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# Frequency of New Onset Salmonella Positive Cases in Children who Received Typhoid Conjugate Vaccine versus Unvaccinated Children

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## ABSTRACT

**Objective:** The objective of the study is to find the frequency of Typhoid Conjugate vaccination in children of age 1-15 years. **Study Design:** It was a descriptive cross-sectional study. **Place and Duration of Study:** Department of Pediatrics, Ghurki Teaching Trust Hospital, Lahore for the period w.e.f July 2023 to January 2024. **Material and Methods:** Two hundred (200) children, who fulfilled the selection criteria, were recruited for study from OPD of Department of Pediatrics, Ghurki Trust Teaching Hospital, Lahore. The written consent was taken from the Parents. Demographics were noted. Then, all the children were managed as per standard protocol. History from children was taken about TCV vaccination. Blood sample were taken in a 3 cc disposable syringe and was sent to pathology department to detect the presence of salmonella typhi. Reports were assessed and if salmonella typhi detected, then it was recorded. Data was analyzed using SPSS version 20.0. **Results:** The study cohort had a mean age of 8.60±4.46 years, with 52% male participants. The mean weight was 25.61±9.33 kg and height 122.00±24.70 cm. Symptoms lasted 11.35±3.40 days. Typhoid conjugate vaccine (TCV) was administered to 56.5% of children, with 18% diagnosed with typhoid. TCV recipients had a significantly lower infection rate (12.4%) compared to non-recipients (25.3%; p=0.019) where p reflects the time internal between vaccination (TCV) and this infection. Differences across age, gender, weight, height, symptoms, and presentation reasons did not achieve statistical significance due to small sample size. **Conclusion:** In conclusion, our study underscores a discernible and significant link between the administration of the Typhoid Conjugate Vaccine (TCV) and a lowered incidence of typhoid infections.

## INTRODUCTION

Typhoid fever is an infectious disease caused by the bacterium Salmonella enterica serovar Typhi (S. Typhi).[1] This illness is prevalent in various regions of Africa and Southeast Asia and is typically marked by symptoms such as fever, vomiting, abdominal pain and diarrhea. In 2017, global estimates reported that S. Typhi was responsible for approximately 10.9 million infections and 116,800 deaths. Notably, South Asia was the most heavily impacted region, accounting for 72% of global cases and 70% of deaths attributed to typhoid fever.[2]

Our country, Pakistan, is currently experiencing the world's largest outbreak of predominantly drug-resistant typhoid. In 2018, a vaccination campaign using the Typhoid Conjugate Vaccine (Typbar TCV®) targeted high-risk districts in Lahore (Punjab), vaccinating children aged 6 months to 10 years.[4] Pakistan became the first country to include TCV in its regular immunization schedule in November 2019.[5] The first phase of the TCV campaign in Punjab and Islamabad was completed by February 15, 2021, vaccinating over 13 million children aged 9 months to 15 years.[6]

The emergence of extensively drug-resistant (XDR) typhoid fever in Pakistan has significantly curtailed treatment options, leaving azithromycin as the primary effective oral antibiotic. To mitigate the need for antibiotics and curb the risk of further drug resistance, vaccination emerges as the most viable preventive measure.[7] In 2017, the World Health Organization prequalified the typhoid conjugate vaccine, Typbar TCV® (Bharat Biotech International Limited, Hyderabad, India), and recommended its prioritization in regions with a high burden of typhoid or drug-resistant strains. Subsequently, Typbar TCV® was utilized in response to the XDR typhoid outbreak in Hyderabad, Pakistan, in February 2018. During this outbreak, Aga Khan University Hospital successfully administered 207,000 doses of the vaccine as part of a mass 4S immunization campaign.[4,8] One study reported that the frequency of TCV vaccination was 57.4% across all districts of Punjab. Overall, the incidence of suspected typhoid fever was 9490 (95% CI 9361-9619) per 100,000 persons per years among vaccinated children

and 20,886 (20,566-21,207) per 100,000 persons per years among unvaccinated children.[9]

The study aimed to assess the frequency of new Salmonella Typhi infections in children with and without Typhoid Conjugate Vaccine (TCV) to evaluate TCV's effectiveness. Given typhoid's significant morbidity and mortality in children, updated evidence on TCV's protective role was crucial. The research provided local data that could refine guidelines and improve future prevention strategies.

## MATERIAL AND METHODS

This descriptive cross-sectional study was conducted in the Department of Pediatrics, Ghurki Teaching Trust Hospital, Lahore, over six months from July 2023 to January 2024. With a sample size of 200 cases,[9] calculated at a 95% confidence level and 7% margin of error, consecutive non-probability sampling was employed. Inclusion criteria included children aged 1-15 years presenting with fever or cough for over 5 days. Exclusion criteria involved children with typhoid fever within 28 days post-vaccination or incomplete vaccination records. Parents were asked to provide the written consent to include their children in the study. Demographics like name, age, sex, weight, gestational age at birth, reason for presentation and duration of symptoms, were obtained. Then, all the children were managed as per standard protocol. History from parents was taken about TCV vaccination and vaccination card of child was obtained from parents. Blood sample was taken in a disposable syringe and was sent to pathology department to detect the presence of salmonella typhi culture settle. Reports were assessed and if salmonella typhi detected, then it was recorded.

All data were entered and analyzed using SPSS v. 20. Numerical variables, such as age, weight, and duration of symptoms, were presented as Mean±SD. Categorical variables, including gender, reason for presentation, TCV vaccination, and Salmonella typhi, were presented as frequency and percentage. Data were stratified by age, sex, weight, reason for presentation, and symptom duration. Salmonella typhi infection was compared between children with and without TCV vaccination using the chi-square test, with a significance level set at $p < 0.05$. Post-stratification, TCV vaccination rates were compared within each stratified group using the chi-square test, and Salmonella typhi was analyzed similarly in each stratum, with $p < 0.05$ considered significant.

## RESULTS

Mean age of the patients in this study was 8.60±4.46 years in the range of 1-15 years wherein 59.5% patients were in the age group of 9-15 years. The study cohort had 52.0% (n=104) male participants with a male to female ratio of 1.08:1. Mean weight of the study cohort was 25.61±9.33 kg while mean height was 122.00±24.70 cm. Mean duration of symptoms was 11.35±3.40 days. Frequency and reasons for presentation included fever (68.0%), aches/pain (12.5%), extreme tiredness (10.0%) and complained cough (9.5%). Data is given in Table 1. Frequency of children who got typhoid conjugate vaccine was 56.5%. Data is given in Table 2. Frequency of TCV across various subgroups of children included in the study is given in Table 3 where it produced insignificant difference between all sub groups. Frequency of typhoid infection in children in this study was found in 18% as shown in Table 4. Stratification of frequency of typhoid infection had insignificant difference between various subgroups as shown in Table 5. Comparison of frequency of typhoid infection between TCV and non TCV children shows significantly less frequency in children with TCV than non TCV children as 12.4% vs. 25.3%; p-value=0.019. Data is given in Table 6. Comparison of frequency of typhoid infection between TCV and non TCV children across various sub groups of age, gender, weight, height, duration of symptoms was consistently less in group A than group B, but for all sub groups statistical significance could not be achieved due to small sample size.

**Table 1**

*Demographic Characteristics of Children included in the Study*

| Characteristics | Participants (n=200) |
|---|---|
| Age (years) | 8.60±4.46 |
| • 1-8 years | 81 (40.5%) |
| • 9-15 years | 119 (59.5%) |
| Gender | |
| • Male | 104 (52.0%) |
| • Female | 96 (48.0%) |
| Weight (kg) | 25.61±9.33 |
| • ≤25 kg | 92 (46.0%) |
| • >25 kg | 108 (54.0%) |
| Height (cm) | 122.00±24.70 |
| • ≤100 cm | 47 (23.5%) |
| • >100 cm | 153 (76.5%) |
| Duration of Symptoms (days) | 11.35±3.40 |
| • 6-10 days | 82 (41.0%) |
| • >10 days | 118 (59.0%) |
| Reasons for Presentation | |
| • Fever | 136 (68.0%) |
| • Aches, Pain | 25 (12.5%) |
| • Extreme Tiredness | 20 (10.0%) |
| • Cough | 19 (9.5%) |

**Table 2**

*Frequency of Children who got Typhoid Conjugate Vaccine in the Study (n=200)*

| TCV | Frequency (n) | Percent (%) |
|---|---|---|
| Yes | 113 | 56.5 % |
| No | 87 | 43.5 % |
| Total | 200 | 100.0 % |

**Table 3**

*Comparison of Frequency of TCV across Various Subgroups of Children included in the Study (n=200)*

| Subgroups | | n | TCV n (%) | P-value |
|---|---|---|---|---|
| Age | 1-8 years | 81 | 49 (60.5%) | 0.347 |
| | 9-15 years | 119 | 64 (53.4%) | |
| Gender | Male | 104 | 55 (52.9%) | 0.283 |
| | Female | 96 | 58 (60.4%) | |
| Weight (kg) | ≤25 kg | 92 | 55 (59.5%) | 0.387 |
| | >25 kg | 108 | 58 (53.7%) | |
| Height (cm) | ≤100 cm | 47 | 28 (59.6%) | 0.627 |
| | >100 cm | 153 | 85 (55.6%) | |
| Duration of Symptoms | 6-10 days | 82 | 44 (53.7%) | 0.499 |
| | >10 days | 118 | 69 (58.5%) | |
| Reasons for Presentation | Fever | 136 | 78 (54.7%) | 0.740 |
| | Aches, Pain | 25 | 15 (60.0%) | |
| | Extreme Tiredness | 10 | 9 (45.0%) | |
| | Cough | 19 | 11 (57.9%) | |

*Chi-square test, observed difference was statistically insignificant*

**Table 4**
*Frequency of Typhoid Infection in Children included in the Study (n=200)*

| Typhoid Infection | Frequency (n) | Percent (%) |
|---|---|---|
| Yes | 36 | 18.0 % |
| No | 164 | 82.0 % |
| Total | 200 | 100.0 % |

**Table 5**
*Comparison of Frequency of Typhoid Infection across Various Subgroups of in Children included in the Study*

| Subgroups | | n | Typhoid Infection n (%) | P-value |
|---|---|---|---|---|
| Age | 1-8 years | 81 | 14 (17.3%) | 0.828 |
| | 9-15 years | 119 | 22 (18.5%) | |
| Gender | Male | 104 | 15 (14.4%) | 0.171 |
| | Female | 96 | 21 (21.9%) | |
| Weight (kg) | ≤25 kg | 92 | 17 (18.5%) | 0.871 |
| | >25 kg | 108 | 19 (17.6%) | |
| Height (cm) | ≤100 cm | 47 | 8 (17.0%) | 0.842 |
| | >100 cm | 153 | 28 (18.3%) | |
| Duration of Symptoms | 6-10 days | 82 | 15 (18.3%) | 0.928 |
| | >10 days | 118 | 21 (17.8%) | |
| Reasons for Presentation | Fever | 136 | 21 (15.4%) | 0.151 |
| | Aches, Pain | 25 | 4 (16.0%) | |
| | Extreme Tiredness | 10 | 4 (20.0%) | |
| | Cough | 19 | 7 (36.8%) | |

*Chi-square test, observed difference was statistically insignificant*

**Table 6**
*Comparison of Frequency of Typhoid Infection between TCV and non-TCV children*

| Typhoid Infection | TCV | | Total | P-value |
|---|---|---|---|---|
| | Yes (n=113) | No (n=87) | | |
| Yes (n=36) | 14 12.4% | 22 25.3% | 36 18.0% | 0.019 |
| No (n=164) | 99 87.6% | 65 74.7% | 164 82.0% | |
| Total | 113 100.0% | 87 100.0% | 200 100.0% | |

*Chi-square test, * observed difference was statistically significant*

## DISCUSSION

The escalating problem of Salmonella outbreaks in children poses a significant public health concern, with rising incidences demanding a closer examination of preventative strategies.[10] Salmonella infections, known for their gastrointestinal manifestations, can lead to severe complications, especially in pediatric populations.[11,12] The vulnerability of children to the severe consequences of Salmonella infection underscores the urgency to assess the effectiveness of available interventions.[13] Among these, the Typhoid Conjugate Vaccine (TCV) stands out as a promising option due to its potential to confer immunity against Salmonella Typhi, a bacterium causing typhoid fever.[14] However, the precise impact of TCV on the occurrence of new onset Salmonella cases in pediatric populations remains elusive.[15,16] Existing literature on the subject sparks controversy, with some studies suggesting a significant reduction in positive cases among vaccinated children, while others dispute this association. The varying outcomes in different studies have led to a lack of consensus in the scientific community regarding the efficacy of the Typhoid Conjugate Vaccine in preventing Salmonella infections in children. This controversy highlights the need for a comprehensive and methodologically sound investigation to provide clarity on the matter.

In this study, the Patient's mean age was 8.60±4.46 years. However, Yousafzai et al reported age range of their patients in a similar study as 6-59 months.[9] Similarly, Jin et al observed a mean age of 9.7±0.8 months in the UK.[17] This variation in mean age highlights difference in geographical and demographic factors and inclusion criteria of each study.

The mean weight of the study cohort was 25.61±9.33 kg while mean height was 122.00±24.70 cm. In contrast, totally different findings were given by Sirima et al in the US where study participants had a lower mean weight of 8.4±1.1 kg and a mean height of 70.4±4.0 cm.[6] These variations may be associated with difference in inclusion criteria of each study but must be considered while generalizing results of each study individually.

The mean duration of symptoms in this study was 11.35±3.40 days where reasons for admission were quite different but fever was predominant factor which was observed in 68.0% participants. Other causes were aches & pain (12.5%), extreme tiredness (10.0%) and cough (9.5). These findings present multifaceted nature of the symptoms in the study cohort which must be considered individually by the healthcare providers before decision making for proper intervention and to address them effectively.

In our study, frequency of children who received the typhoid conjugate vaccine (TCV) was was 56.5%. Our findings closely align with the findings of Yousafzai et al, who reported a similar frequency of 57%.[9] But, it differs noteworthy from results of Batool et al, where a substantially higher frequency of 82% was observed.[2] Our study further delved deep by comparing frequency of TCV across various subgroups of children, revealing insignificant differences among these subgroups. This exploration further sheds light on the uniform distribution of TCV uptake, emphasizing the need for further investigation into factors influencing vaccine coverage to inform targeted public health strategies.

In this study, frequency of typhoid infection in children was determined to be 18%. Frequency of typhoid infection was significantly less in children who received the typhoid conjugate vaccine (TCV) than those who did not receive TCV. The frequency was notably low in children with TCV compared to non TCV children (12.4% vs. 25.3%; p-value=0.019). These findings are consistent with the results reported by Yousafzai et al, where the frequencies of typhoid infection was significantly low in children who received TCV (9.48% vs. 20.87%; p-value <0.05) than those who were not vaccinated.[9]

Likewise, Lightowler et al reported comparable results, indicating frequencies of 35% in TCV and 77% in non TCV groups, with a p-value <0.05.[4] This concordance in results across studies underscores the potential efficacy of TCV in reducing the frequency of typhoid infections in children.

Stratification of typhoid infection frequencies between children who received the typhoid conjugate vaccine (TCV) and those who did not, across various subgroups such as age, gender, weight, height, duration of symptoms, and reason for presentation, revealed a consistent trend of lower infection rates in TCV recipients compared to non

TCV children. However, statistical significance could not be achieved in subgroup analysis due to small sample size in each sub group. Even though, the observed pattern highlights potential protective effect of TCV across diverse demographic and clinical characteristics, emphasizing the need for larger-scale studies to validate these trends conclusively.

The study boasts a robust sample size of 200 children, enabling comprehensive analyses. It explores diverse demographic and clinical factors, shedding light on the potential efficacy of the Typhoid Conjugate Vaccine (TCV). However, statistical significance in subgroup analyses is constrained by small sample sizes, necessitating caution in generalizing findings. Larger cohorts are needed for conclusive validation.

## CONCLUSION

In conclusion, our study underscores a discernible and significant link between the administration of the Typhoid Conjugate Vaccine (TCV) and a lowered incidence of typhoid infections. Although statistical significance was hindered by limited subgroup sizes, the consistent trends hint at the promising effectiveness of TCV across diverse demographic and clinical parameters, prompting the need for more extensive investigations with larger cohorts.

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