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Original Article

Effectiveness of Typhoid Conjugate Vaccination in Preventing Culture-Confirmed Typhoid Fever

Rabia Khalid, Muzammil Ghafoor*, Hasham Khan, Amjad Iqbal

Department of Pediatric, Combined Military Hospital Abbottabad/National University of Medical Sciences (NUMS) Pakistan,
*Department of Pediatric, Combined Military Hospital Bannu/National University of Medical Sciences (NUMS) Pakistan

ABSTRACT

Objective: To compare the effectiveness of Typhoid conjugate vaccine against culture-confirmed typhoid fever.
Study Design: Prospective analytical study.
Place and Duration of Study: Pediatric Department, Combined Military Hospital, Abbottabad Pakistan, July 2023 to Feb 2024.
Methodology: Pediatric age group patients from 2-12 years diagnosed with cases of typhoid fever were included in the study. Demographics, history of vaccination, presenting complaints, systemic exam findings, infective markers, and culture reports were recorded.
Results: A total of 75 children with a diagnosis of typhoid fever were included in the study. The mean age recorded was 8.07±2.38 years with a male predominance of 54(72.0%) as compared to 21(28.0%) females. 43(57.3%) of the children were vaccinated, and the most common presenting symptom was fever in 70(93.3%) patients. Deranged platelets were the most common finding with a frequency of 54(72.0%). Negative culture was observed in 19(44.2%) vaccinated patients as compared to 03(9.4%) in unvaccinated children (p<0.01). In unvaccinated children, positive blood cultures revealed that MDR pathogen strains were most common as compared to non-resistant strains in vaccinated children.
Conclusion: Vaccination against typhoid promotes significant protection against culture-proven typhoid fever. Protection against MDR strains makes typhoid vaccination a suitable choice to decrease the incidence of typhoid fever.

Keywords: Blood Culture, Typhoid Fever, Vaccination.

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INTRODUCTION

Typhoid fever is a common infectious disease encountered in pediatric patients caused by Salmonella typhi. The bacterial pathogen has a protective polysaccharide coating that offers protection against macrophages. Poor sanitation and raw food harvesting harbor these bacterial pathogens, leading to multisystemic manifestations primarily in the gastrointestinal tract.[1]

Globally, typhoid fever affects 9 million people, with an estimated 110000 deaths per annum.[2] In our country, the diagnostic dilemma of typhoid fever and the development of antimicrobial resistance against Salmonella typhi have led to increased systemic complications.[3] Extensively Drug-Resistant (XDR) Salmonella Typhi strains have a documented mortality of 1.6% among patients in Karachi, while the recorded mortality rate was 0.6% in non-XDR Salmonella Typhi.[4]

The pediatric age group is susceptible to bacterial infection, and Salmonella Typhi is the most common infection observed between 5-15 years.[5] A recent trial conducted in a poor locality of Sindh province with a contaminated water supply and poor hygiene revealed a 76.7% positivity of Salmonella Typhi on blood culture.[6] Such high figures of infectivity are a matter of great concern, which overburdens the healthcare system of our country.

The supply of clean water and food is undoubtedly a step towards eradication of typhoid fever, but mass immunization in Pakistan by vaccinating against typhoid might prove useful.[7] Several vaccination campaigns have been conducted recently in Pakistan; however, the complete eradication of the bacterial infection has not been possible.[8] Limited trials have been conducted to assess the effectiveness of vaccination against typhoid fever; however, the main concern and alarming situation of antimicrobial resistance development due to the free availability of antibiotics and lavish prescriptions needs to be addressed. A gap in research still exists about the effectiveness of vaccines against resistant and non-resistant strains.[9]

This cross-sectional research aims at assessing the effectiveness of the typhoid conjugate vaccine in the region of Abbottabad among pediatric age group

Correspondence: Dr Rabia Khalid, Department of Pediatric, Combined Military Hospital, Abbottabad Pakistan
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patients presenting with symptoms of typhoid fever. This will delineate the existing literature and will serve as a guide in predicting the efficacy of the typhoid conjugate vaccine.

METHODOLOGY

This Prospective analytical study was carried out at the Pediatric Department, CMH, Abbottabad, Pakistan, from July 2023 to Feb 2024. The ethical review board of the hospital approved the research work under ERB no CMH-Atd-ETH-149-PAEDS-24.

Previous Research conducted in the province of Balochistan, Pakistan revealed a prevalence of typhoid fever of 19.7%. With 95% power of study when the margin of error of 10%, the sample size was calculated using www.openepi.com. Non-probability consecutive sampling technique was employed with the recruitment of 75 patients in the study.

Inclusion Criteria: Pediatric age group patients between 2-12 years of either gender, having a history of febrile illness, nausea, vomiting, loose motions, or diagnosed with typhoid fever were included in the study.

Exclusion Criteria: Patients with a history of chronic diseases who were severely dehydrated requiring pediatric intensive care unit admission or with end-organ damage were excluded from the study.

At the time of admission, all patients or their attendants were interviewed about vaccination. Demographics, presence or absence of gastrointestinal symptoms, history of use of boiled/unboiled water, vital parameters, and systemic exam findings were recorded. Using a sterile technique, a blood sample was obtained and sent for laboratory investigations and blood culture. After securing an intravenous line, empirical antibiotics and rehydration as per body weight were advised, and treatment commenced. Following the results of laboratory investigations, markers like C-Reactive Protein (CRP), White Blood Cell (WBC) count, Hemoglobin (Hb) level, and number of platelets were recorded. As per our hospital's laboratory, the normal range of WBC was 4–10 x 109/L, CRP was < 6 mg/L, Hb was 12–15 g/dl and platelets were 150–400 x 109/L. For each laboratory parameter, it was recorded as normal if in range and deranged if it deviated from normal limits. After receiving the blood culture, positive and negative culture results were documented. Positive culture results were noted as per the diagnosis of a classified microbiologist as non-resistant Salmonella Typhi, multidrug-resistant (MDR), or Extensively Drug Resistant (XDR).

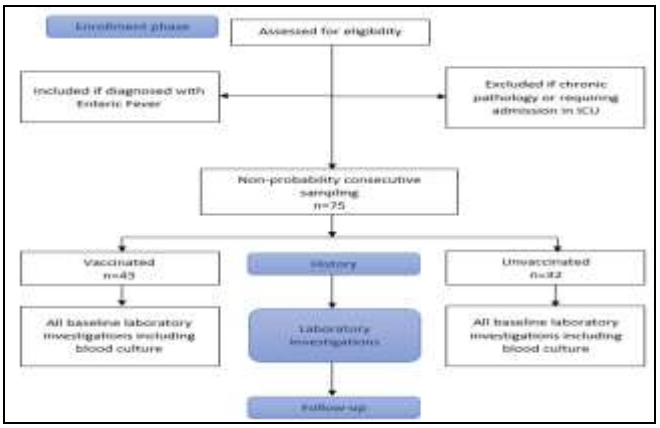

Figure: Patient Flow Diagram

Recorded data was fed into the Statistical Package for the Social Sciences version 23, and analysis was performed. Frequencies and percentages were calculated for categorical variables, while mean and standard deviation values were computed for scale variables. The chi-square test was applied for analyzing the significance between qualitative variables, with a *p*-value of ≤0.05 considered significant.

RESULTS

A total of 75 patients were included in the study with a mean age of 8.07±2.38 years, having a male predominance of 54(72%) as compared to 21(28%) females. The number of unvaccinated patients was 32(42.7%) as compared to 43(57.3%) vaccinated patients. The most common presenting complaint was fever observed in 70(93.3%) patients, followed by gastrointestinal symptoms as reported by 60(80%) patients. Lab parameters revealed that deranged platelets were a common finding in 54(72%) patients, followed by WBC count seen in 53(70.7%) patients. Demographic characteristics and baseline findings are given in Table-I. Typhoid vaccination offered superior protection against culture-confirmed Salmonella Typhi as evident from negative culture reports observed in 19(44.2%) vaccinated patients as compared to 03(9.4%) unvaccinated children (p<0.01). In comparison of the vaccinated population, MDR, XDR, and non-resistant strains were greater in frequency among unvaccinated patients. Among the children with a history of vaccination, the highest number of reported cases were non-resistant strains of the bacteria, followed by XDR and MDR strains of Salmonella typhi. Unvaccinated pediatric patients revealed the highest

frequency of 11(34.4%) MDR strains, followed by non-resistant strains in 10(31.3%) and XDR strains in 08(25%) children. Pathogens reported as per culture findings are given in Table-II.

Table-I: Demographic and Baseline parameters (n=75)

Variables		*Values*
Age in Years (Mean±S.D)		8.07±2.38
Gender	Male n(%)	54(72.0%)
	Female n(%)	21(28.0%)
Use of Unboiled Water	Yes n(%)	31(41.3%)
	No n(%)	44(58.7%)
Typhoid Vaccination	Yes n(%)	43(57.3%)
	No n(%)	32(42.7%)
White Blood Cell Count	Within Limits n(%)	22(29.3%)
	Deranged n(%)	53(70.7%)
Hemoglobin	Within Limits n(%)	59(78.7%)
	Deranged n(%)	16(21.3%)
C-Reactive Protein	Within Limits n(%)	36(48.0%)
	Deranged n(%)	39(52.0%)
Platelets	Within Limits n(%)	21(28.0%)
	Deranged n(%)	54(72.0%)
Fever	Present n(%)	70(93.3%)
	Absent n(%)	05(6.7%)
Gastrointestinal Symptoms	Present n(%)	60(80.0%)
	Absent n(%)	15(20.0%)
Hepatomegaly	Present n(%)	52(69.3%)
	Absent n(%)	23(30.7%)

Table-II: Pathogens on Culture (n=75)

Culture	Pathogen Strains	Vaccinated (n=43)	Unvaccinated (n=32)	*p*-value
Positive (n=54)	Multidrug-Resistant strains	03(7.0%)	11(34.4%)	0.001
	Extensively Drug-Resistant strains	06(13.0%)	08(25.0%)	
	Non-resistant strains	15(34.9%)	10(31.3%)	
Negative (n=21)	Negative culture	19(44.2%)	03(9.4%)	

DISCUSSION

This cross-sectional study studied a cohort with mean age of 8.07±2.38 years who had all been diagnosed with typhoid fever over eight months during the study period. The study's goal was to evaluate the effectiveness of the typhoid conjugate vaccination in preventing culture-proven typhoid fever. It was observed that our patients had a male predominance with 54(72%) males and 21(28%) females presenting with typhoid fever. Literature has also highlighted the similar age group affected in our local population in a study conducted by Hanif *et al.,* revealed that the average age group of the patients presenting with typhoid in Karachi was 5.16±3.44 years.[8] Another descriptive cross-sectional study conducted revealed similar findings, with 56% males as compared to 44% females.[9] Similarly, Rafiq *et al.,* conducted a study in Pakistan that revealed a male predominance of 83(58.04%) as compared to 60(41.95%) children with typhoid fever.[10]

According to the laboratory findings of this study, the most common anomaly, seen in 72% of youngsters, was decreased platelet count. This emphasizes how typhoid fever affects the hematological system. Similar findings highlighted by Ujan *et al.,* of thrombocytopenia in 15% and leukocytosis in 12.3% of pediatric patients were observed.[11] These findings are supported by another study conducted in Quetta, Pakistan, revealing that 26.4% and 35% of patients with non-resistant and resistant typhoid infections were diagnosed with thrombocytopenia.[12]

Interviewing the pediatric patients of Abbottabad revealed that 43(57.3%) patients were vaccinated, which denoted that a large population of children remains unvaccinated in the region. In comparison, a field survey reported by Tashfeen *et al.,* after a vaccination campaign in Sindh province revealed that 80% of the population was vaccinated.[13] This emphasizes the need for vaccination campaigns in the city. Negative culture reports were frequently observed in vaccinated patients as compared to unvaccinated patients in our research. In vaccinated children, culture-negative reports were seen in 19(44.2%), which revealed the effectiveness of typhoid vaccination against culture-confirmed bacteremia. However, local research conducted by Batool *et al.,* in Karachi revealed a higher protection of typhoid vaccination in 95% of the population against culture-proven infection.[14] The rise in the unjust use of anti-biotics during the era of COVID-19 and the leverage of easy availability of antibiotics in the market has led to the misuse of antibiotics.[3] This has caused significant antimicrobial resistance among our population and hence the rise in the number of resistant Salmonella strains.[7] Our study revealed that XDR strains were reported in 13% of the vaccinated children as compared to 25% of the unvaccinated children.

Yousafzai *et al.,* revealed in their research that the overall effectiveness of the typhoid vaccine was 55%, while an effectiveness of 97% against XDR Salmonella was observed.[15] The higher rates of effectiveness reported in the previous studies as compared to ours may be because of the increase in resistant strains of Salmonella Typhi. Like the higher rates of XDR infection as found in our study, a descriptive observational study of Memon *et al.,* revealed that 79% of the blood cultures obtained at Karachi were positive for XDR strains of the bacterial pathogen. Lack of vaccination against typhoid was a significant factor

leading to higher rates of infection (p<0.01).[16] Reported XDR strains in pediatric patients were found to be 75%, which were sensitive to Carbapenems and Azithromycin.[17] Owing to the protective effects of vaccination, our results showed a lesser number of MDR infections in vaccinated 03(7%) as compared to 11(34.4%) unvaccinated children. Higher rates of MDR infections have been reported previously in culture-confirmed Salmonella Typhi infections, with an estimate of 16% in the Pakistani population.[18] Decrease in the number of MDR infections after vaccination is promising; however, the rise in the number of XDR infections needs strict measures and prompt actions.[19,20]

The study's findings support the inclusion of the typhoid vaccine in routine immunization programs to combat the disease more effectively. Moreover, the importance of continuous monitoring of vaccine effectiveness against emerging resistant strains is highlighted.[21] This ongoing surveillance is vital to ensure the sustained efficacy of the vaccine and to adapt public health strategies accordingly.[22] The significant protection conferred by the vaccine against resistant strains of Salmonella Typhi also indicates its potential to alleviate the healthcare system's burden, which is often exacerbated by cases of drug-resistant infections.[23]

This research provides robust evidence supporting the efficacy of typhoid vaccination in preventing culture-proven typhoid fever and reducing the prevalence of drug-resistant strains. The findings advocate for broader implementation of typhoid vaccination programs, especially in regions with high incidence and antimicrobial resistance rates. By promoting widespread immunization and vigilant monitoring, public health authorities can make significant strides in controlling typhoid fever and improving pediatric health outcomes.

LIMITATION OF STUDY

The cross-sectional nature of this study limits the ability to draw conclusions regarding the efficacy of the typhoid conjugate vaccination. Patients without the disease were not included in the study for comparison with the diseased population. Additionally, the study included self-reported vaccination history, which raises the possibility of memory bias. Lastly, there was insufficient investigation of the effects of additional possible confounding variables, such as differences in vaccination coverage and treatment protocol adherence.

CONCLUSION

Vaccination against typhoid promotes significant protection against culture-proven typhoid fever. Protection against MDR and XDR strains makes typhoid vaccination a suitable choice to decrease the incidence of typhoid fever.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

RK & MG: Data acquisition, data analysis, critical review, approval of the final version to be published.

HK & AI: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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