampling – consecutive sampling technique was used. Sample size was calculated using Open Epi calculator keeping 95% confidence interval, 2.8% previously reported frequency of fever after TCV vaccine in children in Pakistan, 1.4% absolute precision and 10% expected dropout rate.[1] Require sample size was 587 clients we enrolled all clients, who came for vaccination to our center clients, and fulfilling the inclusion criteria total patient were 835 but 169 were dropped. All data were analyzed using SPSS 22 and observed in tabulated form. Chi-square test was used as a test of significance. Descriptive statistics were performed on all the variables. All categorical variables were presented in the form of frequencies and percentages. Quantitative variables were presented in the form of mean±standard deviation. P-value of less than 0.05 was considered statistically significant.

RESULTS

In our study, total 835 children were enrolled out of which 666 respond. While 169 did not response or gave wrong contact number. Among 666 children minimum age of 9 months and maximum age of 15 years were recorded, mean age was 4.9±4.06 years. There were 352 (52.5%) males and 314 (47.1%) female children. Site of injection was right arm in 406 (61%) children and right thigh in 260 (39.03%) children. Previously typhoid vaccine was given in 104 (15.6%) children. (Table 1)

Regarding local adverse effects, pain at site of injection was present in 200 (30%) children, which lasted for 24 to 48 hours in 80% of children. Local site reaction was present in 146 (21.9%) children; most common adverse reaction was swelling in 118(17.7%) children followed by redness in 20 (3%) children and limitation of movement in 16 (2.4%) children. (Table 2)

Systemic adverse effects, included fever in 136 (20.4%) children according to parents while documented fever was present in 58 (8.7%) children and antipyretic was given in 166 (24.9%) children for fever and pain control. Most of children developed fever within 12 hours of vaccine in 120 (88%) and fever lasted for 24 to 48 hours in 48% children. Headache was present in 4 (0.6%) children which lasted for 24

Table 1: Demographic data of children (n = 666)

		Frequency	Percent
Gender	Male	352	52.9
	Female	314	47.1
Site of injection	Right arm	406	61.0
	Right thigh	260	39.0
Previous typhoid vaccine	Yes	104	15.6%
	No	562	84.4%

Table 2: Local adverse effects of vaccine (n = 666)

Local side effects of vaccine		YES	NO
Pain at site of infection		200(30%)	466(70%)
Local reaction at site		146(21.9%)	520(78.1%)
Type of local reaction	Swelling	118(17.7%)	478(82.3%)
	Redness	20(3.0%)	646(97%)
	Limitation of movement	16(2.4%)	650(97.6%)

Table 3: Systemic adverse effects of vaccine (n=666)

	YES	NO
Fever	136(20.4%)	530(79.6%)
Documented fever	58(8.7%)	608(91.3%)
Antipyretic for fever and pain	166(24.9%)	500(75.1%)
Headache	4(0.6%)	662(99.4%)
Diarrhea	6(0.9%)	600(99.1%)
Nausea and vomiting	2(0.3%)	664(99.7%)

Syncope Anaphylactic reaction Cold/cough Convulsions was not found

to 48 hours in 99.4% children. GI symptoms were present in small number of populations including diarrhea in 6(0.9%) vomiting and nausea in 2(0.3%) children. No anaphylactic reaction, syncope, convulsions cough or cold occurred in any children. (Table 3) There was no difference in local adverse reactions according to age and gender (p value 0.905&0.085 respectively).

DISCUSSION

This data support the safety profile and no serious effects were noted in this Study. Pakistan faces two-fold problem regarding enteric fever, at one end of spectrum is highest incidence and other end of spectrum is emergence of highly resistant strain of enteric fever.[5] This situation further worsens in 2016 with an outbreak of enteric fever in Hyderabad, Karachi and nearby areas of these two cities. 64.4% of these cases ultimately turned out to be extensively drug resistant cases.[9,10,11] This situation raises concern at national and international level and emphasis to prevent this deadly disease considered by mass immunization by national and international experts.[12] Keeping in view of this resistant typhoid outbreak Punjab government stated extensive campaign for typhoid vaccine across all district free of cost. All children aged 9 months to 15 years were given Typbar-TCV Typhoid Vi conjugate vaccine.

Similar results were seen in local study done in multi-centers across Sindh where children from 6 months to 10 years were vaccinated, 51.5% were male and 48.5% were female children. There was no life-threatening adverse effect like anaphylaxis, requiring hospital admission, morbidity/disability, and mortality reported post immunization during a fortnightly follow up period. The reported incidence of minor adverse reaction 0.24%. The percentage of various untoward effect reported were 0.12 %, & 0.07% & .02 % for fever, local reactogenicity and diarrhea respectively. Rarest reported untoward effect were syncopal attack and immediate emesis following vaccination each in one child out of 207000 vaccination doses. The syncopal attack most likely results from the fear of needle prick rather than vaccination itself. The increasing age has progressive decline in reported side effects up to 6 year of age which was statistically significant (0.54% vs. 0.33% respectively; p-value <0.001). but after six years there were slightly variable change in pattern of adverse event either minimally increased or decreased. The female gender has statistically lesser untoward effect following vaccination. (282/106,522 = 0.3% vs. 217/100,478 = 0.2%; p < 0.01). While in our study no difference in age and gender was observed. Our results were also consistent with phase 3 trial of Typbar-TCV® where the fever was identified among 4% and local reactogenicity among 3% of the children vaccinated with Typbar-TCV.[13]

Our results are similar with a study that was conducted in India which identified 222/113 420 (0.2%) vaccine recipients with adverse effects following immunization through the NMMC AEFI surveillance system: 211 (0.19%) experienced minor AEFIs,

2(0.002%) severe, and 9 serious (0.008%). At 48 hours post vaccination, 1852/5605 (33%) caregivers reported ≥ 1 AEFI, including injection site pain (n = 1452, 26%), swelling (n = 419, 7.5%), and fever (n = 416, 7.4%). Of the 4728 interviews completed at 7 days'post vaccination, the most reported AEFIs included fever (n = 200, 4%), pain (n = 52, 1%), and headache (n = 42, 1%).[15]

Several limitations need to be considered while interpreting results of this study. Firstly, unavailability of control to compare the rate of adverse effects. Secondly adverse effects were only monitored for 14 days so any adverse effects occurring after 14 days of the vaccination could not be found out in this study. Thirdly, lack of education among most of the families and lack of daily recording of any adverse events including fever following immunization. Fourthly, study was conducted on small group.

CONCLUSION

Typbar-TCV Typhoid Vi conjugate vaccine administered among children was safe with fever, pain and local reactogenicity were the most common side effects. Safety profile of TCV can further be assessed with the help of large multi centre trials So Tybar –TCV Typhoid Vi conjugate vaccine can be encouraged to administered safely to all children as the incidence of XDR typhoid is rising.

Ethical Approval:

The ethical Approval was obtained from University College of Medicine and Dentistry, The University of Lahore. (Reference No. ERC4/21/37)

Conflict of Interest: *None*

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REFERENCES

1. Yousafzai MT, Qamar FN, Shakoor S, Saleem K, Lohana H, Karim S, Hotwani A, Qureshi S, Masood N, Rauf M, Khanzada JA. Ceftriaxone-resistant Salmonella Typhi outbreak in Hyderabad City of Sindh, Pakistan: high time for the introduction of typhoid conjugate vaccine. Clinical Infectious Diseases. 2019 Feb 15;68(Supplement_1):S16-21.
2. World Health Organization. Background paper to SAGE on typhoid vaccine policy recommendations. 2017.
3. Dewan AM, Corner R, Hashizume M, Ongee ET. Typhoid fever and its association with environmental factors in the Dhaka metropolitan area of Bangladesh: a spatial and time-series approach. PLoS Negl Trop Dis. 2013 Jan 24;7(1):e1998.
4. Kim JH, Im J, Parajulee P, Holm M, Cruz Espinoza LM, Poudyal N, Mogeni OD, Marks F. A systematic review of typhoid fever occurrence in Africa. Clinical Infectious Diseases. 2019 Oct 30;69(Supplement_6):S492-8.
5. Stanaway JD, Reiner RC, Blacker BF, Goldberg EM, Khalil IA, Troeger CE, Andrews JR, Bhutta ZA, Crump JA, Im J, Marks F. The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet Infectious Diseases. 2019 Apr 1;19(4):369-81.
6. Qamar FN, Yousafzai MT, Sultana S, Baig A, Shakoor S, Hirani F, Wassay A, Khushboo S, Mehmood J, Freeman A, Date K. A retrospective study of laboratory-based enteric fever surveillance, Pakistan, 2012–2014. The Journal of infectious diseases. 2018 Nov 10; 218 (suppl_4):S201-5.
7. Mohan VK, Varanasi V, Singh A, Pasetti MF, 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 study. Clinical Infectious Diseases. 2015 Aug 1;61(3):393-402.
8. Meiring JE, Gibani M, Basnyat B, Bentsi-Enchill AD, Clemens J, Darton TC, Date K, Dougan G, Garrett D, Gessner BD, Gordon MA. The Typhoid Vaccine Acceleration Consortium (TyVAC): vaccine effectiveness study designs: accelerating the introduction of typhoid conjugate vaccines and reducing the global burden of enteric fever. Report from a meeting held on 26–27 October 2016, Oxford, UK. Vaccine. 2017 Sep 12;35(38):5081-8.
9. Klemm EJ, Shakoor S, Page AJ, Qamar FN, Judge K, Saeed DK, et al. Emergence of an Extensively Drug-Resistant Salmonella enterica Serovar Typhi Clone Harboring a Promiscuous Plasmid Encoding Resistance to Fluoroquinolones and Third-Generation Cephalosporins. mBio. 2018;9.
10. Yousafzai M.T., Qamar F.N., Shakoor S., Saleem K., Lohana H., Karim S. Ceftriaxone-resistant Salmonella Typhi Outbreak in Hyderabad City of Sindh, Pakistan: high time for the introduction of typhoid conjugate vaccine. Clin Infect Dis. 2019;68:S16–S21.

11. Qamar F.N., Yousafzai M.T., Khalid M., Kazi A.M., Lohana H., Karim S. Outbreak investigation of ceftriaxone-resistant Salmonella enterica serotype Typhi and its risk factors among the general population in Hyderabad, Pakistan: a matched case-control study. Lancet Infect Dis. 2018;18:1368–1376.

12. Mohan V.K., Varanasi V., Singh A., Pasetti M.F., Levine M.M., Venkatesan R. 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. Clin Infect Dis. 2015;61:393–402.

13. Qamar FN, Yousafzai MT, Khaliq A, Karim S, Memon H, Junejo A, Baig I, Rahman N, Bhurgry S, Afroz H, Sami U. Adverse events following immunization with typhoid conjugate vaccine in an outbreak setting in Hyderabad, Pakistan. Vaccine. 2020 Apr 23;38(19): 3518-3523.

14. Mohan V.K., Varanasi V., Singh A., Pasetti M.F., Levine M.M., Venkatesan R. 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. Clin Infect Dis. 2015;61:393–402.

15. Longley AT, Date K, Luby SP, Bhatnagar P, Bentsi-Enchill AD, Goyal V, Shimpi R, Katkar A, Yewale V, Jayaprasad N, Horng L, Kunwar A, Harvey P, Haldar P, Dutta S, Gidudu JF. Evaluation of Vaccine Safety After the First Public Sector Introduction of Typhoid Conjugate Vaccine-Navi Mumbai, India, 2018. Clin Infect Dis. 2021 Aug 16;73(4):e927-e933.